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Association of Healthy Lifestyle Behaviors and the Risk of Developing Rheumatoid Arthritis among Women

Jill Hahn, ScD, MS[1], **Susan Malspeis, BS**[2], **May Y. Choi, MD, MPH**[2,3], **Emma Stevens, BA**[2], **Elizabeth W. Karlson, MD, MA**[2], **Bing Lu, MD, PhD**[2], **Jing Cui, MD, PhD**[2], **Kazuki Yoshida, MD, ScD**[2], **Laura Kubzansky, PhD**[1], **Jeffrey A. Sparks, MD, MMSc**[2], **Karen H. Costenbader, MD, MPH**[2]

[1]Harvard T.H. Chan School of Public Health, Boston, MA, USA

[2]Brigham and Women's Hospital, Boston, MA, USA

[3]University of Calgary, Calgary, Alberta, Canada

Abstract

Objective: We investigated whether a healthy lifestyle, defined by a healthy lifestyle index score (HLIS), was associated with rheumatoid arthritis (RA) risk, overall and seropositive/seronegative subtypes.

Methods: We analyzed female nurses in Nurses' Health Study (NHS, 1986–2016) and NHSII (1991–2017). Lifestyle and medical information were collected on biennial questionnaires. Medical records confirmed incident RA and serostatus. The HLIS index includes five modifiable components: smoking, alcohol consumption, body mass index, physical activity, and diet. Cox regression, adjusted for confounders, modeled associations between HLIS and incident RA. The population attributable risk (PAR) estimated the proportion of incident RA preventable if participants adopted ≥4 healthy lifestyle factors.

CORRESPONDING AUTHOR Karen H. Costenbader, MD, MPH, Professor of Medicine, Harvard Medical School, Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, 60 Fenwood Road, 2nd floor, Boston, MA 02115, phone: 617-732-6088, fax: 617-732-5766.

CONTRIBUTORSHIP

All authors have participated in the following:

-Substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data

-Drafting the work or revising it critically for important intellectual content

-Final approval of the version published

-Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The study protocol was approved by the institutional review board at Mass General Brigham HealthCare System.

DATA SHARING

Data from this project can be considered for release if the appropriate IRB and publication clearances have been made, and a project is in keeping with and has undergone the Nurses' Health Study Cohorts review and approval process.

PATIENT AND PUBLIC INVOLVEMENT

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

OTHER DISCLAIMERS

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Results: 1,219 incident RA cases (776 seropositive; 443 seronegative) developed in 4,467,751person-years. Higher (healthier) HLIS was associated with lower overall (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.82–0.90), seropositive (HR 0.85, 95% CI 0.80–0.91), and seronegative RA risk (HR 0.87, 95% 0.80–0.94). Women with 5 healthy lifestyle factors had lowest risk (HR 0.42, 95% CI 0.22–0.80). The PAR for adhering to ≥ 4 lifestyle factors was 34% for RA.

Conclusion: In this prospective cohort, healthier lifestyle was associated with lower RA risk. A substantial proportion of RA may be preventable by healthy lifestyle.

Keywords

rheumatoid arthritis; epidemiology; risk factor; lifestyle; prevention

Introduction

Rheumatoid arthritis (RA) is an inflammatory polyarthritis of incompletely understood etiology that attacks and destroys synovial joints, causing systemic complications and early mortality. RA strikes approximately 1% of the general population, with a peak incidence in mid-life, and 2/3 of affected individuals female. Although we have an expanding array of medications to treat RA, none are curative and the costs of therapy, disability and lost productivity are high(1). An autoimmune disease, RA is known to have a strong genetic predisposition(2).

Modifiable lifestyle factors, such cigarette smoking, being obese, lacking physical activity and following an unhealthy diet high in saturated fats and carbohydrates, are strongly linked to increased risk of cardiovascular disease and cancer in the general population. Previous epidemiologic studies in the Nurses' Health Study (NHS) cohorts, the Health Professionals Follow-up study, and other large prospective cohorts, have demonstrated these strong associations repeatedly(3–6). To assess the combined impact of different aspects of an overall healthy lifestyle, the "Healthy Lifestyle Index Score" (HLIS), including the absence of these four risk factors, as well as consuming alcohol only in moderation, was developed(3). Higher scores in this index (a point for each healthy vs. unhealthy behavior) have been strongly predictive of lower lifetime risks of coronary heart disease, including myocardial infarction and stroke, type 2 diabetes mellitus, colorectal cancer, and all-cause mortality(3–6).

Our past NHS cohort studies, and those from other populations, have shown that smoking and obesity were strongly associated with increased risk of RA, in particular seropositive RA(7–9). We also found more hours of recreational physical activity and healthier eating, as measured by the Alternative Healthy Eating Index (AHEI), were associated with reduced RA risk(10). Moderate alcohol consumption (5.0–9.9 g/day vs. none) was associated with a reduction in RA risk(9, 11).

We now investigated the benefit of an overall healthy lifestyle and whether having multiple components defined by the HLIS were associated with the risk of developing RA, overall and of seropositive or seronegative subtypes. We hypothesized that a healthier lifestyle, as

measured by the HLIS, would be associated with reduced risk of RA, and we aimed to estimate the population attributable risk of these behaviors for RA.

Methods

Study Population.

The Nurses' Health Study (NHS) began in 1976 when 121,700 female nurses, aged 30–55 years from 11 U.S. states, were enrolled; NHSII began in 1989 when 116,430 female nurses, aged 25–42 years, from 14 U.S. states were enrolled. Nurses in both cohorts were predominantly White (97%). Follow-up is ongoing and participation rates in both cohorts are high with only ~5% of person-time lost to follow-up. Questionnaires including assessments of lifestyle factors, other relevant covariates, and the development of new diseases including RA and other outcomes were mailed to and completed by participants at baseline and then biennially. A comprehensive self-administered validated Food Frequency Questionnaire (FFQ) with > 130 items was mailed about every four years starting in 1984 in NHS and in 1991 in NHSII. Self-reported incident RA was confirmed by medical record review for 1997 American College of Rheumatology criteria as previously described(7, 8, 10–12). Seropositivity for rheumatoid factor and/or anti-cyclic citrullinated peptide was collected from medical records. The current analysis excluded participants with prevalent RA or other connective tissue disease at each study baseline and followed both cohorts from the first year of FFQ collection (1986–2016 in NHS; 1991–2017 in NHSII). 210,367 women returned a baseline questionnaire. Those missing components of the HLIS at baseline (16%), including 14% missing AHEI, were excluded from the study.

Statistical Analyses.

We derived the healthy lifestyle index score (HLIS), using five established time-updated RA risk factors: cigarette smoking, alcohol consumption, BMI, physical activity, and healthy diet index, as in past studies(3–6). For each factor, we created a binary variable (healthy/unhealthy), using the following criteria for healthy: never smoking; moderate alcohol use (5–15 grams, or about one drink/day), healthy body weight (BMI 18.5–24.9 kg/m^2)); regular exercise (≥19 Metabolic Equivalent of Task [MET]-hours/week, ~30 minutes of daily brisk walking); healthy diet (highest 40th percentile of the Alternative Healthy Eating Index [AHEI])(13). These were summed to create the HLIS ranging from 0–5 as in past studies, using updated risk factor status from each questionnaire cycle. Those missing an item in every questionnaire cycle were excluded; otherwise, individual mean values were imputed for missing data. Data from the two cohorts were then pooled for analyses. Cox regressions modeled associations between HLIS (as continuous or categorical variables) and incident RA, overall and by serostatus. Participants were followed from return of the 1986 (NHS) or 1991 (NHSII) questionnaires through the date of the onset of first RA symptoms in the medical records when incident RA was validated, or through death or loss to follow-up in the cohorts (no further questionnaires returned). The exposure window as in standard NHS cohort analyses was the two-year period prior to the two-year exposure assessment period.

Initial models adjusted for age, questionnaire cycle and cohort; final multivariable models also included the following potential confounders: U.S. census tract median family income

(quartiles), parity and breastfeeding (nulliparous, parous/no breastfeeding, parous/1–12 months breastfeeding, or parous/>12 months breastfeeding), hormone use (premenopausal, postmenopausal with never use, current use, or past use). We tested the proportional hazards assumptions using and it was fulfilled. We calculated the population attributable risk (PAR) to estimate the proportion of incident RA in this population that would be prevented if all participants had adopted four or five healthy lifestyle factors, as well as for each individual factor. We ran models additionally adjusting for geographic location; and conducted sensitivity analyses lagging the physical activity (METS/week) exposure variable by at least 4 years behind the RA outcome assessment window to account for possible reverse causation (early RA symptoms reducing physical activity). This study was approved by the Mass General Brigham Institutional Review Board.

Results

Among 107,092 women (mean age 43.7 years), we identified 1,219 incident RA cases (776 seropositive and 443 seronegative) in 4,467,751 person-years of follow-up (mean 24.0 years/participant, SD 4.0 years). The baseline characteristics of the pooled study population by HLIS in increasing categories (from least to most healthy) are shown in Table 1. Those with healthier lifestyles were younger, lived in U.S. census tracts with higher median household incomes, and, while more were pre-menopausal, a higher proportion of the postmenopausal women used postmenopausal hormones. The women who dropped out or died during follow-up were similar to those who remained in the study, except that they were on average older (Supplementary Table 1).

Increasing continuous HLIS score was associated with lower risk of RA (hazard ratio [HR] 0.86, 95% confidence interval [CI] 0.82–0.90 per unit increase) overall, and with a lower risk of both seropositive RA (HR 0.85, 95% CI 0.80–0.91) and seronegative RA (HR 0.87, 95% 0.80–0.94) for each unit increase in HLIS (equivalent to each healthy behavior adopted). (Table 2) Women with all five healthy lifestyle factors had the lowest risk of developing all (HR 0.40, 95% CI 0.21–0.76) or seropositive RA (HR 0.24, 95% CI 0.09–0.67), compared to those with no healthy lifestyle factors. The PAR for adhering to four or more healthy lifestyle factors was 34% for overall RA (95%CI 0.20–0.47). PAR for each individual factor ranged from 1% (physical activity) to 17.3% (healthy BMI) (Supplementary Table 2). As predicted, alcohol, smoking, and obesity had the highest individual PARs, and after adjustment for other factors, the AHEI and physical activity had little independent effects on PARs for RA in these cohorts.

Additionally adjusting for geographic location did not change our results (Supplementary Table 3). In sensitivity analyses, results were similar (although with larger CIs given fewer cases) with a longer gap between physical activity exposure assessment and the RA outcome window: multivariable HR associated with increasing HLIS for overall RA was 0.90 (95%CI 0.85–0.95), 0.89 95%CI (0.83–0.96) for seropositive RA, and 0.92 (95%CI 0.84–1.01) for seronegative RA.

Discussion

In these two large prospective cohorts with detailed updated lifestyle data and lengthy follow-up, women with heathier lifestyles had lower risks of developing RA, both seropositive and seronegative, even after adjusting for other potential confounders. For each additional healthy lifestyle behavior, RA risk was decreased by 13%. We found that a large proportion, 34%, of incident RA in these cohorts may have been prevented had all women adhered to a healthy lifestyle (≥ four of the five lifestyle factors).

Although past studies have shown that each of these lifestyle factors has been associated with RA risk(14), examination of the combined effect of these risk factors cumulatively acting on RA risk reveals that despite being at low risk in one category, not smoking for example, there remain opportunities for tailored prevention, in particular for those at high risk by virtue of family history or early symptoms. RA pathogenesis is associated with high levels of systemic inflammation and it is possible, but yet unproven, that these modifiable lifestyle risk factors influence RA development priming or amplify cytokine and chemokine networks(14). These risk factors, smoking, obesity, physical activity, diet and low alcohol intake, have known influences on metabolism and systemic inflammation and may exacerbate the brewing systemic inflammation of RA.

There is a possibility for reverse causation in this study if preclinical RA caused less physical activity or led to an increase in BMI (which is less likely). However, when we lagged physical activity by four years our results did not change, suggesting that this may not be a large concern. The NHS cohorts include mainly White women with some sociodemographic variation given the demographics of the profession at enrollment. A recent cross-sectional study conducted in the National Health Assessment Nutrition Examination Study (NHANES) including men and women reported similar results based on self-report of three lifestyle factors, smoking, overweight/obesity and low alcohol intake(15). In that study, the PAR for RA prevention was 32.7% (95%CI 13.4–51.0) based on absence of these risk factors(15). Studies need to be performed in more diverse cohorts, including ranges of age, sex, race, cultural and socioeconomic backgrounds. There are many reasons why individuals may not have the luxury to eat healthfully, stay at an ideal body weight, or have regular physical activity, and sociological, cultural and institutional barriers to healthy lifestyle (e.g., poverty, racism, lack of education) may compound RA risk. The development of an effective lifestyle-based RA prevention interventions must address these socioeconomic barriers to healthy lifestyle.

Our finding that a high proportion (34%) of RA risk in the general female population is attributable to the confluence of *modifiable* lifestyle factors represents something of a paradigm shift in thinking about RA and autoimmune disease risk. Promotion of multiple healthy behaviors to minimize risk is an important message for the general population and in particular those at risk by virtue of family history.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovation:

- Individual modifiable lifestyle factors, including smoking cigarettes, being overweight or obese, lacking physical activity and following an unhealthy diet high in saturated fats and carbohydrates, have all been associated with increased risk of developing RA in past studies, but here they are examined in a continuing scale, the “Healthy Lifestyle Index Score (HLIS)”.
- Increasingly healthy lifestyle, measured by the HLIS, was associated with incrementally reduced risk of developing RA, overall and both seropositive and seronegative RA. Women with 5 healthy lifestyle factors had lowest risk (HR 0.42, 95% CI 0.22–0.80).
- The population attributable risk for adhering to any ≥ 4 of the 5 lifestyle factors was 34% indicating that a substantial proportion of RA may be preventable by following a healthy lifestyle. This is an important message for the general population and in particular those at risk by virtue of family history.

Table 1.

Baseline Characteristics of the Pooled Nurses' Health Study Cohort Population (N=170,092) by Healthy Lifestyle Index Score (HLIS)

	Categories of Healthy Lifestyle Index Score (HLIS)					
Participant Characteristics	**0 (least healthy)**	**1**	**2**	**3**	**4**	**5 (most healthy)**
Number of participants	11,571	42,017	57,483	40,233	16,314	2,474
Age (years), mean (SD)[a]	46.7 (9.3)	45.3 (9.9)	43.6 (10.1)	42.6 (10.0)	41.3 (9.8)	41.1 (9.6)
U.S. Census median income ($), mean (SD)	41,959 (14,181)	42,858 (14,759)	44,726 (16,160)	46,926 (17,492)	49,030 (18,187)	51,887 (19,343)
Nulliparous	12.6	13.5	14.7	18.5	23.2	29.6
Menopausal Status/Hormone use						
Pre-menopausal	65.4	66.7	67.6	68.1	69	69.3
Post-menopausal/ever used post-menopausal hormones	14.5	14.9	15.5	16.4	16.2	17.9
HLIS Components						
Packyears of smoking, mean (SD)[b]	18.7 (16.4)	18.9 (16.5)	17.6 (15.8)	15.5 (14.3)	14.1 (13.5)	0
Alcohol consumption (grams/day), mean (SD)	4.4 (10.0)	4.4 (9.2)	4.2 (7.6)	4.9 (7.0)	5.6 (5.6)	8.6 (2.6)
BMI (kg/m2), mean (SD)	30.5 (5.2)	27.6 (5.7)	24.6 (4.6)	23.1 (3.3)	22.2 (2.1)	21.8 (1.6)
Physical activity (MET[c]-hours/week), mean (SD)	6.3 (5.1)	9.1 (11.8)	15.2 (19.5)	26.8 (27.6)	38.9 (32.7)	46.6 (37.9)
AHEI[d] score- mean (SD)	37.3 (6.2)	39.7 (8.4)	43.1 (9.8)	48.3 (9.9)	53.0 (8.3)	54.6 (6.5)

SD: standard deviation

[a] value is not age adjusted (all other values in table are age-adjusted).

[b] among smokers only.

[c] MET: Metabolic Equivalent of Task (1 MET= 1 kcal/kg/hour)

[d] AHEI: Alternate Healthy Eating Index, score ranges 0–110

Table 2.

Hazard ratios (95% confidence intervals)[a] for risk of incident RA according to Healthy Lifestyle Index Score among women in Nurses' Health Study (1986–2016) and Nurses' Health Study II (1991–2017)

	Continuous HLIS, per unit increase[d]	Categories of Healthy Lifestyle Index Score (HLIS)[d]					
		0	1	2	3	4	5
All RA							
Cases/person-years	1219/4,446,751	144/380,324	385/1,202,925	376/1,416,374	231/979,526	73/416,408	10/72,196
Age-adjusted model[b]	**0.86[j] (0.82, 0.90)**	1 (Ref.)	0.8 (0.72, 1.06)	**0.75[g] (0.62, 0.91)**	**0.68[i] (0.55, 0.84)**	**0.52[j] (0.39, 0.69)**	**0.4[g] (0.21, 0.76)**
Multivariable model[c]	**0.87[j] (0.83–0.91)**	1 (Ref.)	0.88 (0.73–1.07)	**0.77[g] (0.63–0.93)**	**0.7[i] (0.57–0.87)**	**0.54[i] (0.40–0.72)**	**0.42[g] (0.22–0.80)**
Seropositive RA							
Cases/person-years	776/4,462,003	90/379,665	248/1,201,190	238/1,414,608	146/978,425	50/415,990	4/72,125
Age-adjusted model[b]	**0.85[j] (0.80, 0.91)**	1 (Ref.)	0.89 (0.70, 1.14)	**0.75[f] (0.59, 0.96)**	**0.68[g] (0.52, 0.89)**	**0.55[i] (0.39, 0.78)**	**0.24[g] (0.09, 0.67)**
Multivariable model[c]	**0.86[j] (0.81–0.92)**	1 (Ref.)	0.9 (0.71–1.15)	**0.76[f] (0.60–0.97)**	**0.69[g] (0.53–0.90)**	**0.57[g] (0.40–0.81)**	**0.25[g] (0.09–0.69)**
Seronegative RA							
Cases/person-years	443/4,456,842	54/379,244	137/1,199,687	138/1,412,727	85/977,315	23/415,736	6/72,132
Age-adjusted model[b]	**0.87[j] (0.80, 0.94)**	1 (Ref.)	0.84 (0.61, 1.16)	0.76[e] (0.55, 1.04)	**0.68[f] (0.48, 0.96)**	**0.45[g] (0.28, 0.74)**	0.69 (0.30, 1.61)
Multivariable model[c]	**0.88[g] (0.81–0.96)**	1 (Ref.)	0.85 (0.62–1.17)	0.78 (0.57–1.07)	0.72[e] (0.51–1.01)	**0.49[g] (0.30–0.80)**	0.75 (0.32–1.76)

[a] Hazard ratios calculated using time-varying Cox proportional hazards models.

[b] Age-adjusted model adjusted for age, questionnaire cycle, cohort.

[c] Multivariable model adjusted for age, questionnaire cycle, cohort, census tract median family income (quartiles), parity and breastfeeding (nulliparous, parous/no breastfeeding, parous/1–12 mo breastfeeding, or parous/>12 mo breastfeeding), hormone use (premenopausal, postmenopausal with never use, current use, or past use).

[d] Healthy lifestyle index score (HLIS) as a continuous score from 0 (no low-risk factors) to 5 (all low risk factors), where a higher score reflects a healthier lifestyle. Low risk factors were defined as: never smoking; moderate alcohol consumption (5 – 15g/day); healthy body weight (body mass index 18.5–24.9 kg/m^2); healthy diet (Alternative Healthy Eating Index in top 40th percentile); and healthy level of physical activity (≥19 metabolic equivalent of task [Met]-hours/week).

[e] p<0.10

[f] p<0.05

[g] p<0.01

[h] p=0.001

[i] p<0.001

[j] p<0.0001