Ideal physical activity in association with incident ankylosing spondylitis: a community-based, prospective cohort study

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Abstract

Objective

Only limited risk factors for ankylosing spondylitis (AS) have been identified to date. Therefore, we aimed to explore whether cardiovascular health (CVH) behaviours and factors are associated with the risk of developing AS.

Methods

Patients with incident AS were identified in cohorts from two ongoing prospective studies. Assessments were made of the association of AS with individual baseline cardiovascular health lifestyle behaviours (including smoking status, body mass index, physical activity and diet) and cardiovascular health factors (including total cholesterol levels, blood pressure levels and fasting plasma glucose levels), and with a cardiovascular health metric determined by the number of ideal behaviours and factors. Cox regression analysis was used for the estimation of hazard ratios (HRs) for AS.

Results

Among 124,303 participants, incident AS was identified in 53 individuals within the 8 years of follow-up. For participants with ideal physical activity (>80 min/week) the HR was 0.21 (95% CI 0.05–0.89) compared with participants without ideal physical activity after adjusting for potential confounders. No significant risk of developing AS was associated with baseline smoking, diet, body mass index, blood pressure, fasting blood glucose or total cholesterol status, nor did cardiovascular health metrics.

Conclusion

Adherence to ideal physical activity may reduce the risk of developing AS.

Key words

ankylosing spondylitis, risk factors, cohort study, physical activity, cardiovascular health

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Introduction

Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease with a prevalence of between 0.1% and 1.4% globally, which results in serious impairment of spinal mobility and physical function, thereby affecting quality of life (1, 2). It takes, on average, 6–8 years from the onset of back pain until a clinician establishes a definitive diagnosis of AS. Exploration of predictors for incident AS is very important because early treatment with effective drugs can significantly slow down the progress of ankylosis (3).

Previous studies have demonstrated that ideal healthy statuses, defined as cardiovascular health (CVH) metric (4) including being a non-smoker, having a body mass index (BMI) <25 kg/m^2, participating in physical activity daily, having a healthy diet, untreated total cholesterol <200 mg/dl, untreated systolic blood pressure (BP) <120 mm Hg, diastolic BP<80 mm Hg, and untreated fasting blood glucose <100 mg/dl, are associated with the lower risks for incidence of several chronic diseases such as coronary heart disease (CHD) (5), stroke (6), or diabetes (7). It has been shown that partial components of CVH metrics are associated with incident AS directly or indirectly. For example, smoking and hypertension appear to be associated with the incidence of AS (8); increasing BMI was associated with increased risk of incident psoriatic arthritis (PsA) which shares overlapping clinic features with AS (9, 10); physical activity has been shown to reduce long-term inflammation, which has an important role in both the initiation and the progression of AS (11); in contrast, hypercholesterolaemia leads to cholesterol accumulation in macrophages and other immune cells, which promotes inflammatory responses (12). However, the association between overall CVH profile and incident AS remain unknown, and the association between individual component of CVH metrics and incident AS is uncertain.

To address these issues, we collected baseline information on CVH behaviours (smoking status, BMI, physical activity, diet) and CVH factors (blood cholesterol levels, BP levels, blood glucose levels) in a community-based cohort study; AS subsequently developed in 53. We investigated whether CVH metrics (combined CVH behaviours and CVH factors) (4) or individual component are associated with incident AS in a prospective, community-based study involving 124,303 Chinese adults followed for ~8 years.

Materials and methods

Study design and population

The Kailuan study, a prospective cohort study involving the Kailuan community in Tangshan City in northern China, was designed to enable the investigation of risk factors for common chronic diseases (13, 14). In 2006, 155,418 participants ≥18 years old were invited to participate in questionnaire assessments and clinical and laboratory examinations conducted in the 11 hospitals responsible for the healthcare of this community. Kailuan Study I comprised a total of 101,510 participants who completed the questionnaires and clinical examinations between 2006 and 2007. During 2008–2010, 35,856 adults who did not participate in Kailuan Study I were enrolled in Kailuan Study II, and they also completed the questionnaires. Participants in both studies were followed up with the same questionnaires and clinical and laboratory examinations again every 2 years, to provide further, ongoing information on their health and lifestyles.

A total of 137,366 participants from Kailuan Studies I and II were considered for inclusion in this study; we excluded of 13,018 individuals for whom information on age, sex or CVH metrics was missing, as well as 45 with AS at baseline, leaving 124,303 participants who were included in the current analyses. The last follow-up was on December 31, 2015 and the analyses were conducted in 2016.

The protocol for this study was designed in accordance with the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of the Kailuan Medical Group, Kailuan Company. Written informed consent was obtained from all the participants.

Incidence of ankylosing spondylitis

Incident AS cases were identified by searching the Municipal Social Insur-

ance Institution database and the Hospital Discharge Register of the 11 hospitals (with an ICD-10 search code of M45 for AS). Three rheumatologists (Drs. Wenhao Yang, Huijing Shi, and Jinmei Su) reviewed all medical records and confirmed that the diagnosis of AS fulfilled the modified New York classification criteria (15).

Assessment of cardiovascular health metric

The CVH metric comprised seven components (smoking status, BMI, physical activity level, healthy diet score, BP, fasting blood-glucose level and total cholesterol level) (4). Because the aim of the analysis was to evaluate the association between ideal CVH-metric components and AS risk, we scored each component as zero (non-ideal status) or one (ideal status), on the basis of American Heart Association (AHA) recommendations (4). The number of ideal CVH-metric components was used as the primary exposure variable. Therefore, the total CVH-metric scores ranged from zero (no ideal components) to seven (all ideal components).

Information on smoking status, salt intake and physical activity was collected via a questionnaire. Because the questionnaire did not include dietary questions, salt intake was used as a surrogate for overall diet quality, which is supported by the fact that salt intake has consistently been found to be associated with CVD risk in previous epidemiological studies (16, 17). The ideal diet was defined as a daily salt consumption of <6 g, as previously described (18). The ideal smoking status was defined as having never smoked; ideal physical activity was defined as moderate or vigorous physical activity for >80 min/week. During the interview, the height of each participant was measured to the nearest 0.1 cm by trained field workers using the height meter of a platform scale. Weight was measured to the nearest 0.1 kg using the weight meter of the platform scale. BMI was then calculated as the patient's weight divided by the square of their height (kg/m^2). BMI <25 kg/m^2 was defined as ideal.

Systolic and diastolic BP were measured following standard procedures. BP was measured three times in the sitting position and the mean was used for data analysis. BP was defined as ideal if the systolic BP was <120 mmHg and the diastolic BP was <80 mmHg, in the absence of any antihypertensive medications.

After fasting for 8–12 h, venous blood samples were drawn at each study visit, and analysed at the Central Laboratory of Kailuan Hospital on the day of collection. Fasting blood glucose and total cholesterol were measured using an autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan) as previously described (18). Fasting blood glucose was defined as ideal if <100 mg/dL without hypoglycemic treatment; total cholesterol was defined as ideal if the untreated total cholesterol level was <200 mg/dL.

Assessment of covariates

Information on demographic variables (age, sex), socioeconomic status (marital status, education, occupation, income), lifestyle behaviour (alcohol consumption) and medical history was collected via a questionnaire administered by the research doctors at the baseline interview. Alcohol consumption was divided into five categories: never, ever, light (<0.5 servings per day in women, <1 serving per day in men), moderate (0.5–1.5 servings per day in women, 1–2 servings per day in men) and heavy (>1.5 servings per day in women, >2 servings per day in men), where a serving contained 15 g of alcohol.

Plasma high-sensitivity C-reactive protein (hs-CRP) concentrations were measured with a high-sensitivity particle-enhanced immunonephelometric assay (Cias Latex CRP-H, Kanto Chemical, Tokyo, Japan); creatinine and uric acid were measured with an autoanalyzer (Hitachi 747) as previously described (14). The estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration two-level race equation (19).

Statistical analyses

Demographic and baseline characteristics are summarised with respect to numbers of ideal CVH metrics (0–2, 3 or 4–7) at baseline. Continuous variables are represented by the mean ± standard deviation, and discrete variables are represented by counts and percentages. Statistical analyses were performed with SAS software, version 9.3 (SAS Institute, Cary, NC, USA). *p*-values were two-tailed, and values <0.05 were considered to indicate statistical significance.

The person-time of follow-up for each participant was measured from the finishing date of the Kailuan Study I or Study II survey to either the date of AS onset or the end of follow-up (December 31, 2015), whichever came first. Cox proportional hazard regression was used to calculate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for AS risk in relation to numbers of ideal CVH metrics. Three multivariate proportional hazards models were fitted, to account for potential confounders. Model 1 was adjusted for sex and age. Model 2 was adjusted as model 1 and also for education, average monthly income of each family member, marital status, alcohol consumption and occupation. Model 3 was adjusted as Model 2 and also for hs-CRP, uric acid and eGFR.

Because changes in the ideal CVH metrics may have been the result of impending AS, a 2-year-lag analysis was conducted by excluding AS events from the first 2 years of follow-up, to reduce the potential for reverse causality. The influence of sex and age on the association between numbers of ideal CVH metrics and the risk of AS (with adjustment for potential confounders) was also explored.

Results

In comparison with participants with lower CVH scores (<4), those with CVH metrics scores of 4–7 were younger, with higher proportions of women, unmarried individuals, those who had never drunk, white-collar workers and those with college/university education. The high-CVH-score group also had lower uric acid and hs-CRP concentrations and higher eGFR (Table I).

In the 1,004,390 person-years of follow-up (on average, 8.08±1.25 years per person), we documented 53 new AS cases. Relative to a CVH score of 0–2,

Table I. Participant (n=124,303) characteristics according to the number of ideal CVH metrics at baseline (2006-2007)*.

Characteristics	Number of ideal CVH metrics			
	0-2 n=47,472	3 n=37,516	4-7 n=39,315	*p*-value
Men	42,419 (42.50)	30,846 (30.91)	26,534 (26.59)	**<0.001**
Women	5,053 (20.62)	6,670 (27.22)	12,781 (52.16)	
Age, years	52.0 ± 11.4	51.7 ± 12.8	49.1 ± 14.6	
Marital status				**<0.001**
Single	520 (17.26)	710 (23.57)	1,782 (59.16)	
Married	45,402 (38.69)	35,676 (30.40)	36,260 (30.90)	
Other	1,543 (39.18)	1,126 (28.59)	1,269 (32.22)	
Education				**<0.001**
Illiteracy/elementary	5,497 (41.76)	3,974 (30.19)	3,691 (28.04)	
Middle school	38,999 (38.84)	30,940 (30.81)	30,478 (30.35)	
College/university	2,962 (27.71)	2,593 (24.26)	5,134 (48.03)	
Occupation				**<0.001**
Blue collar	35,356 (39.17)	28,005 (31.02)	26,922 (29.82)	
White collar	1,890 (29.50)	1,613 (25.18)	2,903 (45.32)	
Income§				**<0.001**
<¥500/month	12,601 (43.44)	8,379 (28.88)	8,029 (27.68)	
¥500-3,000/month	28,635 (36.44)	24,374 (31.02)	25,569 (32.54)	
>¥3,000/month	3,816 (36.54)	2,907 (27.84)	3,720 (35.62)	
Alcohol consumption				**<0.001**
Never	23,247 (31.12)	23,679 (31.70)	27,764 (37.17)	
Light**	6,618 (44.09)	4,255 (28.35)	4,138 (27.57)	
Moderate**	2,482 (45.11)	1,593 (28.95)	1,427 (25.94)	
Heavy**	9,569 (57.36)	4,427 (26.54)	2,685 (16.10)	
Ever	2,015 (50.81)	1,113 (28.06)	838 (21.13)	
Uric acid, mg/dl	307 ± 87.3	289 ± 82.2	273 ± 78.9	
eGFR, ml/minute/1.73m^2	81.8 ± 19.8	83.1 ± 20.0	83.9 ± 20.3	
Hs-CRP, mean, mg/L	2.33 ± 3.58	2.13 ± 3.94	1.85 ± 4.07	

*Values are the number (%) or the mean±SD. §Average monthly income of every family member. **Light is defined as 0–0.4 servings/day for women and 0–0.9 servings/day for men; moderate 0.5–1.5 servings/day for women and 1-2 servings/d for men, heavy >1.5 servings/day for women and >2 servings/day for men. CVH: cardiovascular health; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein.

Table II. HRs for AS according to the number of ideal CVH metrics*

Number of ideal CVH metrics	n.	Cases	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
0–2	47,472	20	1 (reference)	1 (reference)	1 (reference)
3	37,516	22	1.47 (0.80-2.70)	1.46 (0.79-2.69)	1.61(0.87-2.97)
4–7	39,315	11	0.79 (0.38-1.67)	0.75 (0.35-1.60)	0.85 (0.40-1.82)
p for trend			0.70	0.60	0.88

*Model 1 was adjusted for sex and age (years). Model 2 included the variables in model 1 and was further adjusted for education (illiteracy/elementary school, middle school, college/university), average monthly income of each family member (<¥500, ¥500–3000, >¥3000), marital status, alcohol consumption (never, light, moderate, heavy, ever), and occupation (miner, blue collar, white collar). Model 3 included the variables in model 2 and was further adjusted for high-sensitivity C-reactive protein (<1, 1-3, >3, <10, ≥10 mg/L), uric acid, and estimated glomerular filtration rate (<30, ≥30 and <60, ≥60 and <90, ≥90 and <120, ≥120 ml/min). AS: ankylosing spondylitis; CVH: cardiovascular health; HR: Hazard ratio; 95% CI: 95% confidence interval.

the HR for AS for a CVH score of 3 was 1.59 (95% CI 0.86–2.94), and the HR for a CVH score of 4–7 was 0.84 (95% CI 0.39–1.80; *p*=0.85 for trend) after adjusting for potential confounders (Table II). Exclusion of AS cases that occurred in the first 2 years of follow-up generated similar results (data not shown), as did stratification by sex or age (Table III).

Among participants with ideal physical activity (>80 min/week) the HR was 0.21 (95% CI 0.05–0.89) compared with participants with nonideal physical activity. However, among the individual CVH metrics, no significant associations were observed between the risk of developing AS and the ideal status at baseline for smoking, BMI, diet, BP, total cholesterol, BP, or fasting blood glucose (Table IV).

Discussion

In this large-scale, community-based, prospective study, we have explored the association between CVH metrics or individual component of CVH metrics and the risk of incident AS. We observed that the group of individuals who performed >80 min of moderate or vigorous physical activity per week had a 79% lower risk of developing AS than those with ≤80 min of physical activity per week, suggesting that physical activity is a protective factor for AS. In contrast, it appeared to be no association between smoking, BMI, diet, blood cholesterol level, blood glucose level, blood pressure level and incident AS; nor did ideal CVH metrics.

In current study, we observed a 79% reduction in the risk of developing AS in participants who engaged in physical activity. To date, there is no direct evidence available on the association between physical activity and incident AS. However, physical activity reduced inflammation, which is a critical process in the pathogenesis of AS (11). Moreover, a systematic review of 24 studies with a total of 1,498 participants with chronic back pain, physical activity might reduce pain severity and improve physical function (20). As a possible pathophysiological explanation, physical activity may ease the inflammation associated with back pain, which is a critical early step in the osteoproliferation process in AS. Furthermore, physical activity may directly affect disc metabolism by improving metabolic exchange in lumbar discs and aiding repair (20).

In a previous study, incident AS was associated with current smoking (8). However, the study might be limited for false-positive diagnoses because of self-reported diagnoses method or for nonrepresentative sample. Our data did not demonstrate an association between the ideal smoking status (having never

Table III. HRs for AS according to the number of CVH metrics stratified by sex and age*

Number of idea	Men		Women		Age <45 y		Age ≥45 y	
CVH metrics	n.	HR (95% CI)	n.	HR (95% CI)	n.	HR (95% CI)	n.	HR (95% CI)
0–2	42,399	1 (reference)	5,053	1 (reference)	11,504	1 (reference)	35,948	1 (reference)
3	30,825	1.56 (0.85-2.90)	6,669	-	10,367	1.36 (0.46-4.01)	27,127	1.81 (0.85-3.85)
4–7	26,525	0.75 (0.33-1.68)	12,779	-	14,827	0.72 (0.20-2.57)	24,477	0.97 (0.36-2.59)
p for trend		0.72		0.74		0.65		0.78
p for interaction	0.34				0.96			

*Model was adjusted for sex and age (years), education (illiteracy/elementary school, middle school, college/university), average monthly income of each family member (<500, 500-2999, ≥3000¥), marital status, alcohol consumption (never, light, moderate, heavy, ever), occupation (miner, blue collar, white collar), high-sensitivity C-reactive protein, uric acid, and estimated glomerular filtration rate. AS: ankylosing spondylitis; CVH: cardiovascular health; HR: Hazard ratio; 95% CI: 95% confidence interval.

Table IV. HRs for AS according to the status of components (ideal *vs*. non-ideal) of CVH metrics*

Number of ideal CVH metrics	Model 1 HR (95% CI)	Model 2 HR (95% CI)	Model 3 HR (95% CI)
Smoking	0.91 (0.52-1.59)	0.85 (0.45-1.62)	0.88 (0.46-1.69)
Physical activity	0.22 (0.05-0.90)	0.18 (0.04-0.76)	0.21 (0.05-0.89)
Diet	0.92 (0.37-2.30)	0.88 (0.35-2.23)	0.98 (0.39-2.49)
Body mass index	1.37 (0.79-2.36)	1.33 (0.77-2.30)	1.49 (0.85-2.62)
Blood pressure	0.75 (0.35-1.62)	0.73 (0.34-1.60)	0.75 (0.34-1.63)
Fasting blood glucose	1.33 (0.71-2.50)	1.36 (0.72-2.57)	1.43 (0.76-2.69)
Total cholesterol	0.85 (0.49-1.47)	0.85 (0.49-1.48)	0.84 (0.48-1.48)

*All variables were adjusted for each other. Model 1 was adjusted for sex and age (years). Model 2 included the variables in model 1 and was further adjusted for education (illiteracy/elementary school, middle school, college/university), average monthly income of each family member (<500, 500–2999, ≥3000¥), marital status, alcohol consumption (never, light, moderate, heavy, ever), and occupation (miner, blue collar, white collar). Model 3 included the variables in model 2 and was further adjusted for high-sensitivity C-reactive protein, uric acid, and estimated glomerular filtration rate. AS: ankylosing spondylitis; CVH: cardiovascular health; HR: Hazard ratio; 95% CI: 95% confidence interval.

smoked) and a low risk of developing AS, suggesting that, compared with genetic and environmental factors, smoking status might not be sufficiently powerful to change the outcome. Alternatively, as the incidence of AS in the Kailuan population was low, the predictive power of smoking status for the risk of AS may have been underestimated by our analyses; smoking status may have more predictive power in populations with higher incidence of AS.

To date, there is no evidence available on the effect of diet on the risk of developing AS. In current study, daily salt consumption of <6 g was not associated with a lower risk of developing AS than salt consumption of ≥6 g. Similarly, ideal BMI, BP and blood glucose were not associated with lower risks of developing AS, which is consistent with results from previous studies (8, 21). In a meta-analysis including 15 case-control studies and 14 observational cohort studies with consideration of classic cardiovascular risk factors (including BMI, BP and blood glucose), patients with AS had a weighted mean BMI of 25.0±4.0 kg/m^2, normal systolic and diastolic BP and normal blood glucose levels, with no differences in BMI, BP or blood glucose between AS patients and healthy controls (21). Our data also showed that there was no association between ideal total cholesterol status and incidence of AS. The effect of lipid profiles on AS remains unknown, although hypercholesterolemia leads to cholesterol accumulation in macrophages and other immune cells, which promotes inflammatory responses (12).

Although partial components of CVH metrics appeared to be associated with incident AS (8), in current study no significant associations were found between the number of ideal CVH-metric components and the risk of developing AS. We did not observe a significant reduction in the risk of developing AS in association with adherence to ideal CVH metrics, yet it is very important for patients with established AS to avoid CVD risk factors, as they have an increased risk of vascular death and CVD events compared with controls (22, 23).

The strengths of the current study include its prospective design and large, community-based population. However, our study was limited by its nonrepresentative sample, which was drawn from a population living in a northern industrial city in China, so that the results may not be generalizable to other populations. Furthermore, physical activity was measured via self-reported and thus can introduce measurement error. However, self-reported physical activity remains a standard approach to collect data on physical activity in large population-based samples. Reverse causation is possible because AS patients have a long pre-clinical period. Although 2-year-lag analyses have the same results reverse causation is still possible. The reason is that the AS criteria (15) proved to be impractically insensitive for the purpose of diagnosing early disease although it is quite specific. In 2009, the new Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axial spondyloarthritis has evolved magnetic resonance imaging as an important diagnostic tool (24). According to the ASAS criteria, the diagnosis of axial spondyloarthritis encompasses two subsets - classic AS and nonradiographic axial spondyloarthritis which is considered an early stage of AS. Therefore, prospective studies using new classification criteria to identify AS

patients at early stage will be necessary to confirm these observations. Finally, as in all observational studies, uncontrolled and residual confounding is a potential limitation.

In conclusion, we observed a clear inverse relationship between physical activity and the risk of developing AS in this large-scale Chinese cohort. Prospective studies including participants with different cultural backgrounds and using new classification criteria will be necessary to confirm these observations.

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