

# Current Smoking is Associated with Incident Ankylosing Spondylitis — The HUNT Population-based Norwegian Health Study

Vibeke Videm, Adrian Cortes, Ranjeny Thomas, and Matthew A. Brown

**ABSTRACT. Objective.** Smoking contributes to progression of ankylosing spondylitis (AS). Because smoking is also a risk factor for incident rheumatoid arthritis (RA) and psoriatic arthritis, our aim was to test whether smoking habits are associated with incident AS.

**Methods.** Using data from the HUNT health study of the entire adult population of Nord-Trøndelag, Norway, participants in HUNT2 (1995–1997) and HUNT3 (2006–2008) were identified who reported a diagnosis of AS in HUNT3 but not in HUNT2 (n = 107). Incident AS cases were compared with AS-unaffected individuals (n = 35,278) in a case-control design. Participants with RA were excluded.

**Results.** Present smoking was significantly associated with incident self-reported AS in logistic regression adjusted for potential confounders (OR 1.99, 95% CI 1.28–3.11, p = 0.002). Previous smoking (OR 1.15, 95% CI 0.66–2.02, p = 0.62) or total pack-years at HUNT2 (OR 1.01, 95% CI 0.99–1.04, p = 0.21) were not significant. The association with present smoking remained significant in various sensitivity analyses: including only cases with high probability of true AS diagnosis (OR 1.82, 95% CI 1.03–3.19, p = 0.04); including only cases with AS reported more than 3–5 years after HUNT2 (OR 2.34, 95% CI 1.09–5.03, p = 0.029), or including only participants genotyped for *HLA-B27* (94 cases and 859 controls) adjusting for genotype (OR 1.79, 95% CI 1.04–2.85, p = 0.033). Hypertension was also significantly associated with incident AS (OR from 1.65 to 2.81).

**Conclusion.** In the HUNT population-based study, incident AS was associated with current smoking and hypertension. If verified in further studies, this suggests that smoking should be discouraged in those at a higher AS risk, e.g., with a family history or carrying *HLA-B27*. (First Release Aug 15 2014; *J Rheumatol* 2014;41:2041–8; doi:10.3899/jrheum.140353)

## Key Indexing Terms:

ANKYLOSING SPONDYLITIS  
EPIDEMIOLOGY

AXIAL SPONDYLOARTHRITIS  
RISK FACTOR

SMOKING  
HUNT

From the Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, and the Department of Immunology and Transfusion Medicine, Trondheim University Hospital, Trondheim, Norway; University of Queensland Diamantina Institute, Translational Research Institute, Princess Alexandra Hospital, Woolloongabba, Brisbane, Queensland, Australia.

Funding from the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (VV, project 46051000). MAB is funded by a National Health and Medical Research Council (NHMRC) Senior Principal Research Fellowship, and support for this study was received from an NHMRC program grant (566938) and project grant (569829), and from the Australian Cancer Research Foundation and the Rebecca Cooper Medical Research Foundation.

V. Videm, MD, PhD, Professor of Immunology/Consulting Physician, Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, and Department of Immunology and Transfusion Medicine, Trondheim University Hospital; A. Cortes, PhD, Postdoctoral fellow; R. Thomas, MD, Professor of Rheumatology; M.A. Brown, MD, Professor of Immunogenetics/Director, University of Queensland Diamantina Institute, Translational Research Institute, Princess Alexandra Hospital.

Address correspondence to Dr. V. Videm, Department of Immunology and Transfusion Medicine, St. Olavs University Hospital, NO-7006, Trondheim, Norway. E-mail: [vibeke.videm@ntnu.no](mailto:vibeke.videm@ntnu.no)

Accepted for publication June 13, 2014.

Spondyloarthritis (SpA) comprises a number of etiopathogenically related clinically overlapping inflammatory rheumatic conditions, including ankylosing spondylitis (AS) and nonradiographic axial spondyloarthritis (nr-axSpA), in which arthritis is more prominent in the spine and sacroiliac joints, as well as psoriatic arthritis (PsA), reactive arthritis, and arthritis associated with inflammatory bowel disease.

Patients with AS who smoke fare worse than non-smokers, including in functional disability<sup>1,2</sup>, disease activity<sup>2,3</sup>, and radiographic progression<sup>4</sup>, as summarized in a recent review<sup>5</sup>. Smokers also have earlier disease onset<sup>3</sup>. The mechanisms for these effects of smoking are not well known, but may be related to proinflammatory effects, as indicated by increased concentrations of C-reactive protein, interleukin 6, and matrix metalloproteinases<sup>6,7</sup>.

Smoking is an established risk factor for development of autoantibody-positive rheumatoid arthritis (RA) in individuals with HLA-DR susceptibility alleles<sup>8</sup>. Further, data from almost 95,000 participants with 14 years followup in the Nurses' Health Study showed an increased risk of incident PsA in past and current smokers<sup>9</sup>. The effects were

dose-related, and smokers had more severe phenotypes. Two smaller case-control studies have given different results<sup>10,11</sup>. Smoking doubles the risk of Crohn disease (CD), yet paradoxically reduces the risk of ulcerative colitis (UC).

Given that smoking may contribute to the pathogenesis of different forms of inflammatory arthritis through diverse mechanisms, that smoking increases progression in established AS, and that smoking affects the risk of both CD and UC, which are closely genetically associated with AS<sup>12</sup>, we hypothesized that smoking may be a risk factor for incident AS. The primary aim of our present study was therefore to test the hypothesis that smoking habits are associated with incident AS in the Norwegian HUNT population-based health study.

## MATERIALS AND METHODS

For the HUNT population-based health study, the entire adult population (> 20 yrs) in the Norwegian county of Nord-Trøndelag was invited. About 70% (75,000) of those invited participated in HUNT2 (1995–1997), as described in detail<sup>13</sup>. HUNT3 (2006–2008) followed a similar design, and had a participation rate of about 54% (51,000). About 37,071 participated both in HUNT2 and HUNT3. The study did not include contact with participants between enrollment in HUNT2 and HUNT3. All participants gave written, informed consent. The study was approved by the Regional Committee on Medical Research Ethics, Central Norway, the Norwegian Data Safety Authorities, and the Norwegian Department of Health.

The study cohort consisted of all participants in HUNT2 and HUNT3 who at both times answered whether they had a diagnosis of AS, excluding participants with RA (n = 35,780, i.e., 96.5% of 37,071). In Norway, the term “Bekhterev’s disease” is used instead of AS. The questionnaires included the following questions: “Has a doctor ever said that you have/have had Bekhterev’s disease?” in HUNT2, and “Have you had or do you have Bekhterev’s disease? If yes, how old were you the first time?” in HUNT3. Participants who reported a diagnosis of AS in HUNT3 but not in HUNT2 (n = 107) were defined as incident cases of AS. Participants reporting AS in both HUNT2 and HUNT3 were excluded (n = 395). Incident AS cases were compared to the remaining participants (n = 35,278). The selection process of participants is shown in Figure 1. There were 174 participants who indicated a diagnosis of AS in HUNT2 but not in HUNT3. The AS diagnosis was then considered false-positive and those participants were included in the control group (i.e., 0.5% of the controls).

Where possible, the diagnosis of AS in our study was confirmed through the hospital diagnosis registries of Levanger and Namsos hospitals (the 2 primary hospitals in Nord-Trøndelag), and Trondheim University Hospital, the nearest secondary referral hospital. As search items, the International Classification of Diseases, 9th ed (ICD-9) code 720 and ICD-10 code M45 with subcodes were used. From the Norwegian Prescription Database, data on use of drugs in the following groups during the years from 2004 through 2012 were made available: nonsteroidal antiinflammatory drugs (NSAID), steroids, tumor necrosis factor (TNF) inhibitors, disease-modifying antirheumatic drugs (DMARD, i.e., sulfasalazine, methotrexate, leflunomide, hydroxychloroquine, or cyclosporine) or immunosuppressive drugs (i.e., cyclophosphamide or azathioprine).

The questionnaires completed by the participants at enrollment in HUNT2 and HUNT3 included questions regarding medical history and cardiovascular (CV) risk factors. Height, weight, and blood pressure were measured. At HUNT3 a blood sample was drawn for DNA isolation by HUNT Biobank. Pack-years of smoking at HUNT2 were calculated as average number of cigarettes smoked per day × years of smoking history/20. Body mass index (BMI) was calculated as weight/height<sup>2</sup> (kg/m<sup>2</sup>). Systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥

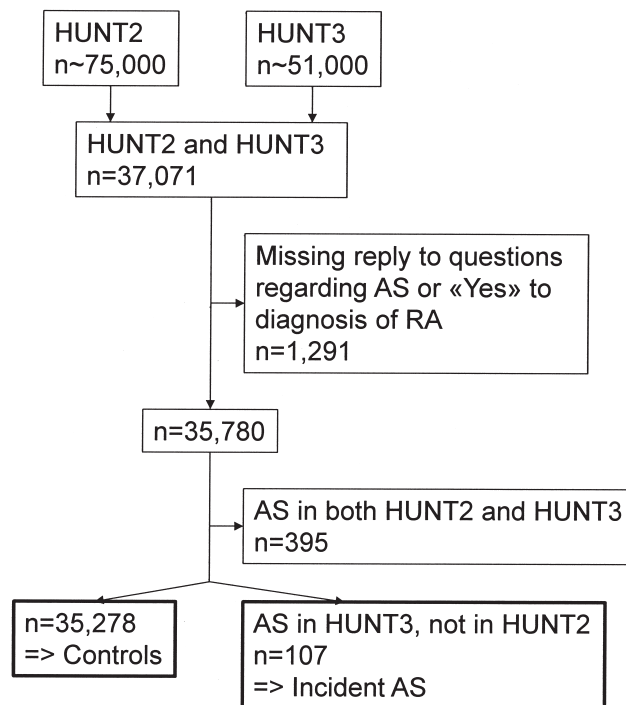


Figure 1. Inclusion and exclusion of study participants. The resulting study groups are shown in the boxes with thick lines. AS: ankylosing spondylitis; RA: rheumatoid arthritis.

90 mmHg, or the answer “yes” to the question “Are you using medication for high blood pressure?” were defined as hypertension (HTN). A composite variable of angina, myocardial infarction, or stroke was defined as previous CV disease. For participants with self-reported AS where DNA was available and for 924 randomly chosen controls, genotyping for *HLA-B27* was performed using imputation as previously reported<sup>14</sup>.

**Statistical analysis.** Data are presented as number (percentage), mean, or median (95% CI), as appropriate. The chi-square test, t test, and Mann-Whitney U test were used for between-group comparisons of categorical and continuous variables. Correlation between age and smoked pack-years was assessed using Pearson’s R and Spearman’s  $\rho$  correlation coefficients. Risk factors associated with the development of AS between HUNT2 and HUNT3 were identified using multivariate logistic regression models adjusting for sex, age, BMI, HTN, diabetes, and previous CV disease. Linearity of logits for continuous variables was checked by plotting. SPSS (v19.0, SPSS) was used for statistical analysis. Calculation of the attributable risk of smoking was performed using the “aflogit” package in Stata (version 12.1, StataCorp). P values < 0.05 were considered statistically significant.

In the main analysis, smoking at baseline was represented as a categorical variable (current, former, or never smoker). We performed several sensitivity analyses to support our main analysis because this was a population-based survey with self-reported AS. First, smoking was alternatively represented as total pack-years or as a change in smoking habits from HUNT2 to HUNT3. To account for a potential correlation between age and pack-years confounding the analysis because the mean age of the controls was higher than that of the incident AS cases, pack-year models were also developed excluding controls older than 60 years or older than 50 years.

Second, we repeated the main analysis in a subgroup of the self-reported incident AS cases after selecting cases with higher probability of a true AS diagnosis (“higher probability of AS”, n = 65) according to the following criteria: *HLA-B27*-positive cases were included only if they had a hospital diagnosis of AS and/or had a record of using medication from the

drug groups NSAID, steroids, TNF inhibitors, DMARD or immunosuppressive drugs, according to Prescription Database data. *HLA-B27* negative cases and cases with unknown *HLA-B27* type were excluded if they had a record of NSAID use only, disregarding whether an AS hospital diagnosis was found; otherwise the same criteria were used as for the *HLA-B27* positive cases. Some patients had a hospital diagnosis of both AS and RA, and were also excluded.

Third, we repeated the main analysis after excluding all cases where the age given as answer to the question regarding “first time” of AS in HUNT3 corresponded to a year before participation in HUNT2 ( $n = 32$ ), even though the phrasing of this question did not distinguish between age at symptom onset or AS diagnosis. In other alternative models, this exclusion criterion was also combined with higher probability of AS. To reduce possible reverse causation, i.e., influence from smoking effects in established AS from cases with delayed diagnosis and erroneously considered incident AS, we finally further restricted by also excluding cases in which a hospital diagnosis was found the first 3–5 years after HUNT2, up to the year 2002.

Finally, models were developed in which participants reporting in HUNT3 that they had psoriasis were either excluded or psoriasis was included as an adjustment variable, a model was developed including fibromyalgia (FM) as an adjustment variable, and a model was developed including only AS cases and controls with known *HLA-B27* genotype. We did not have information regarding education/occupation or income. For calculation of AS incidence, person-years of observation were obtained using the dates for each participant’s inclusion in HUNT2 and HUNT3.

## RESULTS

Characteristics of the participants are shown in Table 1. Participants with incident AS were significantly younger than the controls. The male:female ratio was 0.7:1, which was not significantly different from among the controls (0.8:1). Of the genotyped incident AS cases, 48.5% were *HLA-B27*-positive, as compared to 12.1% of the genotyped controls ( $p < 0.001$ ). Eight incident AS cases (7.5%)

reported having psoriasis, compared to 1880 controls (5.3%;  $p = 0.32$ ). Among the incident higher probability of AS cases, the male:female ratio was 0.8:1 and 67.7% were *HLA-B27* positive (DNA missing from 3 individuals).

Our study included 395,668 person-years of followup with a mean followup time of 11.2 years, and the calculated self-reported incidence of AS was 27.0 per 100,000 person years (29.0 for women and 24.7 for men). When including only the higher probability of AS cases, the corresponding numbers were 16.6 (16.3 for women and 16.4 for men).

The level of missingness at baseline for most key variables was  $< 1\%$ , with the exception of smoking (12.3% missing data) and the question in HUNT3 about age for AS (32% missing data). Missingness for smoking was evenly distributed among cases and controls. Incomplete cases for any key variable were omitted from analysis.

*Factors associated with incident AS.* The incident AS cases were more often former or current smokers and fewer had quit smoking from HUNT2 to HUNT3, but their pack-year history was comparable to that of the controls. Total pack-years were correlated with age independent of group (control or incident AS,  $R = 0.22$ ,  $\rho = 0.17$ ,  $p < 0.001$ ). By multivariate logistic regression, being a current smoker but not a former smoker at HUNT2 significantly increased the risk of incident AS (OR 1.99, 1.28–3.11; Table 2A). As expected, the risk was also higher with younger age. The results were identical if the 174 participants who reported a diagnosis of AS in HUNT2 but not in HUNT3 were excluded from the analysis. Smoking was not associated with incident AS when represented as total pack-years at HUNT2 (OR 1.01, 0.99–1.04; Table 2B), and this finding

Table 1. Baseline characteristics of individuals with and without incident ankylosing spondylitis (AS).

	Control Group, $n = 35,278$	Incident AS, $n = 107$	p value <sup>i</sup>
Age <sup>ii</sup> (years)	46.7 (46.6–46.8)	40.8 (38.5–43.1)	$< 0.001$
Males/females	15,905 (45.1%)/19,373 (54.9%)	44 (41.1%)/63 (58.9%)	0.41
Body mass index <sup>iii</sup> (kg/m <sup>2</sup> )	25.7 (25.7–25.7)	25.7 (25.2–26.4)	0.58
Hypertension	12,807 (36.3%)	44 (41.1%)	0.31
Diabetes	507 (1.4%)	2 (1.9%)	0.71
Previous CVD	1,242 (3.5%)	4 (3.7%)	0.91
Smoking HUNT2			$< 0.01$
Never smoker	15,784 (44.7%)	38 (35.5%)	
Former smoker	8,395 (23.8%)	19 (17.8%)	
Present smoker	9,223 (26.1%)	41 (38.3%)	
Pack-years HUNT2 (former and present smokers) <sup>iii</sup>	9.6 (9.5–10.0)	7.7 (5.3–10.3)	0.12
Change in smoking habits, HUNT2 to HUNT3			0.08
Never smoker	13,698 (38.8%)	34 (31.8%)	
Quit smoking	10,812 (30.6%)	33 (30.8%)	
Started smoking or continuous smoker	6,434 (18.2%)	28 (26.2%)	
<i>HLA-B27</i> genotypes <sup>iv</sup>			$< 0.001$
<i>HLA-B27</i> -positive	112 (12.1%)	50 (48.5%)	
<i>HLA-B27</i> -negative	812 (87.9%)	53 (51.5%)	

<sup>i</sup>t test, Mann-Whitney U test, or chi-square test. Data are given as <sup>ii</sup>mean or <sup>iii</sup>median (95% CI) or frequency (%). <sup>iv</sup>Data available for 924 controls and 103 incident AS cases. CVD: cardiovascular disease.

Table 2. Effects of possible risk factors on self-reported incident AS, by multivariate logistic regression.

	OR	95% CI	p
A. Main model (n = 98 patients and 33,127 controls) <sup>i</sup>			
Female sex	1.38	0.91–2.09	0.13
Age <sup>ii</sup>	0.96	0.94–0.97	< 0.001
BMI <sup>iii</sup>	1.03	0.98–1.08	0.22
Diabetes	1.96	0.47–8.12	0.35
HTN	1.69	1.07–2.67	0.025
Previous CVD	1.02	0.24–4.27	0.98
Smoking			
Never smoker	1	Reference	
Former smoker	1.15	0.66–2.02	0.62
Current smoker	1.99	1.28–3.11	0.002
B. Smoking represented as total pack-yrs (n = 100 patients and 32,573 controls) <sup>i,iiii</sup>			
Female sex	1.44	0.95–2.19	0.09
Age <sup>ii</sup>	0.95	0.93–0.97	< 0.001
HTN	1.78	1.13–2.81	0.013
Total pack-yrs <sup>ii</sup>	1.01	0.99–1.04	0.21
C. Smoking represented as change in smoking habits from HUNT2 to HUNT3 (n = 95 patients and 30,678 controls) <sup>i,iii</sup>			
Female sex	1.14	0.75–1.74	0.53
Age <sup>ii</sup>	0.95	0.93–0.97	< 0.001
HTN	1.65	1.04–2.63	0.03
Change in smoking habits			
Never smoker	1	Reference	
Quit smoking	1.47	0.91–2.40	0.12
Started smoking or continuous smoker	1.92	1.16–3.17	0.012

<sup>i</sup>Cases with complete data. No. missing for control cases: sex and age: 0; BMI: 132 (0.4%); diabetes 33 (0.1%); HTN: 122 (0.4%); previous CV disease: 107 (0.3%); never/present/former smoker: 1876 (5.3%); pack-yrs HUNT2: 2432 (6.9%); change in smoking habits HUNT2 to HUNT3: 4334 (12.3%). No. missing for incident AS cases: sex, age, BMI, diabetes, HTN, previous CV disease: 0; never/present/former smoker: 9 (8.4%); pack-yrs HUNT2: 7 (6.5%); change in smoking habits HUNT2 to HUNT3: 12 (11.2%). No. missing for the smoking-related variables was not significantly different between cases and controls ( $p > 0.15$ ). <sup>ii</sup>Continuous variable, OR per 1 unit change. <sup>iii</sup>The model was also adjusted for BMI, diabetes, and previous CV disease. AS: ankylosing spondylitis; BMI: body mass index; HTN: hypertension; CVD: cardiovascular disease.

was unchanged when excluding controls older than 50 or 60 years from the analysis. The risk was significantly increased in persons who started smoking (n = 2) or were continuous smokers between HUNT2 and HUNT3 (OR 1.92, 1.16–3.17, Table 2C). HTN was also significantly associated with incident AS in all the logistic regression models (Tables 2 and 3).

The increased risk associated with current smoking remained significant in all the alternative models developed as sensitivity analyses, i.e., when including only higher probability of AS cases (Table 3A), when excluding incident AS cases where the age given as answer to the question regarding “first time” of AS in HUNT3 corresponded to a year before participation in HUNT2 (Table 3B), when these criteria were combined (Table 3C), and when the remaining cases were further restricted by excluding those with a hospital diagnosis of AS the first 3–5 years after HUNT2 (Table 3D). In further alternative multivariate models either excluding cases reporting psoriasis in HUNT3, or including psoriasis (yes/no) or FM (yes/no) as an adjustment variable,

present smoking remained significant with moderate changes to the OR (data not shown). Further, in an alternative multivariate model including only incident AS cases and controls genotyped for *HLA-B27* (94 cases and 859 controls with complete data) and adjusting for *HLA-B27* genotype (positive/negative), present smoking at HUNT2 was significant (OR 1.79, 1.04–2.85,  $p = 0.033$ ). In this model, the attributable risk fraction of present smoking was 6.9%.

## DISCUSSION

In this population-based study, current smoking, HTN, and younger age were significantly associated with incident AS, whereas increased BMI, diabetes, and previous CV disease were not. The study included a large cohort with about 396,000 person-years followup time. Because onset of AS is typically insidious, the long followup time is a strength.

*Diagnostic accuracy.* The major limitation of the study is that AS diagnoses were self-reported and that magnetic resonance imaging or radiographic confirmation were not

Table 3. Sensitivity analyses for effects of risk factors on incident AS, by multivariate logistic regression.

	OR	95% CI	p
A. Cases with higher probability of true AS diagnosis (n = 60 patients and 33,127 controls) <sup>i,iii</sup>			
Female sex	0.79	0.47–1.34	0.39
Age <sup>ii</sup>	0.95	0.93–0.97	< 0.001
HTN	2.08	1.17–3.70	0.013
Smoking			
Never smoker	1	Reference	
Former smoker	1.03	0.50–2.13	0.93
Current smoker	1.82	1.03–3.19	0.04
B. Excluding “first time” AS before HUNT2 (n = 64 patients and 33,127 controls) <sup>i,iii</sup>			
Female sex	1.6	0.95–2.70	0.08
Age <sup>ii</sup>	0.96	0.94–0.98	0.001
HTN	2.19	1.25–3.84	0.006
Smoking			
Never smoker	1	Reference	
Former smoker	1.11	0.53–2.32	0.77
Current smoker	2.61	1.51–4.53	0.001
C. Cases with higher probability of true AS diagnosis excluding “first time” AS before HUNT2 (n = 36 patients and 33,127 controls) <sup>i,iii</sup>			
Female sex	1.28	0.65–2.53	0.48
Age <sup>ii</sup>	0.96	0.93–0.99	0.006
HTN	2.47	1.18–5.12	0.017
Smoking			
Never smoker	1	Reference	
Former smoker	0.77	0.27–2.18	0.62
Current smoker	2.27	1.12–4.62	0.024
D. Cases with higher probability of true AS diagnosis excluding “first time” AS before HUNT2 and hospital diagnosis 1997–2002 (n = 31 patients and 33,127 controls) <sup>i,iii</sup>			
Female sex	1.71	0.80–3.63	0.17
Age <sup>ii</sup>	0.96	0.93–0.99	0.006
Hypertension	2.81	1.26–6.27	0.012
Smoking			
Never smoker	1	Reference	
Former smoker	0.74	0.23–2.32	0.60
Current smoker	2.34	1.09–5.03	0.029

<sup>i</sup>Cases with complete data. No. missing for control cases: sex and age: 0; BMI: 132 (0.4%); diabetes 33 (0.1%); HTN: 122 (0.4%); previous CV disease: 107 (0.3%); never/present/former smoker: 1876 (5.3%); pack-yr HUNT2: 2432 (6.9%); change in smoking habits HUNT2 to HUNT3: 4334 (12.3%). No. missing for incident AS cases: sex, age, BMI, diabetes, HTN, previous CV disease: 0; smoking panel A: 5 (7.7%); smoking panel B: 8 (11.1%); smoking panel C: 4 (10.0%); smoking panel D: 3 (8.8%). <sup>ii</sup>Continuous variable, OR per 1 unit change. <sup>iii</sup>Model also adjusted for BMI, diabetes, and previous CV disease. AS: ankylosing spondylitis; BMI: body mass index; HTN: hypertension; CVD: cardiovascular disease.

available. Data on the incidence of AS and axSpA are scarce, but the calculated incidence in our study is much higher than the previously reported incidence of 10.6 per 100,000 person-years for AS in Norway<sup>15</sup>. In a German study of blood donors, the prevalence of AS was 0.55% and that of SpA was 1.9%<sup>16</sup>, and one would expect the incidence of SpA to be considerably higher than that of AS.

The most likely cause for the high number of self-reported AS cases in our study is probably that cases of nr-axSpA were also included. Classification of axSpA is complicated and has undergone several changes<sup>17,18</sup>. Non-rheumatologists and the patients themselves may not make the distinctions clearly and may use the term “Bekhterev’s disease” for both, especially because this term

is much more familiar to the general public in Norway than are AS, SpA, axSpA, or nr-axSpA. This is also consistent with the lower rate of *HLA-B27* positivity than expected, as well as the higher frequency of women<sup>18</sup>. The frequency of women is also partly explained by the sex-specific participation rates in HUNT, which were skewed toward fewer men in the younger age groups. Of the invited men below 40 years of age, 51.5% participated in HUNT2, as compared to 65.1% of women, and the corresponding numbers for HUNT3 were 30.3% and 44.1%, respectively<sup>19,20</sup>. Because we included only participants at both HUNT2 and HUNT3, female participants were more numerous.

It is difficult to determine which *HLA-B27* positivity rate to expect in the higher probability of AS cases, where the

observed rate was 67.7%. Using the Assessment of SpondyloArthritis international Society criteria, axSpA cases diagnosed in the clinical arm will have 100% *HLA-B27* positivity because that is 1 of the 2 diagnostic criteria<sup>21</sup>. Cases classified using the imaging criteria, which do not require the presence of *HLA-B27*, typically have a lower *HLA-B27* carriage rate (58% in 2 recent publications<sup>22,23</sup>). The overall percentage in any mixed cohort of AS and nr-axSpA will therefore depend on which diagnostic arm the patients belong to, which is unknown when using self-reported diagnoses.

Alternatively, some of the AS cases could have had PsA or FM, but the OR of the model barely changed when participants with psoriasis were excluded or adjustment was made for psoriasis or FM. Participants reporting RA were excluded from all models, and the finding that incident AS was related to younger age is another indication that misdiagnosis due to RA is unlikely. Information on inflammatory bowel disease for our participants was not available.

It is important to consider that the effect of including cases of nr-axSpA or other false-positive diagnoses as incident AS would be to reduce the power of our study, and not to increase the likelihood of false-positive findings. Our data showing higher OR for both HTN and current smoking in the model with strictest inclusion criteria for AS, i.e., selecting cases with a higher probability of AS and further excluding cases that might represent established AS erroneously reported as incident AS and thereby leading to reverse causation (Table 3D), are consistent with such reduced power in the main analysis. We cannot exclude that a larger study permitting exclusion of participants with a hospital diagnosis even further than 3–5 years into the observation period might have given another result.

As in all epidemiological research, residual confounding cannot be excluded. Further, the participants in HUNT may not be representative of the entire population. We did not have data on socioeconomic variables such as education/occupation or income. However, we consider that smoking may partly act as a proxy for socioeconomic status.

Even though the median age of the incident AS cases was lower than that of the controls, it was still relatively high. Thus, they may represent a group with many late-onset cases, partly due to the mentioned lower participation rate by men < 40 years of age in HUNT. We cannot exclude that this age distribution may have biased our results when comparing to the general population. Age was included in the regression models, thereby adjusting for the effect of the difference in age between incident AS cases and controls.

*Effect of smoking on risk of AS.* Our findings support the hypothesis that smoking may be causally related not only to progression but also to development of AS. We cannot exclude that smoking is acting as a proxy of other factors influencing incident AS, and association is no proof of causality. However, the relationship seems biologically

plausible because it is likely that proinflammatory and pro-oxidative effects of smoking could conceivably contribute to the evolution of nr-axSpA into AS. An alternative hypothesis, given that smoking is associated with younger onset and worse outcome of AS, is that patients with a diagnosis of AS at HUNT3 were already more likely to have undiagnosed nr-axSpA at the time of HUNT2, and that smoking promotes the progression of nr-axSpA to AS. This would be consistent with the known strong association of smoking with more rapid progression of osteoproliferative disease in AS. The attributable risk fraction of smoking was only 7%, consistent with AS being more strongly related to genetic risk factors. Only 2 individuals with incident AS started smoking between HUNT2 and HUNT3, so it is highly unlikely that the association was due to new-onset smoking.

The previously mentioned data regarding smoking effects on RA and PsA indicate that several mechanisms may be involved, influenced by the individual's genetic profile and characteristics of each form of arthritis. In RA positive for anticitrullinated protein antibodies, there is a strong interaction between *HLA-DRB1* and smoking<sup>24</sup>. However, smoking more than 10 pack-years increases the risk of RA in African Americans both in autoantibody-positive and -negative disease<sup>25</sup>, which may be related to different genotypes of *NAT2*, coding for the enzyme N-acetyltransferase 2, which is involved in the metabolism of carcinogens<sup>26</sup>. According to a metaanalysis, both present and former smoking increases the risk of RA roughly to the same extent<sup>27</sup>, but the mechanism related to protein citrullination and *HLA-DRB1* interaction is clearly more important in antibody-positive disease<sup>8</sup>. In our study, current smoking but not previous smoking or pack-year history was a significant risk factor for incident AS, including when removing the oldest controls from analysis to avoid any confounding due to their higher mean age. Tobacco smoke contains a large number of chemically active compounds, and further research is needed to clarify the exact mechanisms involved in incident AS.

Several large studies have shown that patients with established AS have an increased prevalence of HTN, with reported OR of 1.65 and 1.87 or a prevalence ratio of 1.3<sup>28,29,30</sup>. In a recent Swedish study, the standardized morbidity rate for HTN was 1.98<sup>31</sup>. In our study, the OR for HTN in incident AS was of a comparable size. It has been hypothesized that HTN in AS may be related to use of NSAID<sup>28</sup>. NSAID are also commonly used to treat musculoskeletal complaints with an unclear diagnosis, including incident AS. Alternatively, patients with musculoskeletal complaints may have more contact with the healthcare system and thereby a higher possibility of receiving a diagnosis of HTN.

Regardless of the mechanism, the combined association of smoking and HTN with incident AS probably places

these individuals at increased risk of future CV disease. Indeed, several studies indicate that patients with AS are more likely to have ischemic heart disease<sup>29,30,31,32</sup>, whereas others have given contradictory findings<sup>28</sup>. These differences may be explained by population characteristics, profiles of other CV risk factors, and treatment effects. No increase in CV disease was noted in the current study prior to the onset of AS.

Both in a large population-based study in the United Kingdom and in the Nurses' Health Study in the United States, increasing BMI was associated with increased risk of incident PsA<sup>33,34</sup>. In contrast, BMI was not a significant risk factor for AS in the current study. The probable difference in effect of BMI on risk for AS and PsA is supported by a Greek study comparing patients with AS, PsA, and matched control subjects. The patients with AS were more often smokers and had lower mean BMI than their controls, whereas the patients with PsA had higher waist-to-hip ratios as an indication of more abdominal obesity<sup>35</sup>.

In the HUNT population-based study, incident AS was associated with young age, current smoking, and presence of HTN. Increased BMI was not a risk factor for incident AS, in contrast to previous findings in PsA.

## ACKNOWLEDGMENT

The HUNT study is a collaboration between the HUNT Research Centre (Faculty of Medicine, Norwegian University of Science and Technology NTNU), Nord-Trøndelag County Council, Central Norway Health Authority, and the Norwegian Institute of Public Health. We are grateful to Levanger, Namsos, and Trondheim University hospitals for giving access to their diagnostic registries, and to the Norwegian Institute of Public Health for providing data from the Norwegian Prescription Database. Johanna Hadler, Katie Cremin, Karena Pryce, and Jessica Harris are acknowledged for excellent technical assistance.

## REFERENCES

1. Ward MM. Predictors of the progression of functional disability in patients with ankylosing spondylitis. *J Rheumatol* 2002;29:1420-5.
2. Matthey DL, Dawson SR, Healey EL, Packham JC. Relationship between smoking and patient-reported measures of disease outcome in ankylosing spondylitis. *J Rheumatol* 2011;38:2608-15.
3. Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. Smokers in early axial spondyloarthritis have earlier disease onset, more disease activity, inflammation and damage, and poorer function of health-related quality of life: results from the DESIR cohort. *Ann Rheum Dis* 2012;71:809-16.
4. Poddubnyy D, Haibel H, Listing J, Märker-Hermann E, Zeidler H, Braun J, et al. Cigarette smoking has a dose-dependent impact on progression of structural damage in the spine in patients with axial spondyloarthritis: results from the GERman SPondyloarthritis Inception Cohort (GESPIC). *Ann Rheum Dis* 2013;72:1430-2.
5. Wendling D, Prati C. Spondyloarthritis and smoking: towards a new insight into the disease. *Expert Rev Clin Immunol* 2013; 9:511-16.
6. Divecha H, Sattar N, Rumley A, Cherry A, Lowe GD, Sturrock R. Cardiovascular risk parameters in men with ankylosing spondylitis in comparison with non-inflammatory control subjects: relevance of systemic inflammation. *Clin Sci* 2005;109:171-6.
7. Matthey DL, Packham JC, Nixon NB, Coates L, Creamer P, Hailwood S, et al. Association of cytokine and matrix metalloproteinase profiles with disease activity and function in ankylosing spondylitis. *Arthritis Res Ther* 2012;14:R127.
8. Arend WP, Firestein GS. Pre-rheumatoid arthritis: predisposition and translation to clinical synovitis. *Nature Rev Rheumatol* 2012;8:573-86.
9. Li W, Han J, Qureshi AA. Smoking and risk of incident psoriatic arthritis in US women. *Ann Rheum Dis* 2012;71:804-8.
10. Eder L, Shanmugarajah S, Thavaneswaran A, Chandran V, Rosen CF, Cook RJ, et al. The association between smoking and the development of psoriatic arthritis among psoriasis patients. *Ann Rheum Dis* 2012;71:219-24.
11. Pattison E, Harrison BJ, Griffiths CE, Silman AJ, Bruce IN. Environmental risk factors for the development of psoriatic arthritis: results from a case-control study. *Ann Rheum Dis* 2008;67:672-6.
12. Parkes M, Cortes A, van Heel DA, Brown MA. Genetic insight into common pathways and complex relationships among immune-mediated diseases. *Nature Rev Genet* 2013;14:661-73.
13. Holmen J, Midthjell K, Krüger Ø, Langhammer A, Holmen TL, Bratberg GH, et al. The Nord-Trøndelag Health Study 1995-97 (HUNT2): Objectives, contents, methods and participation. *Norsk Epidemiologi* 2003;13:19-32. [Internet. Accessed July 16, 2014.] Available from: <https://www.ntnu.no/ojs/index.php/norepid/article/viewFile/305/283>
14. International Genetics of Ankylosing Spondylitis Consortium (IGAS), Cortes A, Hadler J, Pointon JP, Robinson PC, Karaderi T, et al. Identification of multiple risk variants for ankylosing spondylitis through high-density genotyping of immune-related loci. *Nat Genet* 2013;45:730-8.
15. Bakland G, Nossent HC. Epidemiology of spondyloarthritis: a review. *Curr Rheumatol Rep* 2013;15:351.
16. Braun J, Bollow M, Remlinger G, Eggens U, Rudwaleit M, Distler A, et al. Prevalence of spondyloarthropathies in HLA-B27 positive and negative blood donors. *Arthritis Rheum* 1998;41:58-67.
17. Rudwaleit M, Khan MA, Sieper J. The challenge of diagnosis and classification in early ankylosing spondylitis. *Arthritis Rheum* 2005;52:1000-8.
18. Chung HY, Machado P, van der Heijde D, D'Agostino MA, Dougados M. HLA-B27 positive patients differ from HLA-B27 negative patients in clinical presentation and imaging: results from the DESIR cohort of patients with onset axial spondyloarthritis. *Ann Rheum Dis* 2011;70:1930-6.
19. Norwegian University of Science. Attendance HUNT2 (based on questionnaire 1). [Internet. Accessed July 14, 2014.] Available from: [www.ntnu.no/c/document\\_library/get\\_file?uuid=e5fce69f-ba93-4376-bd03-b1581e7936c0&groupId=10304](http://www.ntnu.no/c/document_library/get_file?uuid=e5fce69f-ba93-4376-bd03-b1581e7936c0&groupId=10304)
20. Norwegian University of Science. Attendance HUNT3 (based on questionnaire 1). [Internet. Accessed July 14, 2014.] Available from: [www.ntnu.no/c/document\\_library/get\\_file?uuid=c406d439-9412-4c8d-afc8-0bc7771c3fde&groupId=10304](http://www.ntnu.no/c/document_library/get_file?uuid=c406d439-9412-4c8d-afc8-0bc7771c3fde&groupId=10304)
21. Rudwaleit M, van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. *Ann Rheum Dis* 2009;68:777-83.
22. Sieper J, van der Heijde D, Dougados M, Mease PJ, Maksymowych WP, Brown MA, et al. Efficacy and safety of adalimumab in patients with non-radiographic axial spondyloarthritis: results of a randomized placebo-controlled trial (ABILITY-1). *Ann Rheum Dis* 2013;72:815-22.
23. van den Berg R, de Hooge M, van Gaalen F, Reijnen M, Huizinga T, van der Heijde D. Percentage of patients with spondyloarthritis in patients referred because of chronic back pain and performance of classification criteria: experience from the Spondyloarthritis Caught Early (SPACE) cohort. *Rheumatology*

- 2013;52:1492-9.
24. Källberg H, Ding B, Padyukov L, Bengtson C, Rönnelid J, Klareskog L, et al. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. *Ann Rheum Dis* 2011;70:508-11.
  25. Mikuls TR, Sayles H, Yu F, LeVan T, Gould KA, Thiele GM, et al. Associations of cigarette smoke with rheumatoid arthritis in African Americans. *Arthritis Rheum* 2010;62:3560-8.
  26. Mikuls TR, LeVan T, Gould KA, Yu F, Thiele GM, Bynote KK, et al. Impact of interactions of cigarette smoke with NAT2 polymorphisms on rheumatoid arthritis risk in African Americans. *Arthritis Rheum* 2012;64:655-64.
  27. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2010;69:70-81.
  28. Brophy S, Cooksey R, Atkinson M, Zhou SM, Husain MJ, Macey S, et al. No increased rate of acute myocardial infarction or stroke among patients with ankylosing spondylitis – a retrospective cohort study using routine data. *Semin Arthritis Rheum* 2012;42:140-5.
  29. Kang JH, Chen YH, Lin HC. Comorbidity profiles among patients with ankylosing spondylitis: a nationwide population-based study. *Ann Rheum Dis* 2010;69:1165-8.
  30. Han C, Robinson DW Jr, Hackett MV, Paramore LC, Fraeman KH, Bala MV. Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. *J Rheumatol* 2006;33:2167-72.
  31. Bremander A, Petersson IF, Bergman S, Englund M. Population-based estimates of common comorbidities and cardiovascular disease in ankylosing spondylitis. *Arthritis Care Res* 2011;63:550-6.
  32. Huang YP, Wang YH, Pan SL. Increased risk of ischemic heart disease in young patients with newly diagnosed ankylosing spondylitis: a population-based longitudinal follow-up study. *PLoS One* 2013;8:e64155.
  33. Love TJ, Zhu Y, Zhang Y, Wall-Burns L, Ogdie A, Gelfand JM, et al. Obesity and the risk of psoriatic arthritis: a population-based study. *Ann Rheum Dis* 2012;71:1273-7.
  34. Li W, Han J, Qureshi AA. Obesity and risk of incident psoriatic arthritis in US women. *Ann Rheum Dis* 2012;71:1267-72.
  35. Papagoras C, Markatseli TE, Saougou I, Alamanos Y, Zikou AK, Voulgari PV, et al. Cardiovascular risk profile in patients with spondyloarthritis. *Joint Bone Spine* 2014;81:57-63.