EPIDEMIOLOGICAL SCIENCE

HLA-B27, axial spondyloarthritis and survival

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ABSTRACT

Introduction Ankylosing spondylitis (AS), and carriage of *HLA-B27* gene in otherwise healthy individuals, are reportedly associated with increased mortality. We evaluated this hypothesis, using data from both a 35-year AS follow-up study and UK Biobank data.

Methods In 1985, 363 members of the Swiss AS Patient Society and 806 relatives were screened clinically and then radiographically for AS/axial spondyloarthritis (axSpA). Life expectancy was analysed in 377 axSpA patients having available pelvic radiographs and HLA-B27 status, comparing with matched Swiss population data. Survival in relation to HLA-B27 status in the general population was studied in UK Biobank European-ancestry participants (n=407 480, n=30 419 deaths).

Results AS patients have increased standardised mortality rate (SMR) compared with the general population (1.37, 95% CI 1.11 to 1.62). This increase was significant for HLA-B27-positive AS (SMR 1.38, 95% CI 1.11 to 1.65). Shortened life expectancy was observed among both HLA-B27-positive AS women (SMR 1.77, 95% CI 1.09 to 2.70) and men (SMR 1.31, 95% CI 1.02 to 1.59). Patients with non-radiographic axSpA (nr-axSpA) had significantly lower SMR: 0.44 (95% CI 0.23 to 0.77), compared with the general population. In the UK Biobank European-ancestry population cohort, HLA-B27 carriage was not significantly associated with any change in mortality (HR 1, 95% CI 0.97 to 1.1, p=0.349, adjusted by sex), in either males (HR 1, 95% CI 0.98 to 1.1, p=0.281) or females (HR 0.96, 95% CI 0.9 to 1, p=0.232), and no increase in vascular disease mortality was observed.

Discussion AS patients, but not nr-axSpA patients, have a significantly shortened life expectancy. Increased mortality is particularly significant among women with HLA-B27-positive AS. *HLA-B27* carriage in the European-ancestry general population does not influence survival, or the risk of death due to vascular disease.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ankylosing spondylitis (AS) is strongly associated with carriage of HLA-B27. The disease is associated with a shortened life expectancy.
⇒ A previous North American study suggested that HLA-B27 carriage in the general population is associated with shortened life expectancy, perhaps due to an increase in cardiovascular disease.

WHAT THIS STUDY ADDS

⇒ This study shows that HLA-B27-positive AS patients, both males and females, but not non-radiographic axial spondyloarthritis (nr-axSpA) patients, have a significantly shortened life expectancy, compared with sex matched general population. This is particularly significant among women with HLA-B27-positive AS.
⇒ HLA-B27 carriage in the general population is not associated with shortened life expectancy and is also not associated with increased cardiovascular mortality.
⇒ Such individuals can be reassured that the fact that they carry *HLA-B27* gene is irrelevant to their future life expectancy.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ More research is required into the causes of increased mortality in AS patients, the reasons for which are incompletely understood. Sex effects on mortality of AS should be explored further.
⇒ nr-axSpA patients and unaffected subjects carrying *HLA-B27* in the general population can be reassured that they do not have a reduced predicted life expectancy.
⇒ Insurance providers should not consider *HLA-B27* carriage on its own in assessing mortality risk of their clients.

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Ankylosing spondylitis (AS) is among the most common forms of immune-mediated arthritis, affecting ~0.5% of the population worldwide, except for people of African ancestry where its prevalence is much lower.[1] It primarily affects the pelvis and spinal vertebral column, causing pain and stiffness, and can affect extramusculoskeletal sites, including the eye, gut, skin and vascular tree. Nowadays, the notion of its wider clinical spectrum and increased emphasis on early diagnosis at its non-radiographic phase have led to the concept of axial spondyloarthritis (axSpA), comprising both radiographic disease (classified as AS by the modified New York (mNY) criteria)[2] and non-radiographic axSpA (nr-axSpA). In this paper, we use the terms AS and radiographic axSpA (r-axSpA) synonymously. AS is defined by the mNY criteria. Previous studies have suggested that AS is associated with increased mortality,[3–10] although this has not been universally confirmed.[11] Cardiovascular

disease has been reported in several studies to be the leading cause of death in AS, potentially related to use of NSAIDs or corticosteroids.[4 7 12–16] A recent meta-analysis reports that AS patients have a higher risk of death from all causes (relative risk (RR) 1.64, 95% CI 1.49 to 1.80) and cardiovascular causes (RR 1.35, 95% CI 1.01 to 1.81) compared with the general population.[17] Whether nr-axSpA influences mortality is unknown.

It has also been reported that carriage of *HLA-B27*, the major genetic risk factor for AS, is associated with increased mortality.[18] The prevalence of HLA-B27 in European-ancestry population is approximately 6.1%–9.5%.[19 20] Overall, 80%–95% of AS patients of European ancestry are HLA-B27 positive but only between 1% and 5% of HLA-B27-positive individuals develop AS.[20–23] Data from the US National Health and Nutrition Examination Survey 2009 showed the US age-adjusted prevalence of HLA-B27 decreased from 6.1% overall, to 2.9% in the age group 50–59 years, although there was an apparent increase from 60 to 69 years of age (4.6%).[24] This observation was interpreted as suggesting that individuals carrying HLA-B27 but not affected by classical HLA-B27-associated diseases have increased mortality. Studying a cohort of American war veterans clinically selected for HLA-B27 testing, Walsh *et al* reported that HLA-B27-positivity was significantly associated with an increased mortality rate in a subgroup with spondyloarthritis (SpA), but not in those without.[18] In this study, HLA-B27 testing was performed on only 0.2% of the total cohort, and it is therefore potentially affected by biases related to the indication for HLA-B27 testing. Moreover, the study did not present data on cause of death, which makes it difficult to draw a firm conclusion as to how HLA-B27 may affect mortality risk in general population.

The purpose of our study was to compare mortality in AS and nr-axSpA, and to better investigate the relationship between HLA-B27 and mortality, by comparing mortality in HLA-B27-positive and HLA-B27-negative-individuals with data of age at death and disease status, as compared with well-characterised, representative general population cohorts. This study also aimed to test the reported association between HLA-B27 and cardiovascular disease.

METHODS

Swiss Ankylosing Spondylitis Family Study

In 1985, all members of the nation-wide Swiss Ankylosing Spondylitis Patient Society (Schweizerische Vereinigung Morbus Bechterew), and their spouses and first-degree relatives (FDRs), were invited to participate in this family study. FDRs were invited irrespective of whether they were known to have any rheumatic disease.

A total of 1178 persons were recruited to the study, and completed questionnaires about their health status, were examined for axial or peripheral arthritis by a rheumatologist, and a clinical diagnosis was made as to whether the participant had AS according to the mNY criteria. Nowadays, the term axSpA is used that encompasses AS and nr-axSpA. Blood samples were drawn for HLA typing by serological methods, and to obtain peripheral nucleated blood cells which were stored in liquid nitrogen for subsequent studies. To assess the presence of sacroiliitis, consenting non-pregnant participants, aged 18 and over, underwent pelvic radiography unless a recent radiograph was available.

All 1081 pelvic radiographs of 360 probands and 713 FDRs and 8 spouses were twice assessed for sacroiliitis by each of up to 4 experienced readers blind to participants' clinical and HLA-B27 status. Sacroiliac (SI) joints were assessed as per the mNY scoring system.[2] This could be performed only once for 46% of the 360 radiographs of the probands and 3% of 713 radiographs of the FDR because these radiographs were only available on-site at the time of participant's physical examination in the local hospital. Overall, 79.2% of 1081 radiographs were assessed 8–9 times and 17.2% were read once. The sum of scores for each individual SI joint was divided by the number of assessments (range 1–9), and scores below bilateral grade 2.0 or unilateral grade 3.0 were considered not fulfilling the mNY criteria. Interobserver and intraobserver reliability were assessed by reading a subset of 243 pelvic radiographs twice. The interval between both readings was ≥7 days. The interobserver and intraobserver reliability coefficients were 0.865 and 0.903, respectively.[25] Using the radiographic data together with the clinical diagnosis, patients were then classified as to whether they had AS/r-axSpA, as defined by the mNY criteria,[2] or nr-axSpA (where they had a clinical diagnosis of axSpA but negative radiographs of the SI joints by mNY criteria).

Following ethical approval (#2017-00536, Kantonale Ethik Kommission Bern, Switzerland), a follow-up study was performed from January 2018 to December 2019. Contact details and information as to whether participants in the original study were alive or not was sought by extensive searches of Swiss city or village administrative records. Year of death was obtained for deceased participants, but information as to cause of death was not available. Surviving participants were contacted by mail and invited to participate in the follow-up study for which they were then asked to provide a written informed consent. Consenting participants received a postal questionnaire about their health status. The last questionnaires were returned by December 2019. The questionnaire data were then coded and anonymously stored in an Excel database for further analysis.

Mortality among HLA-B27 carriers not affected with axSpA

The influence of HLA-B27 on mortality was studied in the UK Biobank. There are 488 378 participants in the UK Biobank who have imputed *HLA-B27* genotypes, and 35 033 participants with records of date of death from UK Biobank data portal. Participants with posterior probability of imputed *HLA-B27* alleles greater than 0.7 were considered as HLA-B27-positive while the samples with posterior probability equals 0 were considered as HLA-B27-negative. Analyses were performed including and excluding deaths due to COVID, to enable findings to be comparable with those reported in the pre-COVID-19 era. Genetic ethnicity record, sex information, the primary causes of death in International Classification of Diseases-10 (ICD-10) codes and primary/main and secondary diagnosis in ICD-10 codes were obtained. Together there are 33 655 participants in the biobank which have both high confidence imputed *HLA-B27* status and records of age at death (excluding 1181 COVID-19 deaths). Genetic ethnicity record, sex information, the primary causes of death in ICD-10 codes and primary/main and secondary diagnosis in ICD-10 codes were obtained. Together, there are 407 480 European-ancestry participants, of whom 30 419 have a recorded date of death (after excluding COVID-19 deaths). The birth year and month of each participant were retrieved, and the birthdate set to 15th of the corresponding birth month. The age at death was calculated by the date of death and the defined birthdate above.

In order to determine if *HLA-B27* is associated with cardiovascular disease, we collected the ICD-10 codes for cardiovascular disease, as well as its component diseases: ischaemic heart disease, aortic aneurysm, cerebrovascular disease and peripheral

vascular disease (online supplemental table 1).[26] A total of 6567 participants who died of cardiovascular disease were identified, as well as 45 781 participants with cardiovascular disease, and 361 699 participants without cardiovascular disease (by primary and secondary diagnosis from hospital inpatient records).

Statistics

To compare the survival of axSpA patients with that of the general population, standardised mortality ratio (SMR), as described by Colton,[27] was calculated. Actuarial tables in the National Vital Statistics Report[28] provide rates of death and life expectancy in the Swiss population according to age, birth year and sex. Starting at the participant's age in 1985, the cumulative conditional probability of dying over the years of follow-up for that person was calculated based on the life table for the Swiss general population. The sum of all individually probabilities of death provides the number of expected deaths for the SMR calculation at the group level. SMR is computed from the ratio of the observed deaths in the study group to the number of expected deaths in the demographically matched population.

In the Swiss Ankylosing Spondylitis Family Study, we performed univariable and multivariable Cox regression analysis to assess the effect of age (in years), sex (male vs female), genetic status (HLA-B27 positive vs negative) and radiologic status (AS vs nr-axSpA) on mortality. Patients with an unknown death status in 2019 were considered alive at their last follow-up (the year they moved to another address unknown to us), for example, in 1986, which means they were considered censored from that point on.

To account for possible effect modification of sex, genetic and radiologic status, a three-way interaction between these three variables and all lower-order terms were included as independent variables, next to age. A top-down procedure was used to see whether the interaction terms added significantly to the model. Linearity assumption for age was checked by adding and testing age×ln(age), multicollinearity by variance inflation factors (>10 indicates a collinearity problem), proportional hazard assumption by adding and testing time-dependent covariates (X*×time) and the independence of event and censored times by applying sensitivity analyses (pessimistic and optimistic scenario, where censored times are either considered as event times or set equal to the maximum follow-up time, respectively). For the final model, HR and 95% CIs are reported.

Survival probability in the UK Biobank data was assessed by Kaplan-Meier estimator and log-rank test, stratified by sex. Risk of death and the respective HR were assessed using Cox proportional hazard analyses, stratified by sex. The last observation date was set as the latest date of death from death register (6 December 2021). The association of *HLA-B27* and occurrence of cardiovascular disease was calculated using a χ^2 test. Two-sided t-test was used to test association between age of death and *HLA-B27* status. Two-sided p values ≤0.05 were considered statistically significant. IBM SPSS Statistics for Windows (V.28.0) was used for the univariable and multivariable Cox regression analysis.

RESULTS

Baseline (1985) demographic and clinical data of the 377 axSpA patients (363 probands and 14 FDRs with AS diagnosed at baseline) are shown in table 1 and the flow chart (figure 1). Online supplemental table 2 provides clinical data for axSpA patients who participated in the follow-up study. The survival status at follow-up after up to 35 years for these patients is shown in table 2. Overall, the male/female ratio was 2.1 (256/121), and the prevalence of HLA-B27 was 86.6%. AS occurred significantly more often among male (211/256 or 82.4%) than female family members with axSpA (76/121 or 62.8%) (p<0.001, OR 2.78, 95% CI 1.70 to 4.53). Of note, in the overall group of 123 deceased axSpA patients (ie, 111 AS and 12 nr-axSpA deceased patients), among women the proportion with AS (92.3%, 24/26) was much higher than the baseline proportion of females with AS (62.8%, 76/121) (p=0.003), suggesting increased mortality among women with AS compared with women with nr-axSpA. In contrast, comparing the ratio AS to nr-axSpA, the proportion of deceased male AS patients was non-significantly increased (89.7%, 87/97) compared with baseline (82.4%, 211/256) (p=0.09). Altogether 148 patients were alive as of 31 December 2019. For 5 of the 123 who had died the year of death was not available (censoring at 1986). For the remaining 106 patients who were lost to follow-up, the year they moved to another city or village was taken as year of last follow-up (right censoring). The mean duration of follow-up for this group was 21.5 years. There were no statistically significant differences in sex distribution or axSpA status (AS or nr-axSpA) among those that remained available for study compared with those lost to follow-up (table 2). The prevalence of HLA-B27 is lower among

Table 1 Baseline (1985) demographic and clinical data, HLA-B27 and radiographic status of patients with axSpA

	No	Age, year (SD)	AS total (male/female)	nr-axSpA total (male/female)
All patients	377* †	43.79 (11.15)	283 (208/75) mean age 44.10±11.44 year	86 (42/44) mean age 42.80±10.13 year
Chronic back pain‡			72.3%	70.8%
HLA-B27(+)	322†	43.53 (11.11)	261 (192/69)	58 (32/26)
HLA-B27(–)	50	46.14 (11.53)	22 (16/6)	28 (10/18)
All probands	363* †	44.19 (11.12)	269 (201/68)	86 (42/44)
HLA-B27(+)	308†	43.99 (11.10)	247 (185/62)	58 (32/26)
HLA-B27(–)	50	46.14 (11.53)	22 (16/6)	28 (10/18)
FDR having AS	14	33.50 (5.29)	14 (7/7)	–
HLA-B27(+)	14	33.50 (5.29)	14 (7/7)	–
HLA-B27(–)	–			

Patients were classified as AS by modified New York criteria or nr-axSpA.
*HLA-B27 status unknown for five patients.
†Pelvic radiograph missing for three patients.
‡Chronic inflammatory back pain by Calin criteria (positive if ≥4 of 5 criteria are met).
AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; FDR, first-degree relative; nr-axSpA, non-radiographic axSpA.

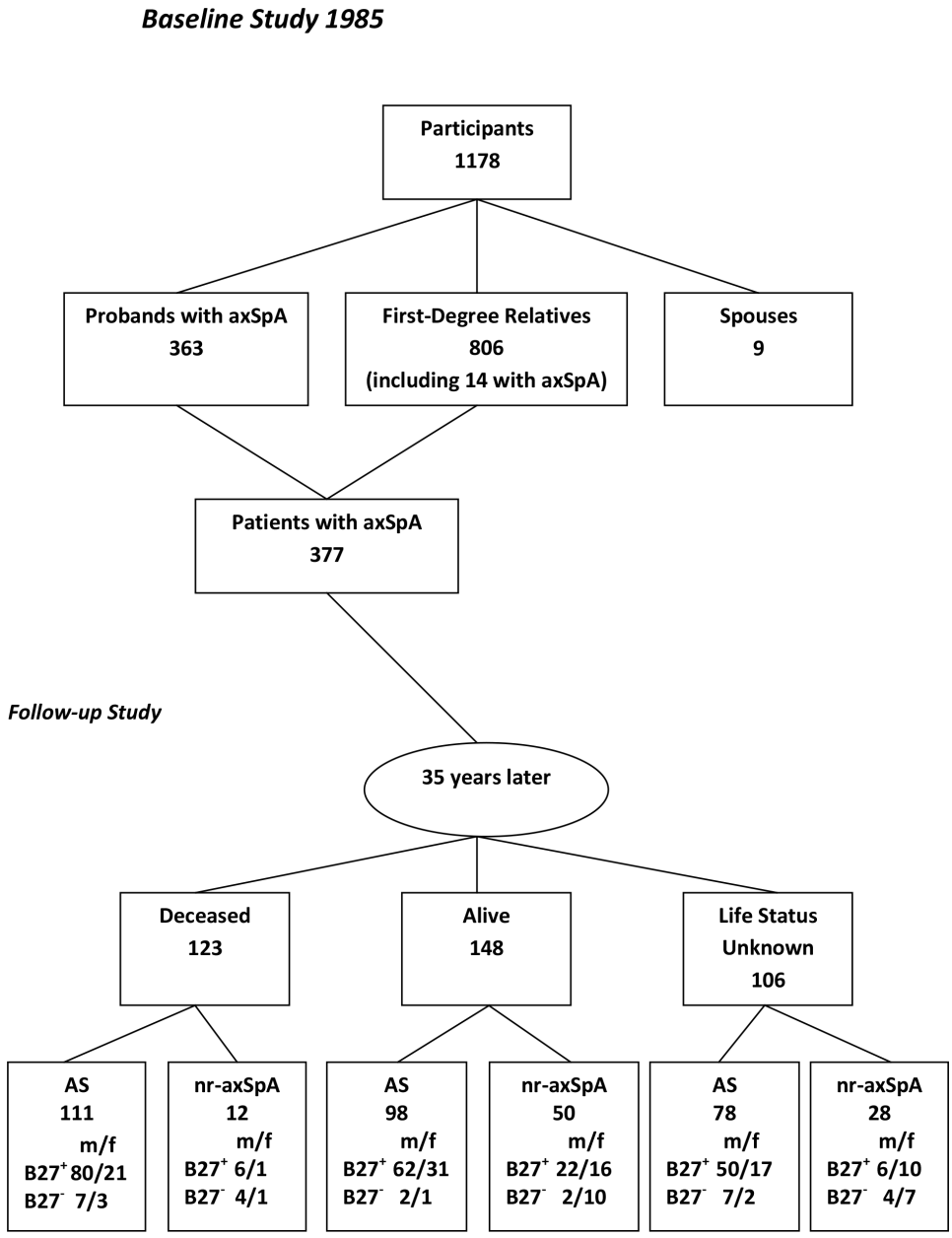

Figure 1 Flow chart of Swiss Ankylosing Spondylitis Family Study. AS, ankylosing spondylitis; axSpA, axial spondyloarthritis; nr-axSpA, non-radiographic axSpA.

those lost to follow-up compared with those available 80.6% (83/103) vs 88.8% (239/269) (OR 0.52, p=0.037).

All 377 axSpA patients were available for the analysis of mortality of axSpA compared with the general Swiss population, taking age, sex, HLA-B27 status and disease severity as assessed by radiographic damage to the SI joints (by mNY criteria) into account (table 3). Clearly, the numbers of participants in HLA-B27 negative subgroups are relatively small. Please note that the 95% CIs for all SMR values subgroups of axSpA include the value one (1.00) and are therefore not statistically significant. The picture looks quite different if one splits axSpA into AS and nr-axSpA. All (except HLA-B27 negative subgroups) AS patients have significantly increased SMR. This applies in particular to women. In contrast, patients with nr-axSpA have decreased SMR or SMR that is not significantly different from 1.

Female AS patients (n=24) died on average at age 66.6 (expected 82.2), whereas male AS patients (n=83) died on average at age 73.0 (expected 77.7). Therefore, women lost a mean of 15.6 years (95% CI 10.5 to 20.6), and men 4.7 years of expected life (95% CI 2.4 to 7.1, p<0.001). In contrast, among the nr-axSpA patients who had died (n=10, 8 men, 2 women), life expectancy was close to the general Swiss population (mean gain of 1.1 years) (figure 2).

To further explore relationships between mortality, age, sex, HLA-B27 and radiographic status, we performed Cox regression. Univariable Cox regression analysis showed that age (p<0.001), sex (p=0.002) and radiologic status (p<0.001) were significantly related to mortality, whereas genetic status (HLA-B27 positive vs negative) was not (p=0.501). Multivariable analysis showed similar results, but also indicated that there was an interaction between sex and radiologic status. Specifically, patients with AS had a significantly higher mortality rate (expressed as hazard rate) than those with nr-axSpA, especially for women (HR 2.01, 95% CI 1.04 to 3.88, p=0.038 for men; HR 9.76, 95% CI 2.25 to 42.35, p=0.002 for women). Figure 3 shows the Kaplan-Meier curves of the AS and nr-axSpA groups for men (top) and

Table 2 Survival status at follow-up (2019) of the 377 axial spondyloarthritis (axSpA) patients who had participated in the 1985 baseline study

	Total	Age, year (SD)	AS total (male/femae) (mean years observed male/female)	nr-axSpA total (male/female) (mean years observed male/female)
Deceased patients	123*	72.35† (12.40)	111 (87/24) (20.8/23.5)	12 (10/2) (19.9/26.0)
HLA-B27(+)	108 (87.8%)	71.87† (12.50)	101 (80/21) (19.7/23.9)	7 (6/1) (22.2/23.0)
HLA-B27(–)	15 (12.2%)	76.23† (11.29)	10 (7/3) (26.4/20.5)	5 (4/1) (17.0/29.0)
Alive patients	148‡	73.09 (7.51)	98 (65/33)	50 (24/26)
HLA-B27(+)	131 (89.7%)	72.76 (7.40)	93 (62/31)	38 (22/16)
HLA-B27(–)	15 (10.3%)	76.33 (8.36)	3 (2/1)	12 (2/10)
Life status not known	106§	Unknown	78 (59/19) (20.0/19.5)	28 (11/17) (18.8/22.9)
HLA-B27(+)	83 (80.6%)		67 (50/17) (20.0/18.0)	16 (6/10) (19.3/15.9)
HLA-B27(–)	20 (19.4%)		9 (7/2) (19.8/30.3)	11 (4/7) (18.0/33.0)

*Year of death is unknown for five patients.
†Mean age at death.
‡HLA-B27 status unknown for two patients.
§HLA-B27 status unknown for three patients.
AS, ankylosing spondylitis; nr-axSpA, non-radiographic axSpA.

women (bottom), respectively. Note, the mean age (SD) for AS patients is 44.1 (11.4) year and for nr-axSpA patients 42.8 (10.1) year, a mean difference of 1.3 years (p=0.335). There is also no statistically significant difference between mean ages of AS and nr-axSpA patients when split up by sex: females—mean age (SD) 40.9 (10.0) vs 42.6 (8.3), p=0.363; males—mean age (SD) 45.2 (11.7) vs 43.0 (11.8), p=0.255.

To assess whether difference in disease severity underpin the increased mortality in female compared with male AS patients, we studied differences in severity of SI joint radiographic change between sexes. Deceased male patients with AS had significantly more radiographic damage at the SI joints on average than their female counterparts. Bilateral grade 3 or 4 sacroiliitis occurred in 73/86 (84.9%) male AS patients compared with 14/23 (60.9%) female AS patients (p=0.011). For bilateral grade 4 (ie, fully ankylosed SI joints) the figures are 50/86 (58.1%) and 7/23 (30.4%) for men and women with AS, respectively (p=0.018). This implies that deceased male AS patients, but not their female counterparts (who lose on average more life years), had more severely affected SI joints.

UK Biobank study

The HLA-B27 antigen prevalence in the overall UK Biobank (486 954 participants) and (genetically defined) European-ancestry participants (485 711) is 7.70% and 8.08%, respectively (table 4). Among European-ancestry participants, 2444 *HLA-B27*-positive participants and 27 975 *HLA-B27*-negative participants had died. The mean age was 70.34 years for *HLA-B27*-positive participants and 70.18 for *HLA-B27*-negative

Table 3 Standardised mortality rate (SMR) for patients with overall axial spondyloarthritis (axSpA), AS and non-radiographic axSpA (nr-axSpA) by HLA-B27 carriage status and sex

	axSpA mean age 43.79±11.15 years				AS mean age 44.10±11.44 years				nr-axSpA mean age 42.80±10.13 years			
	Total	# Deaths observed	# Deaths expected	SMR (95% CI)	Total	# Deaths observed	# Deaths expected	SMR (95% CI)	Total	# Deaths observed	# Deaths expected	SMR (95% CI)
All patients	377	123	108.3	1.14 (0.93 to 1.34)	287	111	81.1	*1.37* (1.11 to 1.62)	90	12	27.2	*0.44* (0.23 to 0.77)
By HLA-B27 status*												
HLA-B27+	322 86.6%	108	91.0	1.19 (0.96 to 1.41)	261 92.2%	101	73.1	*1.38* (1.11 to 1.65)	61 68.5%	7	17.8	*0.39* (0.16 to 0.81)
HLA-B27–	50	15	16.4	0.91 (0.51 to 1.50)	22	10	7.0	1.42 (0.68 to 2.62)	28	5	9.4	0.53 (0.17 to 1.24)
By sex												
Males	256 67.9%	97	83.0	1.17 (0.94 to 1.40)	211 73.5%	87	67.3	*1.29* (1.02 to 1.57)	45 50.0%	10	15.8	0.63 (0.30 to 1.17)
Females	121	26	25.3	1.03 (0.67 to 1.50)	76	24	13.8	*1.73* (1.11 to 2.58)	45	2	11.5	*0.17* (0.02 to 0.63)
By sex and HLA-B27												
Male and HLA-B27+	226 89.7%	86	74.2	1.16 (0.91 to 1.40)	192 92.3%	80	61.3	*1.31* (1.02 to 1.59)	34 77.3%	6	13.0	0.46 (0.17 to 1.01)
Male and HLA-B27–	26	11	8.0	1.37 (0.68 to 2.45)	16	7	5.2	1.34 (0.54 to 2.75)	10	4	2.8	1.43 (0.39 to 3.67)
Female and HLA-B27+	96 80.0%	22	16.8	1.31 (0.82 to 1.99)	69 92.0%	21	11.9	*1.77* (1.09 to 2.70)	27 60.0%	1	4.9	0.21 (0.01 to 1.14)
Female and HLA-B27–	24	4	8.4	0.48 (0.13 to 1.22)	6	3	1.8	1.68 (0.35 to 4.91)	18	1	6.6	*0.15* (0.00 to 0.85)

At a glance: SMR (italics) means value one (1.00) not included in 95% CI; SMR means value one (1.00) included in 95% CI (NS).
*HLA-B27 status unknown for five patients (four patients with AS and one patient with nr-axSpA).
AS, ankylosing spondylitis; NS, not significant.

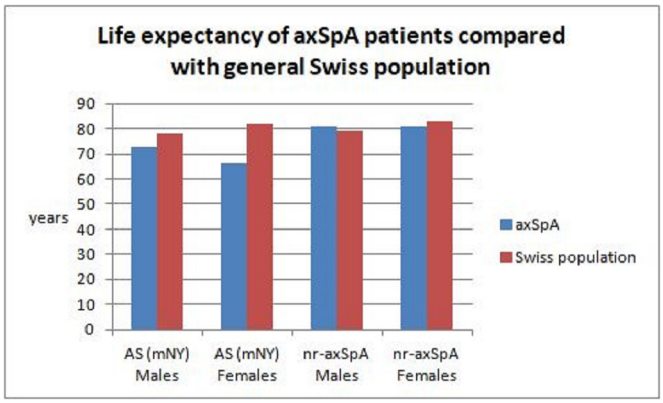

Figure 2 Life expectancy. Compared with the matched Swiss general population and patients with non-radiographic axial spondyloarthritis (nr-axSpA), patients with AS by modified New York criteria (mNY) have clearly reduced lifespan. This applies in particular to women with AS who lost on average 15.6 years of life in contrast to men with AS who lost a mean of 4.7 years. Population controls were matched for sex, birth year and being alive at the time of the baseline study in 1985. AS, ankylosing spondylitis.

participants in the study cohort. Comparing *HLA-B27*-positive and *HLA-B27*-negative European-ancestry participants, there is no significant difference between age at recruitment into the UK Biobank study nor age at last follow-up in (p=0.28 and 0.33, respectively).

Considering the 45 781 UK Biobank European-ancestry participants with cardiovascular disease, 3661 (8.00%) are *HLA-B27*-positive and 42 120 *HLA-B27*-negative (online supplemental table 3). Compared with the remaining 361 699 participants without cardiovascular disease, there was no significant difference in *HLA-B27* carriage (29 264 (8.09%) *HLA-B27*-positive participants and 332 435 *HLA-B27*-negative participants, p=0.493, online supplemental table 3. Stratifying the analysis by sex, again no significant association of *HLA-B27* carriage with cardiovascular disease was observed (males p=0.087, females p=0.587). No association was observed between *HLA-B27* carriage and major subdivisions of cardiovascular disease (either diagnosis of or death due to ischaemic heart disease, aortic aneurysm, cerebrovascular disease or peripheral vascular disease, p>0.05, online supplemental table 4).

Cox proportional hazard analysis demonstrated that there is no significant difference in survival probability between *HLA-B27*-positive and *HLA-B27*-negative carriers (HR 1.0 (95% CI 0.96 to 1.0), p=0.959, figure 4), either after adjusting for sex in the overall cohort, or in males or females separately (figure 4). Considering death primarily caused by cardiovascular disease, the HR of *HLA-B27*-positive compared with *HLA-B27*-negative participants was 0.96 (95% CI 0.88 to 1.00, p=0.313) with adjustment of sex (online supplemental tables 3 and 4), and no significant association was seen in males or females considered separately (online supplemental figure 1). Similar findings were found where cardiovascular disease was either the primary or contributory cause of death (online supplemental figure 2).

To study *HLA-B27* prevalence in different age groups of deceased participants, we divided the participants into four age groups (40–49, 50–59, 60–69, 70–80) by their age at recruitment. The *HLA-B27* prevalence was similar across age groups in European-ancestry participants (online supplemental tables 5 and 6). No difference in *HLA-B27* carriage was observed between those who died from COVID-19 or from other causes (p=1), nor was there any significant difference in age at death comparing *HLA-B27*-positive and *HLA-B27*-negative participants who succumbed to COVID-19 (p=0.571) (online supplemental table 7). *HLA-B27* carriage demonstrated no association with mortality whether COVID-19 deaths were included or excluded (table 4, figure 4, online supplemental figures 1–5 and online supplemental tables 3–6).

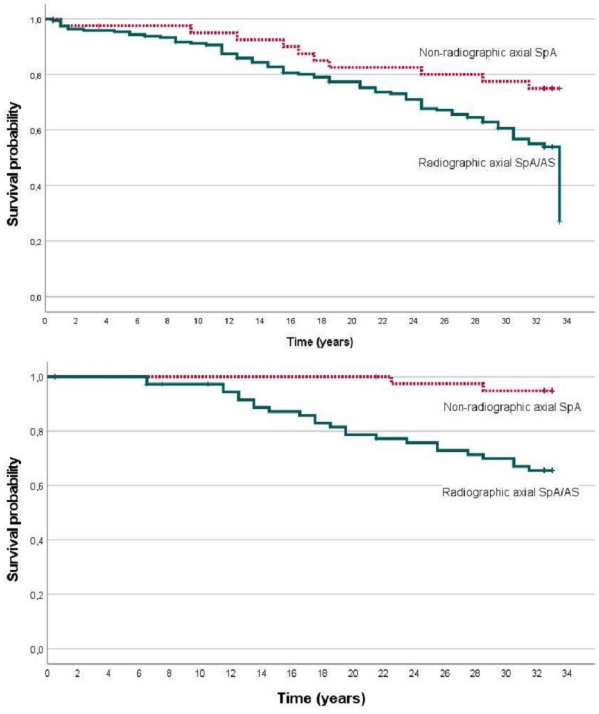

Figure 3 Kaplan-Meier survival probability plot comparing ankylosing spondylitis (AS) with non-radiographic axial SpA for men (*top*) and women (*bottom*). SpA, spondyloarthritis.

DISCUSSION

This study shows that AS, but not nr-axSpA, is associated with increased mortality of both affected men and women, the increase being particularly notable among women. Regarding AS, this finding is in line with a recent study from Israel[9] and a meta-analysis that also shows somewhat higher mortality among female (RR 1.85, 95% CI 1.56 to 2.18) compared with male AS patients (RR 1.56, 95% CI 1.43 to 1.71).[17] Women with AS in our study lost on average 15.6 years, significantly more than men who lost on average 4.7 years of life. No significant difference was observed in mortality between HLA-B27-positive and HLA-B27-negative cases, either in the AS cases or the nr-axSpA group. This is consistent with the disease itself causing the increased mortality, rather than it being an association of HLA-B27. No increase in mortality was observed in those with nr-axSpA (they gained on average 1.1 years). These findings suggest that severity of axSpA, as reflected by presence of radiographic damage, is associated with increased mortality. Radiographic damage might be the outcome of prolonged inflammation.

The significantly shorter lifespan of females with AS was somewhat unexpected, and to our knowledge, it has not been previously reported. It should, however, be interpreted cautiously, and not extrapolated to all AS patients. At follow-up, 148 patients were still alive (table 2), but it is unlikely that their lifespan will compensate for the life-years lost by those who already died. Clearly more studies are needed to provide more definite answers. One might suspect that females with severe

Table 4 Demographic details of the UK Biobank cohort according to *HLA-B27* status

		HLA-B27-positive	HLA-B27-negative	Total/overall	HLA-B27 carriage
Subjects with HLA-B27 genotype					
Passed HLA-B27 filter	Overall	37 470	449 370	486 840	7.70%
	European	33 006	375 486	408 492	8.08%
Passed COVID-19 filter	Overall	37 375	448 214	485 711	7.70%
	European	32 925	374 555	407 480	8.08%
Subjects with date of death, sex and HLA-B27 data, excluding (including) COVID-19 deaths					
	Overall	2729 (2824)	32 452 (33 608)	35 181 (36 432)	7.75% (7.75%)
	European	2444 (2525)	27 975 (28 906)	30 419 (31 431)	8.03% (8.03%)
Male	Overall	1639 (1699)	19 183 (19 926)	20 822 (21 625)	7.87% (7.86%)
	European	1485 (1539)	16 601 (17 198)	18 086 (18 737)	8.21% (8.21%)
Female	Overall	1090 (1125)	13 269 (13 682)	14 359 (14 807)	7.60% (7.60%)
	European	959 (986)	11 374 (11 708)	12 333 (12 694)	7.78% (77.7%)
Age	Overall	70.26 (70.42)	69.97 (70.13)	69.99 (70.15)	
	European	70.34 (70.49)	70.18 (70.34)	70.19 (70.35)	
European subjects deceased due to cardiovascular disease (primary cause of death)					
	European	361	4001	4362	8.28%
Male	European	274	2948	3222	8.50%
Female	European	87	1053	1140	7.63%
European subjects deceased due to cardiovascular disease (primary and contributory cause of death)					
	European	546	6021	6567	8.31%
Male	European	410	4389	4799	8.54%
Female	European	136	1632	1768	7.69%

AS are more likely to be diagnosed or to become member of a patient society. As more severe disease is supposedly associated with earlier death, this bias could theoretically explain our finding with regard to mortality differences between sexes. However, we think this is an unlikely explanation, as AS-affected males in this study had more severe radiographic damage of the SI joints than AS-affected females. This finding is in accordance with earlier reports of less severe disease as judged radiographically in females with AS than in males.[29 30] Notwithstanding these cautions one might speculate why women with AS, while having less damage to SI joints, experience higher mortality rate. Children of women with AS have more often the disease than children of men with AS (reviewed in references 31 32). It is hypothesised that these women are 'enriched' with disease-associated genes, and it is possible that some of such genes are associated with mortality.[32]

Our findings on increased mortality in AS are in accordance with recent findings from a meta-analysis[17] and the study from Israel,[9] although the latter study, while confirming increased HR for men and women with the disease, reports a non-significant difference in life expectancy for patients and controls (76.9 years vs 77.1 years). Note, however, that the study from Israel provides no data on the radiographic status (AS or nr-axSpA) of the deceased patients. Inclusion of nr-axSpA patients might—at least according to our findings—reduce the total number of life-years lost.

We also demonstrate that, in a general population cohort of European-ancestry, *HLA-B27* carriage has no association with mortality, occurrence of cardiovascular disease, or death by cardiovascular disease, or of any major form of cardiovascular disease, regardless of sex. This is consistent with the findings of Walsh *et al* in regard to those subjects who were not affected by spondyloarthritis.[18] In contrast to the study by Reveille *et al*, no reduction in *HLA-B27* prevalence was seen with increasing age.[24] Our findings suggest that the previously reported reduction in HLA-B27 prevalence among older

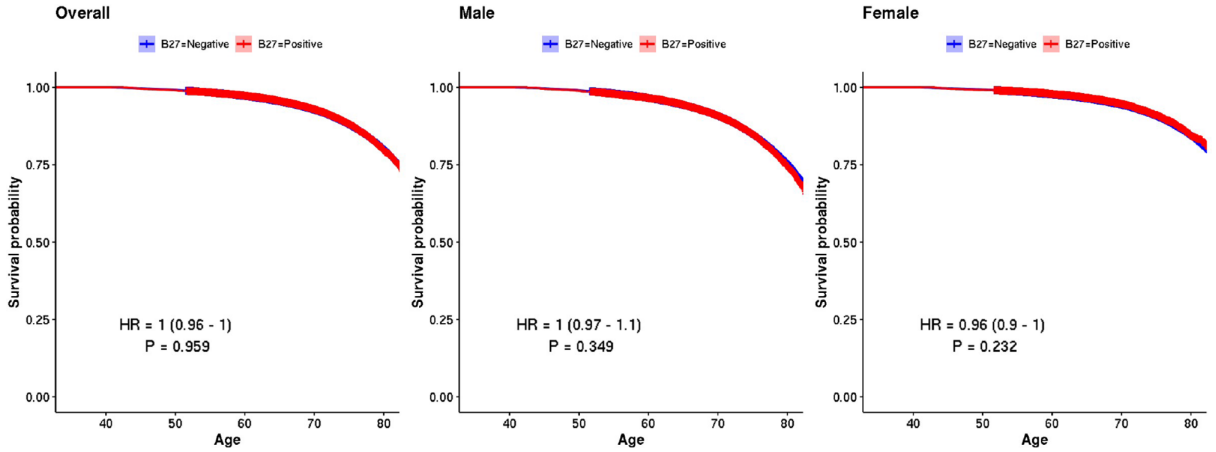

Figure 4 Survival plots for HLA-B27-positive and HLA-B27-negative subjects in European participants in the UK Biobank study (excluding COVID-19 deaths), overall and divided by sex. HLA-B27-positive and HLA-B27-negative carriers are coloured by red and blue, respectively.

Americans is a false positive finding. This may relate to the smaller sample size of the American study, with only 11 HLA-B27 positive subjects among the 50–59 years age group.[24] Furthermore, that study did not have the data to directly test the hypothesis that HLA-B27 is associated with increased mortality. Given the ancestral heterogeneity of the US population and the known wide variation in HLA-B27 prevalence between people of different European ancestries, it is feasible that the findings were due to population stratification rather than any effect on mortality. Indeed, in the UK Biobank, the prevalence of *HLA-B27* varies considerably between those of European and other ancestries (8.08% European, 5.70% other ancestries, $p<10^{-99}$). Since 96.1% of the participants in the UK Biobank are of self-reported European-ancestry, large scale studies of other ancestries will be required to make firm conclusions regarding the potential influence of HLA-B27 in mortality risk in other ancestral groups.

The absence of any effect of HLA-B27 on mortality overall in the population is of particular significance regarding the use of HLA-B27 testing in the life insurance industry to weight premiums. This result indicates that there is no evidence base to support different premiums, or access to life insurance, being based on HLA-B27 testing findings. While some countries do have legislative protection against discrimination in regard insurance biases based on genomics findings, not all countries do, and in countries without genomic non-discrimination legislation, based on our findings, such discrimination would not be justifiable.

Our study, covering 35 years, has inevitably some limitations. At follow-up, the life status of 106/377 (28%) of the patients was not known. Nonetheless they could be followed for a mean of 21.5 years and contributed during that time to the survival analysis. In 45% the current address could not be retrieved, whereas for the remaining 55% of the 106 patients with life status 'unknown', this was due to an incorrect postal address or non-response of the addressee. The groups life status 'known' or 'unknown' did not differ significantly regarding sex, or AS or nr-axSpA status. HLA-B27 prevalence was 8.2% lower in the life status unknown group. Therefore, we think bias to be unlikely. However, if the 'unknowns' had better (or worse) survival prognosis, then our survival estimates would, respectively, be too pessimistic or optimistic. Further, our study was performed prior to the development of MRI scanning. Our approach matches the 'gold-standard' approach used by the Assessment of SpondyloArthritis international Society (ASAS) in the development of the ASAS axSpA classification criteria.[33] Nonetheless, it is possible that participants may have been classified differently if MRI has been available and applied. This would not have affected our findings with regard to AS, but theoretically could have led to the study having lower power to distinguish effects of nr-axSpA on mortality. We also lacked data about the treatments participants received after 1985, and therefore, cannot control for or investigate the effects of treatments such as non-steroidal anti-inflammatory drugs, corticosteroids or biological agents. Interestingly, a recent study from Israel is compatible with the view that early treatment with TNFi may reduce mortality of AS patients.[9] Finally, the term nr-axSpA is nowadays a specific term that refers to an important concept (axSpA) and takes into account the application of modern technology, that is, MRI, to diagnose and characterise nr-axSpA patients. Such a term cannot directly be applied to a cohort established in 1985. However, the patients in our cohort without evidence of radiographic sacroiliitis resemble in our view current nr-axSpA patients rather closely as illustrated by the following considerations. Our primary aim was to assess the long-term outcome of a cohort of diagnosed patients, not to classify by any set of criteria. In this respect, it is important to realise that at the group level our nr-axSpA patients likely do not fully match with current (ie, after the introduction of the ASAS classification criteria for axSpA[33]) nr-axSpA patients. Our cohort was assembled in 1985. The clinical criteria for the diagnosis AS (now axSpA) included the Rome criteria (reviewed in reference 2) that enable the diagnosis in the absence of radiographic sacroiliitis. The Rome criteria share clinical features with the ASAS clinical features.[33] Moreover, it is estimated that most of our nr-axSpA patients would have met more than one ASAS clinical feature implying that HLA-B27 positive nr-axSpA patients in our study would also fulfil current ASAS criteria. It is also assumed that a considerable proportion of the patients would have met MR-imaging criteria for sacroiliitis (if that technique already had been available at that time). One could, however, not dismiss the possibility that some patients would classify as false-positive by current criteria, a feature that applies to any set of criteria, including current ASAS classification criteria.[33] Note further that a positive family history (another ASAS feature) was also reported for nr-axSpA probands[34] as was frequently the case for a positive history of chronic inflammatory back pain or the occurrence of acute anterior uveitis (online supplemental table 2). In addition, the HLA-B27 prevalence among the women and the overall (60%) prevalence of HLA-B27 in our nr-axSpA patients fit very well with current series of patients with nr-axSpA.[35 36] However, much has changed since 1985 as we first described 'spondylitic disease without radiological sacroiliitis' (now nr-axSpA).[37] The awareness of the disease and possibilities for diagnosis (MRI) have increased sharply. Notwithstanding these advances, we strongly believe that the group of patients that we have labelled as nr-axSpA patients and that we have reported in this study can serve as a valuable proxy for current nr-axSpA patients. Assessment of the long-term outcome (survival) of current AS and nr-axSpA patients that includes the disease-modifying effects of modern therapy will require new studies in the years (decades) ahead. Please, note that dealing with the long-term outcome (eg, survival after several decades) of patients with conditions lacking a gold-standard for diagnosis (such as nr-axSpA) an important caveat applies. Even if the name of the disease would not change over time, the concept of the condition might evolve. Further, the diagnostic approach and tools for diagnosis probably will be different, whereas the effectiveness of therapeutic interventions are likely to have increased. At the time the results of a long-term study become available, the profiles and long-term results of the patients studied will therefore almost inevitably not fully match with current or future patients with the condition of interest. Hence, results obtained from cohorts assembled in the past cannot be fully extrapolated to new patients with that condition.

In summary, compared with the general population, AS, but not nr-axSpA, is associated with increased mortality, especially among women, whose lifespan is considerably reduced compared with men with AS. HLA-B27 status itself does not influence mortality risk. The study also demonstrates that in subjects of European-ancestry HLA-B27 in the general population is not associated with increased mortality, nor with increased risk of cardiovascular death. It has previously been demonstrated that 95%–99% of HLA-B27 positive individuals do not develop an HLA-B27-associated disease.[21–23] Such individuals can be reassured that

the fact that they carry HLA-B27 is irrelevant to their future life expectancy.

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Contributors The study was designed by all coauthors. Analysis was performed by ZL, MKK, SMvdL, BW and MAB. Manuscript preparation and approval involved all coauthors. MAB acts as the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting, and dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the University Hospital of Bern and the Ethical Committee of Kanton of Bern, Switzerland, #2017-00536. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data involved in this study regarding the Swiss AS Family Study is available from the authors on reasonable request. Data involved in this study from the UK Biobank can be accessed through that organisation.

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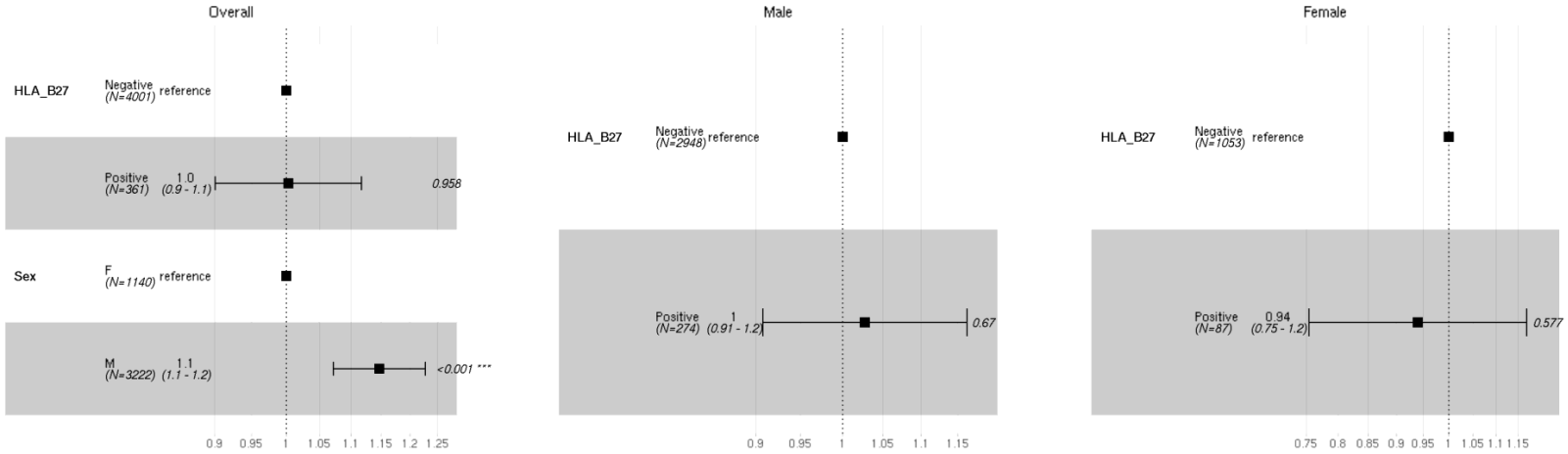
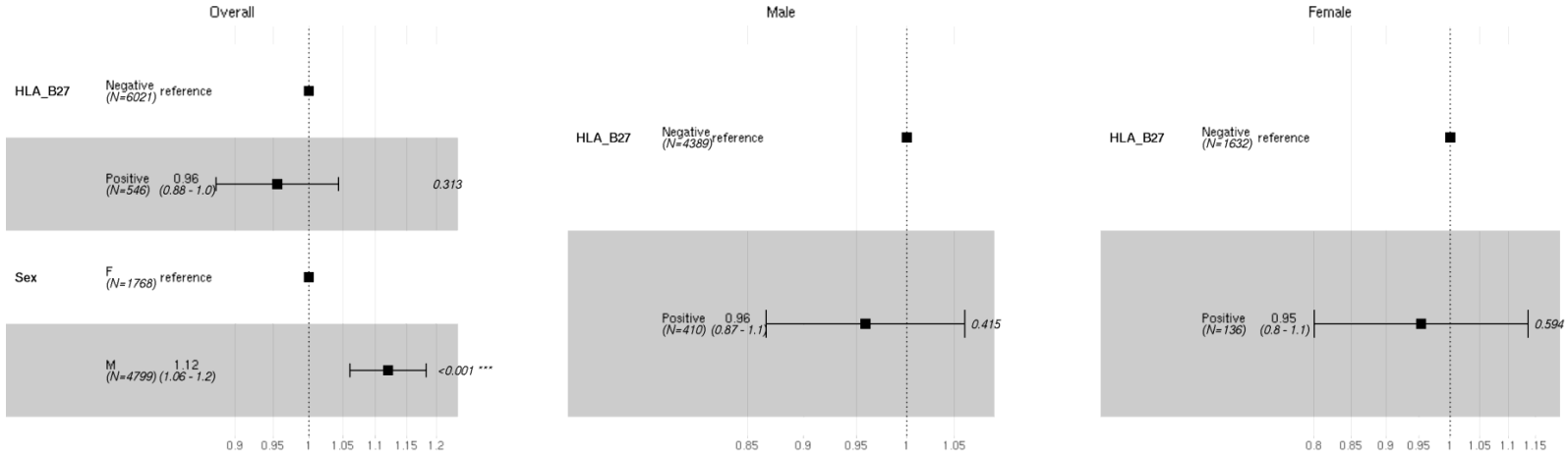
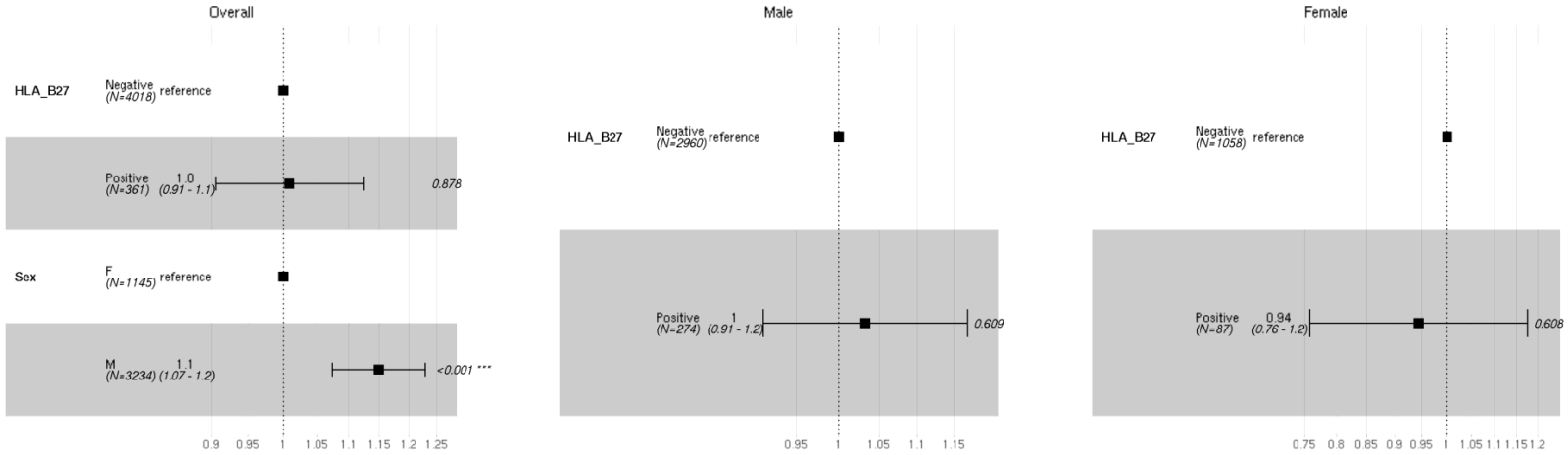


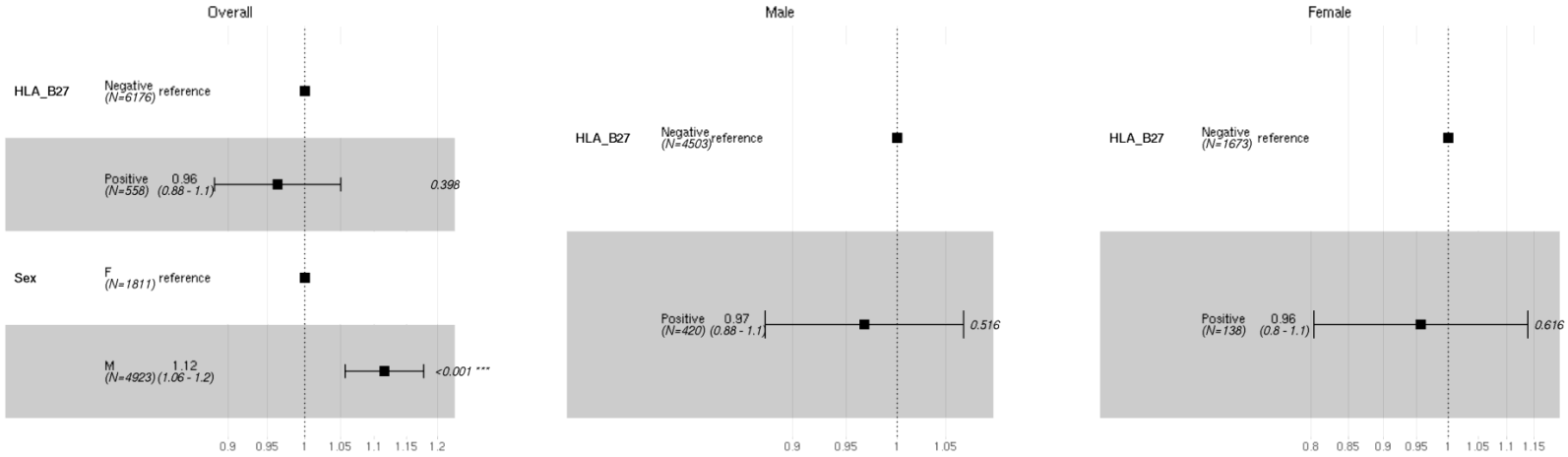
Supplementary Figure 1. Forest plot for Cox Proportional-Hazards Model for *HLA-B27*-positive and *HLA-B27*-negative subjects with primary cause of death a cardiovascular disease in the European cohort and divided by sex (excluding COVID-19 deaths).



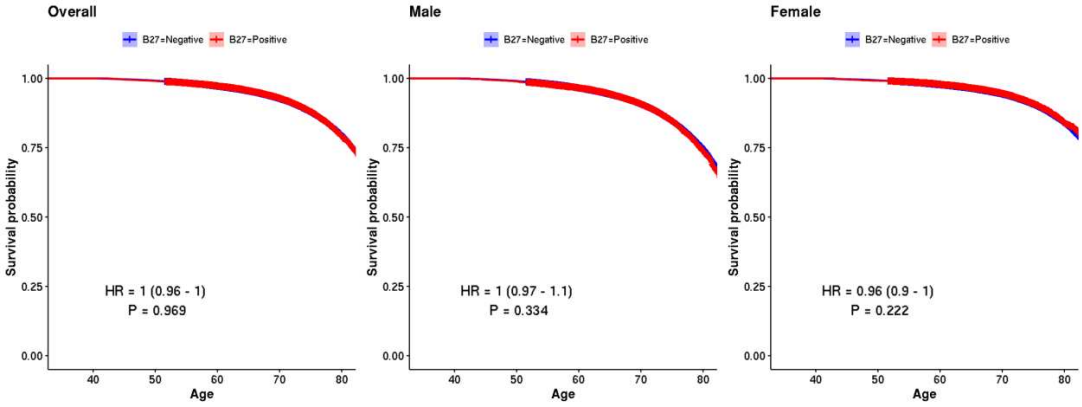
Supplementary Figure 2. Forest plot for Cox Proportional-Hazards Model for *HLA-B27*-positive and *HLA-B27*-negative subjects with primary or contributory cause of death a cardiovascular disease in the European-ancestry cohort and divided by sex (excluding COVID-19 deaths).



Supplementary Figure 3. Forest plot for Cox Proportional-Hazards Model for *HLA-B27*-positive and *HLA-B27*-negative subjects with primary cause of death a cardiovascular disease in the European-ancestry cohort and divided by sex (including COVID-19 deaths).



Supplementary Figure 4. Forest plot for Cox Proportional-Hazards Model for *HLA-B27*-positive and *HLA-B27*-negative subjects with primary or contributory cause of death a cardiovascular disease in the European-ancestry cohort and divided by sex (including COVID-19 deaths).



Supplementary Figure 5. Survival plots for *HLA-B27*-positive and *HLA-B27*-negative subjects in European participants in the UK Biobank study (including the COVID-19 deaths), overall and divided by sex. *HLA-B27*-positive and *HLA-B27*-negative carriers are coloured by red and blue, respectively.

Supplementary Table 1. ICD-10 codes of ischaemic heart disease, aortic aneurysm, cerebrovascular disease, and peripheral vascular disease.

Disease	**ICD-10**
Ischaemic heart disease	I20-I25.9
Aortic aneurysm	I71-I71.9
Cerebrovascular disease	G45-G46.8, I60-I61.9, I62.0-I62.03, I63-I63.9, I65-I66.9, I67.0-I67.3, I67.5-I67.6, I68.1-I68.2, I69.0-I69.39
Peripheral vascular disease	I70.2-I70.799, I73-I73.

Li Z, *et al. Ann Rheum Dis* 2023;0:1–10. doi: 10.1136/ard-2023-224434

Supplementary Table 2. Baseline demographic and clinical data of patients participating in the 2018-19 follow-up study by radiographic status.

	AS (n=98)	Non-radiographic axial SpA (n=50)
Age in 2018 (SD) yr	71.07 (7.41)	72.78 (7.06)
Chronic inflammatory back pain (CIBP)[1]	74.7%	72.5%
Thoracic spinal pain	79.8%	56.8%
Ventral chest pain or discomfort	72.1%	52.8%
Occiput to wall distance[2] (mean) cm	9.5 (SD 7.5)	5.9.2 (SD 5.5)
Acute anterior uveitis[2]	45.0%	36.1%

[1] CIBP considered present if ≥ 4 of 5 Calin criteria are met

[2] Self-reported

Supplementary Table 3. UK Biobank European-ancestry participants with and without cardiovascular diseases, and mean age at death in participants excluding (including) COVID-19 deaths.

	Yes	No	Mean age at death (years)
HLA-B27-positive	3,661 (3,684)	29,264 (29,322)	71.23 (70.48)
HLA-B27-negative	42,120 (42,425)	332,435 (333,061)	70.91 (70.36)
Total	45,781 (46,109)	361,699 (362,383)	70.94 (70.38)
HLA-B27-positive prevalence	8.00% (7.99%)	8.09% (8.09%)	-

Supplementary Table 4. UK Biobank European-ancestry participants with, without, and deceased of, ischaemic heart disease, aortic aneurysm, cerebrovascular disease, and peripheral vascular disease in participants excluding (including) COVID-19 deaths.

Diagnosis								
	Ischaemic heart Disease		**Aortic aneurysm**		**Cerebrovascular disease**		**Peripheral vascular disease**	
	Yes	No	Yes	No	Yes	No	Yes	No
HLA-B27-positive	2812 (2832)	30113 (30174)	131 (134)	32794 (32872)	781 (785)	32144 (32221)	364 (367)	32561 (32639)
HLA-B27-negative	32241 (32458)	342314 (343028)	1716 (1732)	372839 (373754)	9386 (9473)	365169 (366013)	4544 (4586)	370011 (370900)
Total	35053 (35290)	372427 (373202)	1847 (1866)	405633 (406626)	10167 (10258)	397313 (398234)	4908 (4953)	402572 (403539)
HLA-B27-positive prevalence	8.02	8.09	7.09 (7.18)	8.08 (8.08)	7.68 (7.65)	8.09 (8.09)	7.42 (7.41)	8.09 (8.09)
Death								
	Ischaemic heart Disease		**Aortic aneurysm**		**Cerebrovascular disease**		**Peripheral vascular disease**	
	N	Mean age at death	N	Mean age at death	N	Mean age at death	N	Mean age at death
HLA-B27-positive	415 (424)	71.21 (70.31)	39 (39)	71.72 (71.72)	94 (95)	70.94 (70.98)	29 (31)	74.78 (74.89)
HLA-B27-negative	4691 (4817)	70.83 (70.96)	333 (337)	71.34 (71.45)	983 (1000)	71.16 (71.24)	315 (331)	72.54 (72.7)
Total	5106 (5241)	70.86 (70.99)	372 (376)	71.38 (71.48)	1077 (1095)	71.14 (71.22)	344 (362)	72.73 (72.88)
HLA-B27-positive prevalence	8.13 (8.09)		10.48 (10.37)		8.73 (8.68)		8.43 (8.56)	

Supplementary Table 5. HLA-B27 carriage by decade of life based on age at recruitment in UK Biobank European-ancestry participants excluding (including) COVID-19 deaths.

Age (years)	*HLA-B27*-positive	*HLA-B27*-negative	Total	*HLA-B27*-positive prevalence
40-49	6822 (6824)	76601 (76634)	83423 (83458)	8.18 (8.18)
50-59	10522 (10537)	120665 (120817)	131187 (131354)	8.02 (8.02)
60-69	14913 (14972)	169281 (169961)	184194 (184933)	8.10 (8.10)
70-80	668 (673)	8008 (8074)	8676 (8747)	7.70 (7.69)

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Supplementary Table 6. P-value for chi-squared test of HLA-B27 carriage vs reference decade of life in UK Biobank European-ancestry participants. The participants excluding (including) COVID-19 deaths were grouped by the age at recruited (rounded to integer).

Reference decade of life	40-49	50-59	60-69	70-79
40-49	1	0.196 (0.196)	0.481 (0.481)	0.126 (0.126)
50-59		1	0.445 (0.445)	0.295 (0.295)
60-69			1	0.192 (0.192)
70-80				1

Supplementary Table 7. UK Biobank European-ancestry participants deceased of COVID-19 or other causes.

	COVID-19	Other	Mean age of COVID-19 death (years)
HLA-B27-positive	81	2525	74.899
HLA-B27-negative	931	28906	75.244
Total	1012	31431	
HLA-B27-positive prevalence	8.00%	8.03%	
P	1		