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Complete List of Authors:	Harooni, Javad; Yasuj University of Medical Sciences, Department of Public Health, School of Health Pourjavid, Abdollah; Shahid Sadoughi University of Medical Sciences and Health Services, Student Research Committee Amirkhizi , Farshad ; Zabol University of Medical Sciences, Department of Nutrition, School of Public Health Hamedi-Shahraki, Soudabeh; Zabol University of Medical Sciences, Department of Epidemiology and Biostatistics Kiani, Fatemeh; Semnan University of Medical Sciences and Health Services, Student Research Committee Zolghadrpour, Mohammad-Amin; Tehran University of Medical Sciences, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics Monfared, Vahid; Semnan University of Medical Sciences and Health Services, Student Research Committee Asghari, Somayyeh; Tehran University of Medical Sciences, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics Jowshan, Mohammad-Reza; Tehran University of Medical Sciences, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics

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A combined healthy lifestyle score and odds of rheumatoid arthritis: a nested case-control study

Javad Harooni[1], Abdollah Pourjavid[2], Farshad Amirkhizi[3], Soudabeh Hamedi-Shahraki[4], Fatemeh Kiani[5], Mohammad-Amin Zolghadrpour[6], Vahid Monfared[5], Somayyeh Asghari[6]*, Mohammad-Reza Jowshan[6]*

Author's affiliations

[1] Department of Public Health, School of Health, Yasuj University of Medical Sciences, Yasuj, Iran

[2] Student Research Committee, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[3] Department of Nutrition, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran

[4] Department of Epidemiology and Biostatistics, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran

[5] Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran.

[6] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

***Corresponding authors**

Mohammad-Reza Jowshan, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, P.O. Box 14155-6117, Iran. **Email address:** mr-jowshan@alumnus.tums.ac.ir ; mr.jowshan@gmail.com

Somayyeh Asghari, Ph.D., Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran. **Email address:** asghari.nut@gmail.com , sasghari@sina.tums.ac.ir

ORCID

Javad Harooni https://orcid.org/0000-0002-7129-1015
Abdollah Pourjavid https://orcid.org/0009-0004-3084-1959
Farshad Amirkhizi https://orcid.org/0000-0003-1477-0260
Soudabeh-Hamedi-Shahraki https://orcid.org/0000-0003-2270-7421
Fatemeh Kiani https://orcid.org/ 0009-0008-4333-2378
Mohammad-Amin Zolghadrpour https://orcid.org/0000-0002-1856-1338
Somayyeh Asghari https://orcid.org/0000-0002-0501-0115
Mohammad-Reza Jowshan https://orcid.org/0000-0001-8603-5674

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Strengths and limitations of this study

- It is the first study to investigate the relationship between the combined effects of three key healthy lifestyle factors, as represented by Combined Healthy Lifestyle Score (CHLS), and the odds of rheumatoid arthritis.
- The study utilized a large, nationally representative database with standardized data collection protocols, which minimizes potential biases.
- One of the limitations is that the case-control design limits our ability to establish causal relationships, and we did not evaluate stress and alcohol consumption as additional lifestyle factors in this study.

Abstract

Objectives: Lifestyle factors significantly contribute to the development of chronic diseases. While researchers have investigated individual lifestyle components, the combined impact of multiple lifestyle factors on rheumatoid arthritis (RA) remains unclear. This study examined the association between a Combined Healthy Lifestyle Score (CHLS) and the odds of developing RA among Iranian adults.

Methods: In this nested case-control study from the Dena PERSIAN cohort (PDCS), we included 130 RA cases and 260 matched controls. CHLS scores were calculated using three parameters: smoking status, physical activity level, and dietary quality, as assessed by the Healthy Eating Index (HEI-2020). The scores ranged from 0 (least healthy) to 3 (most healthy). Multiple logistic regression was employed to evaluate the association between CHLS and the odds of developing RA.

Results: Participants with higher CHLS presented significantly lower body mass index (BMI) (22.6 ± 2.0 vs. 31.0 ± 3.2 kg/m²) and waist circumference (88.6 ± 9.1 vs. 103.3 ± 8.7 cm) compared to those with lower scores. Furthermore, higher CHLS was associated with increased consumption of fruits, vegetables, and whole grains ($p < 0.001$). Individuals with the highest CHLS had 50% lower odds of RA compared to those with the lowest scores (adjusted OR: 0.5; 95% CI: 0.3-0.8, p-trend = 0.009), after adjusting for potential confounders.

Conclusion: Our findings suggest that adherence to a healthy lifestyle characterized by non-smoking, regular physical activity, and healthy dietary patterns is associated with reduced odds of RA in Iranian adults. The results from this study highlight the potential importance of combinations of lifestyle modifications for the prevention of RA.

Keywords: Rheumatoid arthritis, Lifestyle factors, Combined Healthy lifestyle, Persian cohort

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by widespread inflammation, particularly affecting the joints and surrounding soft tissues [1]. This condition manifests symptoms such as joint swelling, redness, pain, stiffness, and general fatigue, significantly impairing the quality of life [1]. Progressive disability may occur as a result of this condition, along with potential cardiovascular complications and other related health issues, as documented in various studies [1 2]. RA is estimated to affect between 0.5% and 1.0% of the global population, with peak onset typically occurring between 30 and 55 years of age [3]. Women are disproportionately affected by the condition, being two to three times more likely to develop it than men [4]. The disease not only leads to chronic health issues for individuals but also imposes significant socioeconomic burdens. Literature indicates that up to 20-30% of patients may become permanently disabled within the first three years of diagnosis [1]. Recent epidemiological data also suggest that the prevalence of the disease is higher in Western industrialized countries compared to Eastern and developing nations [5].

RA pathogenesis is considered a complex interaction between genetic, epigenetic, and environmental factors, many of which remain incompletely understood [6]. However, recent epidemiological studies have highlighted the significant roles of environmental factors, microbiota, infectious agents, sex hormones, and lifestyle in the development of the disease [4 7]. As with other chronic diseases, modifiable lifestyle factors such as obesity, smoking, physical inactivity, and unhealthy dietary patterns significantly influence the development and progression of RA [8]. Several studies suggest that, when combined, these factors may have a greater impact than when considered individually [8]. The Combined Healthy Lifestyle Score (CHLS) is derived from five modifiable lifestyle factors: smoking, alcohol consumption, body mass index (BMI), physical activity, and diet. These factors significantly influence not only the development of diseases but also their prognosis [9,10].

In recent years, extensive research has highlighted the central role of diet in assessing disease risk and development [5]. Certain nutrients, such as polyunsaturated fatty acids, may function as anti-inflammatory agents and antioxidants, potentially preventing the onset of RA, substances like salt and red meat can negatively impact the development and progression of RA through indirect mechanisms, such as altering gut microbiota and body composition [11]. The Mediterranean diet is considered one of the most promising dietary approaches [11]. Studies have demonstrated its ability to modulate inflammatory pathways and improve disease outcomes [11]. Additionally, adequate vitamin D levels have been linked to better disease management and reduced inflammation in patients with RA [12]. Furthermore, prebiotics, probiotics, and synbiotics may also exert beneficial effects on RA [13].

It is well-supported by substantial evidence that exercise is highly effective in treating RA in all clinical domains [2]. Certain physical activities function as a non-pharmacological treatment strategy due to their numerous benefits, including enhanced muscle mass, strength, and overall efficiency, particularly in patients with RA [14]. During exercise, skeletal muscles release myokines, which exert direct anti-inflammatory effects with each activity [14]. Regular physical activity has been demonstrated to reduce disease activity scores, improve joint function, and promote a better quality of life among patients with RA [15]. Additionally, research indicates that obesity is associated with increased arthritis activity, exacerbating patients' conditions, as evidenced by increased chronic pain and elevated inflammatory markers. Conversely, weight reduction has been shown to improve treatment outcomes [16,17].

Limited data exist regarding the cumulative impact of unhealthy lifestyle factors in individuals with RA [18]. While several studies have assessed individual lifestyle factors, the combined effect of multiple lifestyle components on the odds of developing RA remains poorly understood [9]. Recent studies on various chronic diseases have indicated that the combined impact of lifestyle factors may be more significant than the effects of individual factors [19]. Additionally, preventive measures for rheumatic diseases should be implemented before individuals enter older age groups, emphasizing the importance of maintaining a healthy lifestyle [14]. Therefore, this study aims to investigate the significance of a CHLS in relation to RA among Iranian adults participating in the PERSIAN Dena Cohort Study (PDCS).

Material and methods

Participants

Data from the PDCS was used to conduct this case-control study [20]. To determine the contributing factors to non-communicable diseases in Iran, researchers have been conducting the PERSIAN Cohort Study since 2018, using the Dena PERSIAN cohort as a subcohort. The Dena cohort includes all individuals residing in Dena County (Sisakht region) near the city of Yasuj, aged between 35 and 70, excluding those unable to participate in interviews due to physical or mental health issues. The RA status of the participants (yes or no) was determined based on the results of biochemical tests and consultations with a rheumatologist. Additional information regarding the study design, participants, and data collection methods has been published previously [20]. Participants with reported daily energy intakes below 800 kcal/day or above 4500 kcal/day were excluded from the study.

Anthropometric and physical activity assessment

The demographic data that was collected included age, sex, educational background, and marital status. BMI was calculated by dividing the weight in kilograms by the square of height in meters, and obesity was defined as BMI ≥ 30 kg/m^2. Data were collected on lifestyle factors, including supplement usage and smoking, through the use of questionnaires. Smoking was defined as having smoked at least 100 cigarettes in a lifetime. Supplement usage was defined as taking calcium and vitamin D supplements at least once a week for a minimum of six months. The Metabolic Equivalent of Task (MET Index)—a measure of the intensity of physical activities—was calculated to assess the level of physical activity among the participants. A daily activity questionnaire was utilized to measure the MET for all individuals' activities over a 24-hour period.

Dietary assessment

In this study, a validated 113-item Food Frequency Questionnaire (FFQ) and an additional 127-item FFQ specifically designed to include indigenous foods were used (24). Participants reported the frequency and portion sizes of food items consumed on a daily, weekly, monthly, and annual basis over the past year. All portion sizes and household quantities were converted to grams per day. The software Nutritionist IV (Version 7.0) was then employed to calculate the energy and nutrient content of the foods.

Assessment of combined healthy lifestyle score

Three lifestyle factors were used to determine the CHLS for individuals: smoking, diet quality, and physical activity. The following criteria were employed to categorize individuals into two groups for the purpose of measuring CHLS: current smokers versus non-smokers, and those who are physically inactive/sedentary (< 22.5 metabolic equivalent hours per week (MET/h/w)) vs. versus those who are active (≥ 22.5 MET/h/w). The Healthy Eating Index (HEI)-2020 diet score is used to evaluate the quality of individuals' diets. A maximum score of 100 points can be attained through the 13 components of HEI-2020, which consist of 4 moderation components and 9 adequacy components. The adequacy components—dairy, whole grains, and fatty acids—received scores of 10 and 0, respectively, indicating the highest and lowest levels of intake. For the other six adequacy components, the lowest and highest intakes were 0 and 5, respectively, for total fruits (including fruit, fruit juice, and canned fruit), whole fruits (excluding fruit juice), total vegetables, greens and beans, total protein foods, seafood, and plant proteins. Four moderation components—salt, refined grains, saturated fats, and added sugars—were assigned a maximum of 10 points for the lowest levels of consumption [21]. However, the highest intake of these components was scored as 0. Finally, participants were categorized into quintiles according to their HEI-2020 scores. Individuals in the upper two quintiles were assigned a score of 1 to indicate a higher level of adherence to a healthy diet [21]. The following characteristics were also assigned a score of 1: non-current smoking status, physical activity (≥ 22.5 MET/h/w), and placement in the upper two quintiles of the Alternative Healthy Eating Index 2020 (AHEI-2020) score. To calculate the overall HLS, we summed the participants' scores across each lifestyle component. The scores range from 0 (indicating the lowest adherence to HLS) to 3 (indicating the highest adherence to HLS) [22].

Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics version 25. Statistical significance was determined by P-values of less than 0.05. Qualitative variables were expressed as percentages, while quantitative variables were reported as mean ± standard deviation (SD). The dietary intakes and general characteristics of the patients and controls were evaluated using the chi-square test for categorical variables and the independent samples t-test for continuous data. Additionally, one-way analysis of variance (ANOVA) was employed to analyze continuous variables, while chi-square tests were used for categorical variables to assess the general characteristics of study participants across the categories of the CHLS. Dietary intakes of study participants across categories of the CHLS were examined using analysis of covariance (ANCOVA), adjusting for age and sex in relation to energy intake, and further adjusting for age, sex, and energy intake for all other variables. The association between the combined healthy lifestyle score and the odds of RA was evaluated using conditional logistic regression models. In the second model, adjustments were made for age, sex, physical activity level, cigarette smoking, vitamin D intake, and calcium supplement use.

Results

The total number of participants who entered the study was 390. Table 1 compares the general characteristics of participants between rheumatoid arthritis (RA) cases (n = 130) and controls (n = 260), as well as across different categories of the combined healthy lifestyle score, which ranges from 0 to 3. There was no significant difference in female representation across lifestyle score categories (p=0.409), and the proportion of females was similar between cases and controls (77.7% vs. 76.9%, p=0.865). The mean BMI of RA cases was significantly higher compared to controls (28.1 ± 5.2 vs. 26.8 ± 4.7 kg/m², p=0.014). Additionally, obesity (BMI ≥ 30 kg/m²) was more prevalent among individuals with RA (33.8% vs. 23.1%, p = 0.023). In terms of healthy lifestyle scores, participants with a score of 0 exhibited the highest mean BMI (31.0 ± 3.2 kg/m²), while those with a score of 3 had the lowest mean BMI (22.6 ± 2.0 kg/m², p < 0.001). Similarly, the prevalence of obesity was significantly lower among participants with a score of 3 (0%) compared to those with a score of 0 (61.9%, p < 0.001). Additionally, higher waist circumference and weight were significantly associated with lower healthy lifestyle scores (p < 0.001 for both). Participants with a lifestyle score of 0 exhibited the highest waist circumference (103.3 ± 8.7 cm), whereas those with a score of 3 demonstrated the lowest waist circumference (88.6 ± 9.1 cm, p < 0.001). In this study, the difference between cases and controls was not statistically significant (97.5 ± 12.8 cm vs. 95.7 ± 10.8 cm, p = 0.141). Physical activity levels were positively associated with healthy lifestyle scores, increasing from 34.8 MET-h/day in individuals with a score of 0 to 42.4

MET-h/day in those with a score of 3 ($p < 0.001$). No significant difference in physical activity was observed between RA cases and controls ($p = 0.088$).

Table 2 highlights the dietary intake of selected nutrients and food groups among RA cases, controls, and categories based on healthy lifestyle scores. Regarding energy and macronutrients, although energy intake did not differ significantly between cases and controls ($p = 0.191$), participants with a higher healthy lifestyle score consumed significantly more calories ($p = 0.003$). Higher scores were also associated with a greater intake of carbohydrates ($p = 0.005$), protein ($p < 0.001$), and fat ($p = 0.007$). Significant differences were observed in the intake of several micronutrients across lifestyle scores. Participants with a score of 3 consumed significantly more vitamin A (851 ± 49 μg/day), vitamin C (181 ± 10 mg/day), vitamin E (9.7 ± 0.6 mg/day), and magnesium (387 ± 15 mg/day) compared to those with a score of 0 ($p < 0.001$ for all). No significant differences were observed between cases and controls for these nutrients, with the exception of vitamin B6, which was found to be higher in RA cases ($p = 0.030$). Additionally, participants with higher healthy lifestyle scores consumed significantly more fruits (763 ± 57 g/day for score 3 vs. 323 ± 29 g/day for score 0, $p < 0.001$), vegetables ($p = 0.027$), and whole grains ($p = 0.017$). Conversely, refined grain intake was higher among participants with lower scores ($p < 0.001$). Most food groups did not show significant differences between cases and controls, except for vegetable intake, which was higher in controls ($p = 0.027$).

Figure 1 illustrates the crude and multivariable-adjusted odds ratios (ORs) for the risk of developing RA based on the CLHS. In the crude model, participants with a CLHS of 3 (the healthiest category) had significantly lower odds of developing RA compared to those with a CHLS score of 0 (OR = 0.5, 95% CI: 0.3–0.9, p-trend = 0.004). This suggests that healthier lifestyle choices may have a protective effect against the odds of RA. After adjusting for potential confounders, including age, sex, physical activity, smoking, and the use of vitamin D and calcium supplements, the association remained significant (OR = 0.5, 95% CI: 0.3–0.8, p-trend = 0.009). This further supports the associations between a combined healthy lifestyle and reduced odds of RA.

Discussion

Our study, a nested case-control investigation, found a significant inverse relationship between combined healthy lifestyle scores (CHLS) and the likelihood of rheumatoid arthritis in Iranian adults, even after adjusting for confounders. Specifically, individuals with the highest CHLS showed a 50% reduced risk of RA compared to those with the lowest scores.

RA pathogenesis is multifaceted, involving genetic predispositions and environmental triggers, as well as their interactions, which play a crucial role in determining susceptibility to RA [3]. Despite the strong role of genetics, numerous studies have primarily focused on single lifestyle factors, such as diet, physical activity, and body mass index (BMI), in relation to RA risk. However, given the interconnectivity of these lifestyle factors, considering them collectively provides a more holistic understanding of their influence on RA risk [10 23]. In past studies, comprehensive lifestyle indices like the Healthy Lifestyle Index Score (HLIS) from the Nurses' Health Study (NHS) have shown that maintaining multiple healthy lifestyle habits can reduce RA risk, especially in cases of seropositive RA. A recent cross-sectional study involving 17,532 adult Americans from the NHANES cohort showed that the Life's Simple 7 (LS7) score—developed according to the American Heart Association (AHA) guidelines to evaluate the cumulative effects of lifestyle risk factors for cardiovascular disease (CVD) through seven indicators: blood pressure, total cholesterol, HbA1c, smoking, BMI, physical activity, and diet exhibits a negative association with

RA [19 24]. Our study expands on this by focusing on a synergy between healthy diet, BMI, and physical activity as a unified lifestyle score (HLS) and its connection to RA risk.

In terms of diet, the beneficial health effects of healthy dietary patterns have been established in relation to many chronic diseases, often by modulating levels of systemic inflammation [25 26]. The role of diet in RA risk is well-supported, particularly through its influence on systemic inflammation. Anti-inflammatory diets, like the AHEI-2010 and the Mediterranean diet, have demonstrated protective effects against RA. While some studies associate Mediterranean diet adherence with pain relief in RA patients, its role in preventing RA remains inconclusive [11 23]. The Nurses' Health Study (NHS), which tracked over 150,000 women and documented more than 1,000 new RA cases, found that sustained healthy eating habits were moderately linked to a lower RA risk, especially for women under 55 years [27]. The study used the AHEI-2010 to evaluate dietary quality, with healthy foods—such as fruits, vegetables, whole grains, nuts, long-chain fats, and polyunsaturated fatty acids (PUFAs), as well as moderate alcohol use—associated with a reduced risk of chronic diseases. In contrast, higher risk was linked to consuming sugar-sweetened drinks, red and processed meats, trans fats, and foods high in sodium [11]. Notably, in our study, we used the HEI-2020 to measure the nutritional quality of the diet, whereas the NHS study employed the AHEI-2010 version, which has minor differences in the scoring of dietary items. Additionally, several investigations have focused on the potential anti-inflammatory benefits of the Mediterranean Diet—characterized by its abundance of fruits, vegetables, nuts, legumes, low-fat dairy, seafood, whole grains, and fiber, as well as its high content of antioxidant nutrients and low levels of red and processed meat, animal fat, sweets, and desserts—on the risk of RA [28]. A systematic review assessed how the Mediterranean Diet influences both the prevention and symptom management of RA in prospective studies involving humans. While findings suggested that the Mediterranean Diet might help reduce pain and symptoms for individuals already diagnosed with RA, the evidence was not strong enough to confirm its role in preventing RA development [28]. Another population-based case-control study involving more than 5,000 participants demonstrated a significant reduction in the risk of seropositive RA among individuals with strong adherence to the Mediterranean diet; however, this effect was observed exclusively in male participants [29]. These findings suggest that a generally healthy diet, as part of a healthy lifestyle, may contribute to reduced odds of RA.

Previous research has suggested various biological mechanisms by which excess body weight could affect RA risk. Obesity is known to be an inflammatory state, marked by increased levels of pro-inflammatory cytokines released by fat cells, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), both of which are linked to RA development [29 30]. On the other hand, obesity is linked to relatively higher estrogen levels. Since RA is more common among females, this increase in estrogen might play a role in the disease's development and prevalence among women [31]. A systematic review encompassing 11 studies explored the relationship between BMI and RA risk, finding that obesity is notably associated with a higher RA risk compared to those without obesity [32]. Similarly, a later meta-analysis, which included 400,609 participants and identified 13,562 RA cases, found that obesity correlated with a relative risk (RR) of 1.21 for RA when compared to individuals with normal BMI. Additionally, for every five kg/m^2 increase in BMI, the RA risk rose by 13% [33]. However, these studies primarily examined BMI as a fixed category and did not assess the effects of weight or BMI fluctuations over time on RA risk.

Physical activity may contribute to the pathogenesis of RA through several mechanisms [34]. These include energy consumption, the secretion of myokines (such as IL-6, IL-8, and IL-15), modulation of T helper 1/T helper 2 (Th1/Th2) cell levels, increased levels of natural killer (NK) cells, and the secretion of epinephrine and norepinephrine during exercise [35-37]. Together, these effects tend to reduce systemic inflammation, providing a rationale for the idea that physical activity may protect against RA. Findings from the Swedish Mammography Cohort, which studied 30,112 women aged 54 to 89 years and identified 201 new RA cases, indicated that women who engaged in higher levels of physical activity (over 20 minutes of walking or bicycling daily and more than 1 hour of exercise weekly) had a significantly reduced risk of developing RA compared to those in the lowest physical activity category [38]. Similarly, another prospective cohort study investigated the relationship between recreational physical activity and the risk of RA among women participating in the Nurses' Health Study II. This study utilized repeated measures of physical activity over 26 years and included 113,366 women, identifying 506 new cases of RA. The research focused on the correlation between levels of recreational physical activity and the risk of developing RA. The results indicated that a higher cumulative number of hours spent on recreational physical activities was associated with a significantly lower risk of developing rheumatoid arthritis compared to lower levels of physical activity. These findings underscore the potential protective effects of regular physical activity against the onset of RA [39]. Additionally, A recent meta-analysis, comprising four studies with a total of 255,365 women and 4,213 incident RA cases, identified an inverse relationship between physical activity and RA development. Notably, one study within the meta-analysis reported the progression of joint damage in large joints among individuals with existing extensive joint deterioration when engaging in high-intensity weight-bearing exercises [40]. However, all studies and meta-analyses regard resistance exercise as safe and beneficial for patients with RA [41-43]. Consequently, the European League Against Rheumatism (EULAR) recommends not only aerobic exercise but also specific muscle-strengthening exercises for patients with RA [15].

The present study has several strengths. First, to the best of our knowledge, it is the first study to investigate the relationship between the combined effects of three key healthy lifestyle factors, as represented by HLS, and the odds of RA. Second, the study utilized a large, nationally representative database with standardized data collection protocols, which minimizes potential biases. All data were collected by expert and trained interviewers using reliable and valid questionnaires. Third, the nested case-control design of this study represents a significant strength compared to cross-sectional or traditional case-control designs. A nested case-control analysis offers superior computational efficiency for producing an odds ratio while minimizing selection bias and recall bias. However, this study also has certain limitations. First, the cross-sectional nature of the data suggests that there may be insufficient evidence to infer causality. Second, because this study is observational, other potential confounding factors and biases could not be fully controlled. Also, although the study adjusted for covariates, unmeasured confounding factors may still be present. Additionally, lifestyle factors were assessed only during the baseline phase of the PDCS, whereas each participant's lifestyle is subject to dynamic changes over time. Fourth, although expert and trained interviewers, as well as validated questionnaires, were employed for dietary and physical activity assessments, some measurement errors are inevitable. Fifth, due to the incompleteness of the Iranian Food Composition Table (FCT), the USDA FCT was used for dietary analyses, which may lead to minor measurement errors in the calculations of macro- and micronutrient intake. Finally, we did not consider stress, smoking, and alcohol consumption as additional lifestyle factors in this study, despite their association with RA in some studies [10 23]. It is important to acknowledge that the findings of this study may not be generalizable beyond this sample of adults. Future research should aim to address these limitations.

Conclusion

In conclusion, the results of our population-based nested case-control study indicated that subjects with a higher CHLS have significantly lower odds of developing RA, even after adjusting for potential confounders. This finding suggests a negative association between the healthy lifestyle behaviors represented by the CHLS and the incidence of RA. However, further prospective studies with long-term follow-up are needed to verify the causal relationship indicated by these results.

List of Abbreviations

AHEI: Alternative Healthy Eating Index

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

BMI: Body Mass Index

CI: Confidence Interval

CVD: Cardiovascular Disease

EULAR: European League Against Rheumatism

FCT: Food Composition Table

FFQ: Food Frequency Questionnaire

HEI: Healthy Eating Index

CHLS: Combined Healthy Lifestyle Score

HR: Hazard Ratio

IL: Interleukin

MET: Metabolic Equivalent of Task

NHS: Nurses' Health Study

NK: Natural Killer

OR: Odds Ratio

PDCS: PERSIAN Dena Cohort Study

PERSIAN: Prospective Epidemiological Research Studies in IrAN

PUFA: Polyunsaturated Fatty Acid

RA: Rheumatoid Arthritis

RR: Relative Risk

SD: Standard Deviation

SPSS: Statistical Package for the Social Sciences

TNF-α: Tumor Necrosis Factor-alpha

USDA: United States Department of Agriculture

Authorship Contributions

Conception and Design: F.A, J.H, M.J., S.H.S Acquisition of Data: S.A. Analysis and Interpretation of Data: S.H.S, F.A, J.H. Drafting the Manuscript: A.P, M.Z, F.K, V.M, M.J. Revising Manuscript for Intellectual Content: M.J, S.A., F.A. All authors read and approved the final manuscript.

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Data Availability Statement

On reasonable request, the corresponding author will provide the datasets used and analyzed during the current work. Correspondence and requests for materials should be addressed to M.J.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

The aims of the study were explained in detail, and written informed consent was obtained from all participants [20]. The study was approved by the Ethics Committee of Yasuj University of Medical Sciences (ethics code: IR.YUMS.REC.1401.175).

Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. General characteristics of participants by cases and controls as well as different categories of the combined healthy lifestyle score[a]

Variables	Groups		P^b	Combined healthy lifestyle score				P^c
	Cases (n= 130)	Controls (n= 260)		0 (n=42)	1 (n=167)	2 (n=103)	3 (n=78)	
Females, n (%)	101 (77.7)	200 (76.9)	0.865	35 (83.3)	124 (74.3)	78 (75.7)	64 (82.1)	0.409
Age (year)	49.8 ± 9.7	50.6 ± 9.3	0.484	50.0 ± 10.8	50.8 ± 9.5	51.3 ± 8.9	48.2 ± 9.1	0.145
Weight (kg)	72.4 ± 13.1	70.2 ± 12.8	0.110	78.7 ± 9.5	73.3 ± 12.8	70.9 ± 13.4	61.9 ± 8.8	<0.001
Waist circumference (cm)	97.5 ± 12.8	95.7 ± 10.8	0.141	103.3 ± 8.7	98.6 ± 10.9	95.6 ± 11.9	88.6 ± 9.1	<0.001
BMI (kg/m$^{2)}$	28.1 ± 5.2	26.8 ± 4.7	0.014	31.0 ± 3.2	28.4 ± 4.6	27.2 ± 5.1	22.6 ± 2.0	<0.001
Obesity, n (%)[d]	44 (33.8)	60 (23.1)	0.023	26 (61.9)	49 (29.3)	29 (28.2)	0 (0.0)	<0.001
Educational level, n (%)								
University	8 (6.2)	37 (14.2)	0.019	1 (2.4)	10 (6.0)	22 (21.4)	12 (15.4)	<0.001
Un university	122 (93.8)	223 (85.8)		41 (97.6)	157 (94.0)	81 (78.6)	66 (84.6)	
Marital status, n (%)								
Married	115 (88.5)	229 (88.1)	0.912	30 (71.4)	141 (84.4)	98 (95.1)	75 (96.2)	<0.001
Unmarried/divorced/widowed	15 (11.5)	31 (11.9)		12 (28.6)	26 (15.6)	5 (4.9)	3 (3.8)	
Vitamin D supplement use, n (%)	53 (40.8)	95 (36.5)	0.417	14 (33.3)	54 (32.3)	42 (40.8)	38 (48.7)	0.078
Calcium supplement use, n (%)	27 (20.8)	30 (11.5)	0.015	5 (11.9)	21 (12.6)	21 (20.4)	10 (12.8)	0.289
Physical activity (MET-h per day)	39.3 ± 6.1	40.3 ± 4.5	0.088	34.8 ± 2.5	39.4 ± 4.1	41.1 ± 5.6	42.4 ± 5.0	<0.001
Current smoker, n (%)	18 (13.8)	34 (13.1)	0.833	5 (11.9)	24 (14.4)	16 (15.5)	7 (9.0)	0.584

Abbreviations: BMI, body mass index
[a] All data are reported as means ± standard deviations unless indicated.
[b] Determined using the independent sample t-test or chi-square test, where appropriate.
[c] Determined using the one-way ANOVA test or chi-square test, where appropriate.
[d] Obesity was defined as BMI ≥ 30 kg/m^2
P< 0.05 was considered as statistically significant.

Table 2. Dietary intakes of selected nutrients and food groups of participants by cases and controls as well as different categories of the combined healthy lifestyle score[a]

Variables	Groups		P^b	Combined healthy lifestyle score				P^c
	Cases (n= 130)	Controls (n= 260)		0 (n=42)	1 (n=167)	2 (n=103)	3 (n=78)	
Energy (kcal/d)[d]	2380 ± 62	2486 ± 48	0.191	2165 ± 88	2379 ± 58	2630 ± 77	2521 ± 87	0.003
Nutrients								
Carbohydrate (g/d)	383 ± 10	407 ± 8	0.077	348 ± 15	390 ± 10	426 ± 13	411 ± 15	0.005
Protein (g/d)	75 ± 4.1	78 ± 1.7	0.375	65.6 ± 3.0	72.9 ± 2.0	83.9 ± 2.7	82.5 ± 3.1	< 0.001
Fat (g/d)	66.7 ± 2.0	66.5 ± 1.6	0.934	60.4 ± 3.3	63.3 ± 1.8	72.7 ± 2.7	69.0 ± 2.9	0.007
Saturated fat (g/d)	25.3 ± 1.0	23.9 ± 0.7	0.224	22.4 ± 1.7	25.0 ± 0.8	24.7 ± 1.0	23.9 ± 1.2	0.566
Trans fatty acids (g/d)	0.23 ± 0.02	0.26 ± 0.02	0.397	0.23 ± 0.04	0.23 ± 0.02	0.32 ± 0.03	0.22 ± 0.03	0.023
Vitamin A (RAE/d)	748 ± 57	710 ± 26	0.490	485 ± 31	634 ± 42	868 ± 51	851 ± 49	< 0.001
Vitamin C (mg/d)	130 ± 7	141 ± 6	0.247	90 ± 6	118 ± 8	155 ± 9	181 ± 10	< 0.001
Vitamin E (mg/d)	7.8 ± 0.3	8.2 ± 0.3	0.341	6.1 ± 0.4	7.0 ± 0.3	9.0 ± 0.4	9.7 ± 0.6	< 0.001
Folate (mcg/d)	546 ± 15	580 ± 13	0.109	502 ± 21	562 ± 16	604 ± 21	571 ± 21	0.048
Vitamin B_6 (mg/d)	13.7 ± 0.8	11.8 ± 0.4	0. 030	11.0 ± 1.0	11.7 ± 0.6	12.8 ± 0.8	14.2 ± 0.9	0.059
Zinc (mg/d)	9.2 ± 0.3	9.4 ± 0.2	0.640	7.8 ± 0.0	8.7 ± 0.3	10.3 ± 0.3	10.3 ± 0.4	< 0.001
Selenium (mg/d)	99 ± 4	104 ± 3	0.218	92 ± 5	101 ± 3	110 ± 4	100 ± 5	0.084
Magnesium (mg/d)	335 ± 10	345 ± 8	0.468	277 ± 10	316 ± 9	376 ± 12	387 ± 15	< 0.001
Food groups								
Whole grains (g/d)	30.5 ± 5.4	24.4 ± 4.8	0.441	12.1 ± 2.7	17.8 ± 2.2	43.8 ± 12.5	29.8 ± 6.0	0.0.017
Refined grains (g/d)	515 ± 19	524 ± 14	0.689	442 ± 21	479 ± 19	579 ± 17	546± 29	< 0.001
Fruits (g/d)	551 ± 35	558 ± 24	0.863	323 ± 29	475 ± 24	621 ± 35	763 ± 57	< 0.001
Vegetables (g/d)	479 ± 17	546± 26	0.027	492 ± 45	489 ± 23	504 ± 29	528 ± 26	0.773
Legumes and nuts (g/d)	73.9 ± 4.0	67.4 ± 2.5	0.152	61.5 ± 6.5	65.3 ± 3.3	74.3 ± 4.2	76.5 ± 4.3	0.088
Meats (g/d)	145 ± 7	136 ± 4	0.287	130 ± 11	133 ± 5	148 ± 7	144 ± 7	0.328
Dairy products (g/d)	353 ± 24	304 ± 15	0.081	290 ± 48	328 ± 22	311 ± 21	333 ± 24	0.787
Sugar-sweetened beverages (g/d)	125 ± 10	134 ± 9	0.585	131 ± 27	136 ± 9	143 ± 18	104 ± 13	0.308

[a] All data are reported as means ± S.E. unless indicated.
[b] Determined using the independent samples *t*-test
[c] Determined using the ANCOVA test
[d] Energy intake is adjusted for age and sex, all other values are adjusted for age, sex, and energy intake.
P< 0.05 was considered as statistically significant.

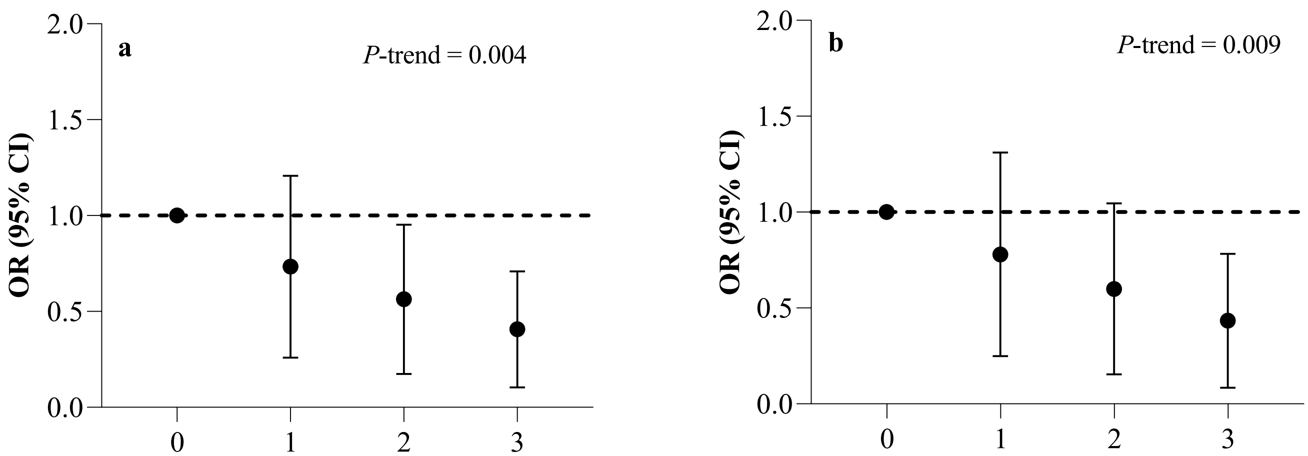
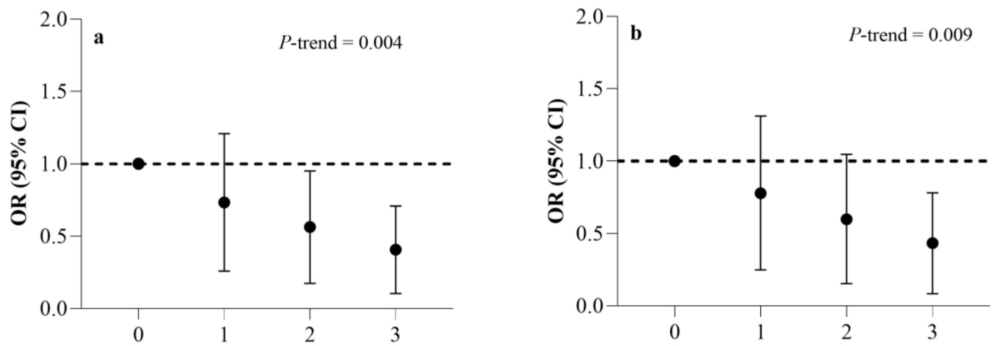


Figure 1. Crude and multivariable-adjusted ORs with 95% CIs for the odds of rheumatoid arthritis across the different categories of the combined healthy lifestyle score (n=390). **(a)** Crude model; **(b)** Adjusted for age (continuous), sex (male/female), physical activity level (continuous), cigarette smoking (smoker/ nonsmoker), vitamin D and calcium supplements use (yes/ no). *P*-trend values were determined by the Mantel-Hanszel extension χ^2 test.



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1 # A combined healthy lifestyle score and odds of rheumatoid arthritis: a nested
2 case-control study

Javad Harooni[1], Abdollah Pourjavid[2], Farshad Amirkhizi[3], Soudabeh Hamedi-Shahraki[4], Fatemeh Kiani[5], Mohammad-Amin Zolghadrpour[6], Vahid Monfared[5], Somayyeh Asghari[6]*, Mohammad-Reza Jowshan[6]*

Author's affiliations

[1] Department of Public Health, School of Health, Yasuj University of Medical Sciences, Yasuj, Iran

[2] Student Research Committee, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[3] Department of Nutrition, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran

[4] Department of Epidemiology and Biostatistics, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran

[5] Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran.

[6] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

***Corresponding authors**

Mohammad-Reza Jowshan, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, P.O. Box 14155-6117, Iran. **Email address:** mr-jowshan@alumnus.tums.ac.ir ; mr.jowshan@gmail.com

Somayyeh Asghari, Ph.D., Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran. **Email address:** asghari.nut@gmail.com , sasghari@sina.tums.ac.ir

ORCID

Javad Harooni https://orcid.org/0000-0002-7129-1015
Abdollah Pourjavid https://orcid.org/0009-0004-3084-1959
Farshad Amirkhizi https://orcid.org/0000-0003-1477-0260
Soudabeh-Hamedi-Shahraki https://orcid.org/0000-0003-2270-7421
Fatemeh Kiani https://orcid.org/ 0009-0008-4333-2378
Mohammad-Amin Zolghadrpour https://orcid.org/0000-0002-1856-1338
Somayyeh Asghari https://orcid.org/0000-0002-0501-0115
Mohammad-Reza Jowshan https://orcid.org/0000-0001-8603-5674

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Strengths and limitations of this study

- It is the first study to investigate the relationship between the combined effects of four key healthy lifestyle factors, as represented by Combined Healthy Lifestyle Score (CHLS), and the odds of rheumatoid arthritis.
- The study utilized a large, nationally representative database with standardized data collection protocols, which minimizes potential biases.
- One of the limitations is that the case-control design limits our ability to establish causal relationships, and we did not evaluate stress and alcohol consumption as additional lifestyle factors in this study.

Abstract

Objectives: Lifestyle factors play a significant role in the development of chronic diseases. While researchers have extensively studied individual lifestyle components, the combined impact of multiple lifestyle factors on rheumatoid arthritis (RA) remains unclear. This study aimed to explore the association between a Combined Healthy Lifestyle Score (CHLS) and the odds of developing RA among Iranian adults.

Methods: In this nested case-control study, conducted as part of the Dena PERSIAN cohort (PDCS), we included 130 RA cases and 260 matched controls. The CHLS score was calculated based on four parameters: smoking status, physical activity level, body mass index (BMI), and dietary quality, as assessed by the Healthy Eating Index (HEI-2020). Scores ranged from 0 (representing the unhealthiest lifestyle) to 4 (representing the healthiest lifestyle). Multiple logistic regression analysis was used to evaluate the association between CHLS and the odds of developing RA.

Results: Participants with higher CHLS exhibited significantly lower body mass index (BMI) and waist circumference compared to those with lower scores. Additionally, higher CHLS was associated with greater consumption of fruits and whole grains ($p < 0.05$). Individuals with the highest CHLS had 90% lower odds of developing RA compared to those with the lowest scores (OR: 0.105; 95% CI: 0.024–0.461, *p*-trend = 0.001), after adjusting for potential confounders.

Conclusion: Our findings suggest that adherence to a healthy lifestyle—characterized by non-smoking, regular physical activity, maintaining a normal BMI, and following a healthy dietary pattern—is associated with a reduced odds of developing RA among Iranian adults. The results of this study underscore the potential importance of combined lifestyle modifications in the

prevention of RA. These insights emphasize the value of promoting comprehensive lifestyle changes as a strategy to mitigate RA risk.

Keywords: Rheumatoid arthritis, Lifestyle factors, Combined Healthy lifestyle, Persian cohort

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by widespread inflammation, particularly affecting the joints and surrounding soft tissues [1]. This condition manifests symptoms such as joint swelling, redness, pain, stiffness, and general fatigue, significantly impairing the quality of life [1]. Progressive disability may occur as a result of this condition, along with potential cardiovascular complications and other related health issues, as documented in various studies [1 2]. RA is estimated to affect between 0.5% and 1.0% of the global population, with peak onset typically occurring between 30 and 55 years of age. [3] Women are disproportionately affected by the condition, being 2-3 times more likely to develop it than men [4]. The disease not only leads to chronic health issues for individuals but also imposes significant socioeconomic burdens, affecting both personal quality of life and healthcare systems. Recent data shows annual healthcare costs are $3,383 higher in RA patients compared to non-RA individuals, with medication costs reaching up to $36,000 annually [5]. Literature indicates that up to 20-30% of patients may become permanently disabled within the first 3 years of diagnosis [1]. Recent epidemiological data also suggest that the prevalence of the disease is higher in Western industrialized countries compared to Eastern and developing nations [6].

RA pathogenesis is considered a complex interaction between genetic, epigenetic, and environmental factors, many of which remain incompletely understood [7]. However, recent epidemiological studies have highlighted the significant roles of environmental factors, microbiota, infectious agents, sex hormones, and lifestyle in the development of the disease [4 8]. As with other chronic diseases, modifiable lifestyle factors such as unhealthy body weight, smoking, physical inactivity, and unhealthy dietary patterns significantly influence the development and progression of RA [9]. Several studies suggest that, when combined, these factors may have a greater impact than when considered individually [9]. The Combined Healthy Lifestyle Score (CHLS) is derived from five modifiable lifestyle factors: smoking, alcohol consumption, body mass index (BMI), physical activity, and diet. These factors significantly influence not only the development of diseases but also their prognosis [10 11].

In recent years, extensive research has highlighted the central role of diet in assessing disease risk and development [6]. While recent French rheumatology guidelines support Mediterranean-type diet and weight management [12], the role of fasting remains controversial. Although historic trials show fasting's positive impact on RA activity for up to one-year [13 14], current evidence suggests that combining fasting with a subsequent plant-based diet may be more beneficial [15]. This combination can reduce inflammatory biomarkers and positively impact gut microbiota through modulation of the mTOR signaling pathway [16 17]. Certain nutrients, such as polyunsaturated fatty acids, may function as anti-inflammatory agents and antioxidants, but substances like salt and red meat can negatively impact RA development and progression through indirect mechanisms, such as altering gut microbiota and body composition [18]. High-fiber diets have been associated with improved T cell regulation and decreased bone erosion markers in RA patients [19], while adequate iron and calcium intake, shows positive correlations with bone health [20-22]. Additionally, adequate vitamin D levels have been linked to better disease management and reduced inflammation in patients with RA [23]. Furthermore, prebiotics, probiotics, and synbiotics may also exert beneficial effects on RA [24].

It is well-supported by substantial evidence that exercise is highly effective in treating RA in all clinical domains [2]. Certain physical activities function as a non-pharmacological treatment strategy due to their numerous benefits, including enhanced muscle mass, strength, and overall efficiency, particularly in patients with RA. During exercise, skeletal muscles release myokines, which exert direct anti-inflammatory effects with each activity [25]. Regular physical activity has been demonstrated to reduce disease activity scores, improve joint function, and promote a better quality of life among patients with RA [26].

Excess body weight appears to be another important environmental factor in the pathogenesis of RA. Obesity is associated with an increased risk of RA, which can be attributed to the secretion of adipokines from white adipose tissue. This increased risk can lead to heightened disease activity, thereby reducing the efficacy of treatment and the likelihood of achieving therapeutic targets [27 28]. Studies have demonstrated that RA patients who are overweight or obese experience heightened degrees of synovial inflammation, both at the time of disease onset and after achieving remission [29]. While the precise mechanisms through which obesity exerts its effects on joint damage remain multifaceted [30], the mechanical stress associated with excess weight appears to contribute to the acceleration of arthritis development in weight-bearing joints [31]. Consequently, effective weight management emerges as a modifiable risk factor in the prevention and management of RA.

Smoking and alcohol have been extensively studied as environmental factors in RA. Meta-analyses show smoking significantly increases RA risk, particularly in men and antibody-positive RA (Anti-citrullinated protein antibodies, ACPA), with nearly 30% of RA patients being smokers [32 33]. Beyond increasing risk, smoking reduces treatment efficacy, especially for anti-TNF-α drugs [34 35]. The relationship between alcohol consumption and RA remains controversial. Although some studies suggest an association between alcohol consumption and antibody-positive RA through downregulation of pro-inflammatory cytokines [36 37], others report no significant effects on disease activity [38]. Furthermore, evidence regarding alcohol's influence on radiological damage and disease progression remains inconsistent [39 40].

Limited data exist regarding the cumulative impact of unhealthy lifestyle factors in individuals with RA [41]. While several studies have assessed individual lifestyle factors, the combined effect of multiple lifestyle components on the odds of developing RA remains poorly understood [10]. Recent studies on various chronic diseases have indicated that the combined impact of lifestyle factors may be more significant than the effects of individual factors [42]. Additionally, preventive measures for rheumatic diseases should be implemented before individuals enter older age groups, emphasizing the importance of maintaining a healthy lifestyle [25]. Therefore, this study aims to investigate the significance of a CHLS in relation to RA among Iranian adults participating in the PERSIAN Dena Cohort Study (PDCS).

Material and methods

Participants

Data from the PDCS was used to conduct this case-control study [43]. To determine the contributing factors to non-communicable diseases in Iran, researchers have been conducting the PERSIAN Cohort Study since 2018, using the Dena PERSIAN cohort as a sub-cohort. The Dena cohort includes all individuals residing in Dena County (Sisakht region) near the city of Yasuj, aged between 35 and 70, excluding those unable to participate in interviews due to physical or mental health issues. The RA status of the participants (yes or no) was determined based on the results of biochemical tests and consultations with a rheumatologist. Additional information regarding the study design, participants, and data collection methods has been published previously [43]. Participants with reported daily energy intakes below 800 kcal/day or above 4500 kcal/day were excluded from the study.

Demographic, anthropometric, medical, and lifestyle assessment

The data, which included demographic (age, sex, educational background, and marital status), anthropometric, medical, and lifestyle measurements, were collected according to the cohort protocol by trained interviewers. Height was measured using a stadiometer (Seca 755 1021994, Germany), ensuring that participants stood against a wall with their heels and buttocks in contact. Weight was measured using a calibrated standing scale (Seca 755 1021994, Germany), with participants wearing light clothing and no shoes. BMI was calculated by dividing the weight in kilograms by the square of height in meters [43]. Smoking status was classified according to standard definitions: non-smokers (< 100 cigarettes in lifetime) and current smokers (≥100 cigarettes in lifetime and currently smoking) [44]. Supplement usage was defined as taking calcium and vitamin D supplements at least once a week for a minimum of six months. Physical activity levels were evaluated using the validated Iranian version of International Physical Activity Questionnaire (IPAQ). A daily activity questionnaire was utilized to measure the MET for all individuals' activities over a 24-hour period, with results expressed as Metabolic Equivalent-hours per week (MET-h/week) [45].

Dietary assessment

In this study, a validated 113-item Food Frequency Questionnaire (FFQ) and an additional 127-item FFQ specifically designed to include indigenous foods were used [46 47]. Participants reported the frequency and portion sizes of food items consumed on a daily, weekly, monthly, and annual basis over the past year. All portion sizes and household quantities were converted to grams per day. The energy and nutrient content of the foods were calculated using Nutritionist IV software (Version 7.0). Due to the incompleteness of the Iranian Food Composition Table (FCT), the USDA FCT was used for dietary analyses.

Assessment of combined healthy lifestyle score

Four lifestyle factors were used to determine the CHLS for individuals: smoking, diet quality, BMI, and physical activity. Diet quality assessed by Healthy Eating Index (HEI)-2020 diet score is used to evaluate the quality of individuals' diets. A maximum score of 100 points can be attained through the 13 components of HEI-2020, which consist of 4 moderation components and 9 adequacy components. The adequacy components—dairy, whole grains, and fatty acids—received scores of 10 and 0, respectively, indicating the highest and lowest levels of intake. For the other six adequacy components, the lowest and highest intakes were 0 and 5, respectively, for total fruits (including fruit, fruit juice, and canned fruit), whole fruits (excluding fruit juice), total vegetables, greens and beans, total protein foods, seafood, and plant proteins. Four moderation components—salt, refined grains, saturated fats, and added sugars—were assigned a maximum of 10 points for the lowest levels of consumption [48]. However, the highest intake of these components was scored as 0. Finally, participants were categorized into quintiles according to their HEI-2020 scores. Individuals in the upper two quintiles were assigned a score of 1 to indicate a higher level of adherence to a healthy diet [48]. The following characteristics were also assigned a score of 1: non-current smoking status, physically active or moderately active (highest and second-highest quartiles of MET-hours per week), BMI < 25 kg/m2, and placement in the upper two quintiles of the Alternative Healthy Eating Index 2020 (AHEI-2020) score. To calculate the overall CHLS, we summed the participants' scores across each lifestyle component. The scores range from 0 (indicating the lowest adherence to CHLS) to 4 (indicating the highest adherence to CHLS) [49].

Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, New York). Statistical significance was determined by p-values of less than 0.05. Qualitative variables were expressed as percentages, while quantitative variables were reported as mean ± standard deviation (SD). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. The dietary intakes and general characteristics of the patients and controls were evaluated using the chi-square test for categorical variables and the independent samples t-test for continuous data. Additionally, one-way analysis of variance (ANOVA) was employed to analyze continuous variables, while chi-square tests were used for categorical variables to assess the general characteristics of study participants across the categories of the CHLS. Dietary intakes of study participants across categories of the CHLS were examined using analysis of covariance (ANCOVA), adjusting for age and sex in relation to energy intake, and further adjusting for age, sex, and energy intake for all other variables. The association between the CHLS and the odds of RA was evaluated using conditional logistic regression models. In the second model, adjustments were made for age, sex, vitamin D and calcium supplement use.

Results

The total number of participants who entered the study was 390. Table 1 compares the general characteristics of participants between RA cases (n = 130) and controls (n = 260), as well as across different categories of the CHLS, which ranges from 0 to 4. While there were no significant differences in the distribution of males and females between cases and controls, significant differences observed in their distribution across CHLS score categories. The mean BMI of RA cases was significantly higher compared to the control group (28.1 ± 5.2 vs. 26.8 ± 4.7 kg/m², p = 0.014). Furthermore, obesity, defined as a BMI ≥ 30 kg/m², was more prevalent among individuals with RA (33.8% vs. 23.1%, p = 0.023). In terms of healthy lifestyle scores, participants with a score of 0 exhibited the highest mean BMI (29.9 ± 2.9 kg/m²), while those with a score of 4 had the lowest mean BMI (22.6 ± 2.0 kg/m², p < 0.001). Similarly, the prevalence of obesity was significantly lower among participants with a score of 4 (0%) compared to those with a score of 0 (60.0%, p < 0.001). Additionally, higher waist circumference and weight were significantly associated with lower healthy lifestyle scores (p < 0.001 for both). Participants with a lifestyle score of 0 exhibited the highest waist circumference (101.7 ± 6.4 cm), whereas those with a score of 4 demonstrated the lowest waist circumference (88.9 ± 9.4 cm, $p < 0.001$). In this study, the difference between cases and controls was not statistically significant (97.5 ± 12.8 cm vs. 95.7 ± 10.8 cm, p = 0.141). Physical activity levels were positively associated with healthy lifestyle scores, increasing from 33.6 ± 4.2 MET-h/day in individuals with a score of 0 to 42.2 ± 5.0 MET-h/day in those with a score of 4 ($p < 0.001$).

Table 2 highlights the dietary intake of selected nutrients and food groups among RA cases, controls, and categories based on healthy lifestyle scores. Regarding energy and macronutrients, although energy intake did not differ significantly between cases and controls (p = 0.191) or across CHLS categories (p = 0.204), participants with a higher CHLS consumed significantly more protein ($p = 0.009$) and fat ($p = 0.039$). Significant differences were observed in the intake of several micronutrients across lifestyle scores. Participants with higher CHLS consumed significantly more vitamin A, vitamin C, vitamin E, zinc, and magnesium compared to those with lower scores (all $p < 0.001$). A statistically significant difference in mean vitamin B6 intakes was observed between cases and controls (13.7 ± 0.8 mg/d vs. 11.8 ± 0.4 mg/d, $p = 0.030$). Regarding food group consumption, individuals with higher score of CHLS showed a significantly greater intake of fruits ($p < 0.001$) and whole grains ($p = 0.038$), along with a notably lower consumption of refined grains ($p < 0.001$). Vegetable consumption was significantly lower in cases compared to controls (479 ± 17 vs. 546 ± 26 g/d, $p = 0.027$).

Figure 1 illustrates the crude and multivariable-adjusted odds ratios (ORs) for the odds of developing RA based on the CLHS. In the crude model, participants with a CLHS of 4 (the healthiest category) had significantly lower odds of developing RA compared to those with a CHLS score of 0 (OR = 0.127, 95% CI: 0.027–0.644, p-trend = 0.006). After adjusting for age (continuous), sex (male/female), and the use of vitamin D and calcium supplements (yes/no), the association remained significant (OR = 0.105, 95% CI: 0.024–0.461, *p*-trend = 0.001).

Discussion

Our study, a nested case-control investigation, found a significant inverse relationship between CHLS and the likelihood of RA in Iranian adults, even after adjusting for confounders. Specifically, individuals with the highest CHLS showed a reduced the odds of RA compared to those with the lowest scores.

RA pathogenesis is multifaceted, involving genetic predispositions and environmental triggers, as well as their interactions, which play a crucial role in determining susceptibility to RA [3]. Despite the strong role of genetics, numerous studies have primarily focused on single lifestyle factors, such as diet, physical activity, and body mass index (BMI), in relation to RA risk. However, given the interconnectivity of these lifestyle factors, considering them collectively provides a more holistic understanding of their influence on RA risk [11 50]. In past studies, comprehensive lifestyle indices like the Healthy Lifestyle Index Score (HLIS) from the Nurses' Health Study (NHS) have shown that maintaining multiple healthy lifestyle habits can reduce RA risk, especially in cases of seropositive RA. A recent cross-sectional study involving 17,532 adult Americans from the NHANES cohort showed that the Life's Simple 7 (LS7) score—developed according to the American Heart Association (AHA) guidelines to evaluate the cumulative effects of lifestyle risk factors for cardiovascular disease (CVD) through seven indicators: blood pressure, total cholesterol, HbA1c, smoking, BMI, physical activity, and diet exhibits a negative association with RA [42 51]. Our study expands on this by focusing on a synergy between healthy diet, BMI, physical activity, and smoking status as a unified CHLS and its connection to RA risk.

In terms of diet, the beneficial health effects of healthy dietary patterns have been established in relation to many chronic diseases, often by modulating levels of systemic inflammation [52 53]. The role of diet in RA risk is well-supported, particularly through its influence on systemic inflammation. Anti-inflammatory diets, like the AHEI-2010 and the Mediterranean diet, have demonstrated protective effects against RA. While some studies associate Mediterranean diet adherence with pain relief in RA patients, its role in preventing RA remains inconclusive [18 50]. The Nurses' Health Study (NHS), which tracked over 150,000 women and documented more than 1,000 new RA cases, found that sustained healthy eating habits were moderately linked to a lower RA risk, especially for women under 55 years [54]. The study used the AHEI-2010 to evaluate dietary quality, with healthy foods—such as fruits, vegetables, whole grains, nuts, long-chain fats, and polyunsaturated fatty acids (PUFAs), as well as moderate alcohol use—associated with a reduced risk of chronic diseases. In contrast, higher risk was linked to consuming sugar-sweetened drinks, red and processed meats, trans fats, and foods high in sodium [18]. Notably, in our study, we used the HEI-2020 to measure the nutritional quality of the diet, whereas the NHS study employed the AHEI-2010 version, which has minor differences in the scoring of dietary items. Additionally, several investigations have focused on the potential anti-inflammatory benefits of the Mediterranean diet—characterized by its abundance of fruits, vegetables, nuts, legumes, low-fat dairy, seafood, whole grains, and fiber, as well as its high content of antioxidant nutrients and low levels of red and processed meat, animal fat, sweets, and desserts—on the risk of RA. A systematic review assessed how the Mediterranean diet influences both the prevention and symptom management of RA in prospective studies involving humans. While findings suggested that the Mediterranean diet might help reduce pain and symptoms for individuals already diagnosed with RA, the evidence was not strong enough to confirm its role in preventing RA development [55]. Another population-based case-control study involving more than 5,000 participants demonstrated a significant reduction in the risk of seropositive RA among individuals with strong adherence to the Mediterranean diet; however, this effect was observed exclusively in male participants [56]. These findings suggest that a generally healthy diet, as part of a healthy lifestyle, may contribute to reduced odds of RA.

Previous research has suggested various biological mechanisms by which excess body weight could affect RA risk. Obesity is known to be an inflammatory state, marked by increased levels of pro-inflammatory cytokines released by fat cells, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), both of which are linked to RA development [56 57]. In our study, using BMI cut-off point of 25 kg/m^2, we found that higher BMI was associated with increased odds of RA, which aligns with previous findings. On the other hand, obesity is linked to relatively higher estrogen levels. Since RA is more common among females, this increase in estrogen might play a role in the disease's development and prevalence among women [58]. A systematic review encompassing 11 studies explored the relationship between BMI and RA risk, finding that obesity is notably associated with a higher RA risk compared to those without obesity [59]. Similarly, a later meta-analysis, which included 400,609 participants and identified 13,562 RA cases, found that obesity correlated with a relative risk (RR) of 1.21 for RA when compared to individuals with normal BMI. Additionally, for every 5 kg/m^2 increase in BMI, the RA risk rose by 13% [60]. These findings support our results showing the importance of maintaining normal BMI (< 25 kg/m^2) as part of a healthy lifestyle pattern for reducing RA risk. However, these studies primarily examined BMI as a fixed category and did not assess the effects of weight or BMI fluctuations over time on RA risk.

Physical activity may contribute to the pathogenesis of RA through several mechanisms [61]. These mechanisms include energy consumption, the secretion of myokines (such as IL-6, IL-8, and IL-15), modulation of T helper 1/T helper 2 (Th1/Th2) cell levels, increased levels of natural killer (NK) cells, and the secretion of epinephrine and norepinephrine during exercise [62-64]. Together, these effects contribute to reducing systemic inflammation, providing a rationale for the idea that physical activity may protect against RA. Findings from the Swedish Mammography Cohort, which studied 30,112 women aged 54 to 89 years and identified 201 new RA cases, indicated that women who engaged in higher levels of physical activity (over 20 minutes of walking or bicycling daily and more than 1 hour of exercise weekly) had a significantly reduced risk of developing RA compared to those in the lowest physical activity category. These findings further support the potential protective role of regular physical activity in reducing RA risk [65]. Similarly, another prospective cohort study investigated the relationship between recreational physical activity and the risk of RA among women participating in the Nurses' Health Study II. This study utilized repeated measures of physical activity over 26 years and included 113,366 women, identifying 506 new cases of RA. The research focused on the correlation between levels of recreational physical activity and the risk of developing RA. The results indicated that a higher cumulative number of hours spent on recreational physical activities was associated with a significantly lower risk of developing RA compared to lower levels of physical activity. These findings underscore the potential protective effects of regular physical activity against the onset of RA, reinforcing the importance of incorporating physical activity into preventive health strategies [66]. Additionally, a recent meta-analysis, comprising four studies with a total of 255,365 women and 4,213 incident RA cases, identified an inverse relationship between physical activity and RA development. Notably, one study within the meta-analysis reported the progression of joint damage in large joints among individuals with existing extensive joint deterioration when engaging in high-intensity weight-bearing exercises [67]. However, all studies and meta-analyses regard resistance exercise as safe and beneficial for patients with RA [68-70]. Consequently, the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) both strongly recommend physical activity in RA management [26 71]. EULAR recommends not only aerobic exercise but also specific muscle-strengthening exercises [26], and ACR similarly provides a strong recommendation for both types of exercise [71]. Guidelines from other regions such as Asia Pacific League of Associations for Rheumatology (APLAR) acknowledge the potential benefits of physical activity but note that evidence and resources for structured physical therapy are limited in many countries [72].

The present study has several notable strengths. First, to the best of our knowledge, it is the first study to investigate the relationship between the combined effects of four key healthy lifestyle factors, as represented by the CHLS, and the odds of RA. Second, the study utilized a large, nationally representative database with standardized data collection protocols, which helps minimize potential biases. All data were collected by expert and trained interviewers using reliable and validated questionnaires. Third, the nested case-control design of this study represents a significant strength compared to cross-sectional or traditional case-control designs. This approach offers superior computational efficiency for estimating odds ratios while reducing the risk of selection bias and recall bias.

However, this study also has certain limitations. First, the cross-sectional nature of the data limits the ability to infer causality. Second, as an observational study, it was not possible to fully control for all potential confounding factors and biases. Although the study adjusted for several covariates, unmeasured confounding factors may still exist. Additionally, lifestyle factors were assessed only during the baseline phase of the PDCS, whereas individuals' lifestyles are dynamic and can change over time. Fourth, despite the use of expert and trained interviewers, as well as validated questionnaires for dietary and physical activity assessments, some degree of measurement error is inevitable. These limitations should be considered when interpreting the findings, and future research should aim to address these gaps to further clarify the relationship between lifestyle factors and RA risk.

Additionally, the FFQ has several known limitations, including recall bias, seasonal variations in food intake, and the potential for over- or underestimation of portion sizes. Fifth, due to the incompleteness of the Iranian Food Composition Table (FCT), the USDA FCT was used for dietary analyses, which may introduce minor measurement errors in the calculations of macro- and micronutrient intake. Furthermore, the study lacked detailed body composition measurements beyond BMI, which could have provided more precise insights into the relationship between body composition and RA risk. Finally, we did not account for additional lifestyle factors such as sleep patterns, fatigue levels, stress, and alcohol consumption, despite their reported associations with RA in some studies. It is important to acknowledge that the findings of this study may not be generalizable beyond the specific sample of adults examined. Future research should aim to address these limitations to provide a more comprehensive understanding of the factors influencing RA risk.

Conclusion

In conclusion, the results of our population-based nested case-control study indicate that individuals with a higher CHLS have significantly lower odds of developing RA, even after adjusting for potential confounders. This finding suggests an inverse association between the healthy lifestyle behaviors represented by the CHLS and the incidence of RA. However, further prospective studies with long-term follow-up are necessary to confirm the causal relationship suggested by these results. Such research would provide deeper insights into the role of lifestyle modifications in RA prevention and management.

List of Abbreviations

AHEI: Alternative Healthy Eating Index

ACPA: Anti-citrullinated Protein Antibodies

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

BMI: Body Mass Index

CI: Confidence Interval

CVD: Cardiovascular Disease

EULAR: European League Against Rheumatism

ACR: American College of Rheumatology

APLAR :Asia Pacific League of Associations for Rheumatology

FCT: Food Composition Table

FFQ: Food Frequency Questionnaire

HEI: Healthy Eating Index

CHLS: Combined Healthy Lifestyle Score

HR: Hazard Ratio

IL: Interleukin

MET: Metabolic Equivalent of Task

NHS: Nurses' Health Study

NK: Natural Killer

OR: Odds Ratio

PDCS: PERSIAN Dena Cohort Study

PERSIAN: Prospective Epidemiological Research Studies in IrAN

PUFA: Polyunsaturated Fatty Acid

RA: Rheumatoid Arthritis

RR: Relative Risk

SD: Standard Deviation

SPSS: Statistical Package for the Social Sciences

TNF-α: Tumor Necrosis Factor-alpha

USDA: United States Department of Agriculture

Authorship Contributions

Conception and Design: F.A, J.H, M.J., S.H.S Acquisition of Data: S.A. Analysis and Interpretation of Data: S.H.S, F.A, J.H. Drafting the Manuscript: A.P, M.Z, F.K, V.M, M.J. Revising Manuscript for Intellectual Content: M.J, S.A., F.A. All authors read and approved the final manuscript. M.J. is the guarantor.

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Data Availability Statement

On reasonable request, the corresponding author will provide the datasets used and analyzed during the current work. Correspondence and requests for materials should be addressed to M.J.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

The aims of the study were explained in detail, and written informed consent was obtained from all participants [43]. The study was approved by the Ethics Committee of Yasuj University of Medical Sciences (ethics code: IR.YUMS.REC.1401.175).

Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Table 1. General characteristics of participants by cases and controls as well as different categories of the combined healthy lifestyle score[a]

	Groups			Combined healthy lifestyle score				
	Cases (n= 130)	Controls (n= 260)	p^b	0 (n=5)	1 (n=61)	2 (n=159)	3 (n=94)	4 (n=71)
Sex, n(%)								
Males	29 (22.3)	60 (23.1)	0.865	5 (100.0)	26 (42.6)	35 (22.0)	14 (14.9)	9 (12.7)[c]
Females	101 (77.7)	200 (76.9)		0 (0.0)	35 (57.4)	124 (78.0)	80 (85.1)	62 (87.3)
Age (year)	49.8 ± 9.7	50.6 ± 9.3	0.484	45.8 ± 9.9	50.4 ± 10.1	50.8 ± 9.5	5[illegible].1 ± 9.0	48.4 ± 9.2
Weight (kg)	72.4 ± 13.1	70.2 ± 12.8	0.110	75.1 ± 8.8	75.8 ± 11.1	73.6 ± 12.6	6[illegible].9 ± 14.1	62.1 ± 8.8[c]
Height (cm)	164.2 ± 11.2	164.7 ± 10.1	0.649	176.4 ± 9.0	167.1 ± 12.0	163.5 ± 10.3	162.7 ± 9.2	166.1 ± 10.1[c]
Waist circumference (cm)	97.5 ± 12.8	95.7 ± 10.8	0.141	101.7 ± 6.4	100.6 ± 10.3	98.4 ± 11.1	95.2 ± 12.0	88.9 ± 9.4[c]
BMI (kg/m^2)	28.1 ± 5.2	26.8 ± 4.7	0.014	29.9 ± 2.9	29.9 ± 4.2	28.3 ± 4.6	2[illegible].9 ± [illegible].3	22.6 ± 2.0[c]
Obesity, n (%) [d]	44 (33.8)	60 (23.1)	0.023	3 (60.0)	29 (47.5)	45 (28.3)	27 (28.7)	0 (0.0)[c]
Educational level, n (%)								
Diploma and lower	122 (93.8)	223 (85.8)	0.019	5 (100.0)	57 (93.4)	148 (93.1)	76 (80.9)	59 (83.1)
University	8 (6.2)	37 (14.2)		0 (0.0)	4 (6.0)	11 (6.9)	18 (19.1)	12 (16.9)
Marital status, n (%)								
Married	122 (93.8)	223 (85.8)	0.912	5 (100.0)	49 (80.3)	133 (83.6)	89 (94.7)	68 (95.8)
Unmarried/divorced/widowed	8 (6.2)	37 (14.2)		0 (0.0)	12 (19.7)	26 (16.4)	5 (5.3)	3 (4.2)[c]
Vitamin D supplement use, n (%)	53 (40.8)	95 (36.5)	0.417	0 (0.0)	18 (29.5)	53 (33.3)	40 (42.6)	37 (52.1)[c]
Calcium supplement use, n (%)	27 (20.8)	30 (11.5)	0.015	0 (0.0)	6 (9.8)	20 (12.6)	23 (24.5)	8 (11.3)[c]
Physical activity (MET-h per day)	39.3 ± 6.1	40.3 ± 4.5	0.088	33.6 ± 4.2	37.2 ± 4.7	39.4 ± 4.1	4[illegible].9 ± [illegible].5	42.2 ± 5.0[c]
Current smoker, n (%)	18 (13.8)	34 (13.1)	0.833	5 (100.0)	24 (39.3)	16 (10.1)	7 (7.4)	0 (0.0)[c]

Abbreviations: BMI, body mass index; MET, metabolic equivalent

[a] All data are reported as means ± standard deviations unless indicated.

[b] Determined using the independent sample t-test or chi-square test, where appropriate.

[c] Significant difference with the lowest combined healthy lifestyle score ($p < 0.05$, determined using the one-way ANOVA test or chi-square test, where appropriate)

[d] Obesity was defined as BMI ≥ 30 kg/m^2

$p < 0.05$ was considered as statistically significant.

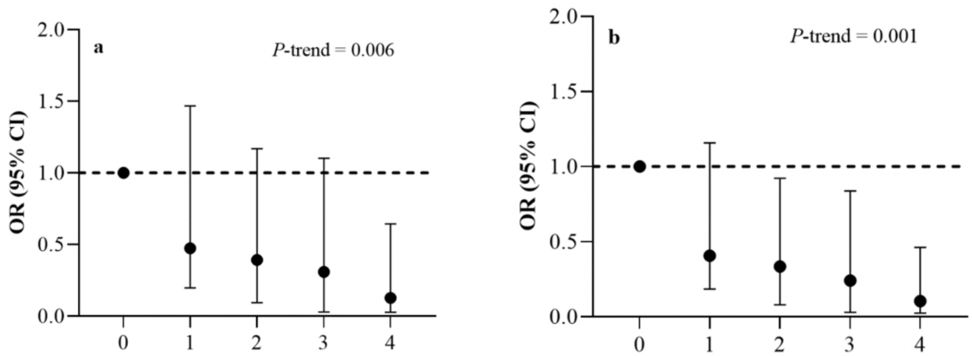
Table 2. Dietary intakes of selected nutrients and food groups of participants by cases and controls as well as different categories of the combined healthy lifestyle score[a]

	Groups			Combined healthy lifestyle score				
	Cases (n= 130)	Controls (n= 260)	p^b	0 (n=5)	1 (n=61)	2 (n=159)	3 (n=94)	4 (n=71)
Energy (kcal/d)[d]	2380 ± 62	2486 ± 48	0.191	2645 ± 198	2369 ± 92	2374 ± 59	2585 ± 78	2498 ± 92
Nutrients								
Carbohydrate (g/d)	383 ± 10	407 ± 8	0.077	429 ± 41	384 ± 16	389 ± 110	416 ± 12	407 ± 16
Protein (g/d)	75.2 ± 2.2	77.8 ± 1.7	0.375	78.0 ± 5.6	73.1 ± 3.1	72.5 ± 2.0	83.3 ± 3.0	81.7 ± 3.3[c]
Fat (g/d)	66.7 ± 2.0	66.5 ± 1.6	0.934	72.4 ± 7.6	63.4 ± 3.0	63.2 ± 1.8	72.7 ± 2.8	68.4 ± 3.1[c]
Saturated fat (g/d)	25.3 ± 1.0	23.9 ± 0.7	0.224	21.5 ± 2.0	22.8 ± 1.3	25.1 ± 0.9	25.0 ± 1.0	23.6 ± 1.2
Trans fatty acids (g/d)	0.23 ± 0.02	0.26 ± 0.02	0.397	0.31 ± 0.11	0.24 ± 0.04	0.23 ± 0.02	0.31 ± 0.03	0.21 ± 0.02
Fiber (g/d)	28.3 ± 0.5	30.7 ± 0.4	0.346	28.1 ± 0.3	28.7 ± 0.3	29.1 ± 0.4	30.8 ± 0.9	30.2 ± 0.7
Vitamin A (RAE/d)	748 ± 57	710 ± 26	0.490	714 ± 131	638 ± 98	602 ± 26	907 ± 58	826 ± 48[c]
Vitamin C (mg/d)	130 ± 7	141 ± 6	0.247	93 ± 9	99 ± 8	122 ± 7	159 ± 10	179 ± 10[c]
Vitamin E (mg/d)	7.8 ± 0.3	8.2 ± 0.3	0.341	6.8 ± 0.6	6.5 ± 0.3	7.1 ± 0.2	9.1 ± 0.4	9.6 ± 0.5[c]
Folate (mcg/d)	546 ± 15	580 ± 13	0.109	612 ± 33	565 ± 24	560 ± 16	588 ± 22	563 ± 22
Vitamin B_6 (mg/d)	13.7 ± 0.8	11.8 ± 0.4	0.030	13.0 ± 4.4	11.0 ± 0.8	11.6 ± 0.6	13.6 ± 0.9	13.5 ± 0.9
Zinc (mg/d)	9.2 ± 0.3	9.4 ± 0.2	0.640	9.4 ± 0.6	8.7 ± 0.4	8.7 ± 0.2	10.2 ± 0.4	10.3 ± 0.4[c]
Selenium (mg/d)	99 ± 4	104 ± 3	0.218	117 ± 7	106 ± 5	99 ± 3	107 ± 4	98 ± 5
Magnesium (mg/d)	335 ± 10	345 ± 8	0.468	311 ± 22	304 ± 12	318 ± 9	374 ± 13	384 ± 16[c]
Calcium (mg/d)	1164 ± 16	1179 ± 15	0.520	1125 ± 14	1156 ± 12	1190 ± 15	1206 ±23	1239 ±35
Iron (mg/d)	9.02 ± 0.23	9.26 ± 0.20	0.319	9.29 ± 0.21	8.94 ± 0.19	9.16 ± 0.12	9.30 ± 0.24	9.73 ± 0.28
Food groups								
Whole grains (g/d)	30.5 ± 5.4	24.4 ± 4.8	0.441	7.9 ± 1.2	14.1 ± 2.5	18.8 ± 2.4	44.6 ± 13.6	31.2 ± 6.4[c]
Refined grains (g/d)	515 ± 19	524 ± 14	0.689	656 ± 62	571 ± 26	569 ± 20	457 ± 17	447± 23[c]
Fruits (g/d)	551 ± 35	558 ± 24	0.863	292 ± 41	375 ± 31	504 ± 26	613 ± 37	765 ± 61[c]
Vegetables (g/d)	479 ± 17	546± 26	0.027	621 ± 136	487 ± 34	479 ± 24	532 ± 31	510 ± 27
Legumes and nuts (g/d)	73.9 ± 4.0	67.4 ± 2.5	0.152	84.7 ± 17.8	59.9 ± 4.7	66.4 ± 3.5	75.6 ± 4.6	75.9 ± 4.4
Meats (g/d)	145 ± 7	136 ± 4	0.287	144 ± 27	129 ± 8	134 ± 6	151 ± 8	143 ± 8
Dairy products (g/d)	353 ± 24	304 ± 15	0.081	224 ± 76	293 ± 38	332 ± 23	316 ± 22	330 ± 25
Sugar-sweetened beverages (g/d)	125 ± 10	134 ± 9	0.585	188 ± 112	130 ± 18	140 ± 13	143 ± 15	92 ± 11

[a] All data is reported as means ± S.E.
[b] Determined using the independent samples *t*-test
[c] Significant difference with the lowest combined healthy lifestyle score ($p < 0.05$, determined using the ANCOVA test)
[d] Energy intake is adjusted for age and sex, all other values are adjusted for age, sex, and energy intake.
$p < 0.05$ was considered as statistically significant

Figure Legend:

Figure 1. Crude and multivariable-adjusted ORs with 95% CIs for the odds of rheumatoid arthritis across the different categories of the combined healthy lifestyle score (n=390). (a) Crude model; (b) Adjusted for age (continuous), sex (male/female), vitamin D and calcium supplements use (yes/ no). P-trend values were determined by the Mantel-Hanszel extension $\chi 2$ test.



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A combined healthy lifestyle score and odds of rheumatoid arthritis in Iranian adults: a nested case-control from PERSIAN Dena Cohort Study (PDCS)

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Manuscripts

1 # A combined healthy lifestyle score and odds of rheumatoid arthritis in Iranian
2 # adults: a nested case-control from PERSIAN Dena Cohort Study (PDCS)

Javad Harooni[1], Abdollah Pourjavid[2], Farshad Amirkhizi[3], Soudabeh Hamedi-Shahraki[4], Fatemeh Kiani[5], Mohammad-Amin Zolghadrpour[6], Vahid Monfared[5], Somayyeh Asghari[6]*, Mohammad-Reza Jowshan[6]*

Author's affiliations

[1] Department of Public Health, School of Health, Yasuj University of Medical Sciences, Yasuj, Iran

[2] Student Research Committee, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

[3] Department of Nutrition, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran

[4] Department of Epidemiology and Biostatistics, School of Public Health, Zabol University of Medical Sciences, Zabol, Iran

[5] Student Research Committee, Semnan University of Medical Sciences, Semnan, Iran.

[6] Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

***Corresponding authors**

Mohammad-Reza Jowshan, Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, P.O. Box 14155-6117, Iran. **Email address:** mr-jowshan@alumnus.tums.ac.ir ; mr.jowshan@gmail.com

Somayyeh Asghari, Ph.D., Department of Clinical Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran. **Email address:** asghari.nut@gmail.com , sasghari@sina.tums.ac.ir

ORCID

Javad Harooni https://orcid.org/0000-0002-7129-1015
Abdollah Pourjavid https://orcid.org/0009-0004-3084-1959
Farshad Amirkhizi https://orcid.org/0000-0003-1477-0260
Soudabeh-Hamedi-Shahraki https://orcid.org/0000-0003-2270-7421
Fatemeh Kiani https://orcid.org/ 0009-0008-4333-2378
Mohammad-Amin Zolghadrpour https://orcid.org/0000-0002-1856-1338
Somayyeh Asghari https://orcid.org/0000-0002-0501-0115
Mohammad-Reza Jowshan https://orcid.org/0000-0001-8603-5674

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Strengths and limitations of this study

- The study utilized a large, nationally representative database with standardized data collection protocols, which minimizes potential biases.
- A comprehensive lifestyle assessment was conducted using a validated scoring system incorporating smoking, physical activity, BMI and dietary quality.
- One of the limitations is that the case-control design limits our ability to establish causal relationships, and we did not evaluate stress and alcohol consumption as additional lifestyle factors in this study.

Abstract

Objectives: Lifestyle factors play a significant role in the development of chronic diseases. While researchers have extensively studied individual lifestyle components, the combined impact of multiple lifestyle factors on rheumatoid arthritis (RA) remains unclear. This study aimed to explore the association between a Combined Healthy Lifestyle Score (CHLS) and the odds of developing RA among Iranian adults.

Design: A nested case-control study.

Setting: The study was conducted in Dena County (Sisakht region) near Yasuj city, Iran, as part of the PERSIAN Cohort Study.

Participants: 130 RA cases and 260 matched controls, aged 35-70 years. Cases were identified based on biochemical tests and rheumatologist consultation.

Outcome Measures: Primary outcome was odds of RA. Secondary outcomes included anthropometric measurements (BMI, waist circumference) and dietary quality indicators.

Methods: The CHLS score was calculated based on four parameters: smoking status, physical activity level, body mass index (BMI), and dietary quality, as assessed by the Healthy Eating Index (HEI-2020). Scores ranged from 0 (representing the unhealthiest lifestyle) to 4 (representing the healthiest lifestyle). Multiple logistic regression analysis was used to evaluate the association between CHLS and the odds of developing RA.

Results: Participants with higher CHLS exhibited significantly lower body mass index (BMI) and waist circumference compared to those with lower scores. Additionally, higher CHLS was associated with greater consumption of fruits and whole grains ($p < 0.05$). Individuals with the highest CHLS had 90% lower odds of developing RA compared to those with the lowest scores (OR: 0.105; 95% CI: 0.024–0.461, *p*-trend = 0.001), after adjusting for potential confounders.

Conclusion: Our findings suggest that adherence to a healthy lifestyle—characterized by non-smoking, regular physical activity, maintaining a normal BMI, and following a healthy dietary pattern—is associated with a reduced odds of developing RA among Iranian adults. The results of this study underscore the potential importance of combined lifestyle modifications in the prevention of RA. These insights emphasize the value of promoting comprehensive lifestyle changes as a strategy to mitigate RA risk.

Keywords: Rheumatoid arthritis, Lifestyle factors, Combined Healthy lifestyle, Persian cohort

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by widespread inflammation, particularly affecting the joints and surrounding soft tissues [1]. This condition manifests symptoms such as joint swelling, redness, pain, stiffness, and general fatigue, significantly impairing the quality of life [1]. Progressive disability may occur as a result of this condition, along with potential cardiovascular complications and other related health issues, as documented in various studies [1 2]. RA is estimated to affect between 0.5% and 1.0% of the global population, with peak onset typically occurring between 30 and 55 years of age. [3] Women are disproportionately affected by the condition, being 2-3 times more likely to develop it than men [4]. The disease not only leads to chronic health issues for individuals but also imposes significant socioeconomic burdens, affecting both personal quality of life and healthcare systems. Recent data shows annual healthcare costs are $3,383 higher in RA patients compared to non-RA individuals, with medication costs reaching up to $36,000 annually [5]. Literature indicates that up to 20-30% of patients may become permanently disabled within the first 3 years of diagnosis [1]. Recent epidemiological data also suggest that the prevalence of the disease is higher in Western industrialized countries compared to Eastern and developing nations [6].

RA pathogenesis is considered a complex interaction between genetic, epigenetic, and environmental factors, many of which remain incompletely understood [7]. However, recent epidemiological studies have highlighted the significant roles of environmental factors, microbiota, infectious agents, sex hormones, and lifestyle in the development of the disease [4 8]. As with other chronic diseases, modifiable lifestyle factors such as unhealthy body weight, smoking, physical inactivity, and unhealthy dietary patterns significantly influence the development and progression of RA [9]. Several studies suggest that, when combined, these factors may have a greater impact than when considered individually [9]. The Combined Healthy Lifestyle Score (CHLS) is derived from five modifiable lifestyle factors: smoking, alcohol consumption, body mass index (BMI), physical activity, and diet. These factors significantly influence not only the development of diseases but also their prognosis [10 11].

In recent years, extensive research has highlighted the central role of diet in assessing disease risk and development [6]. While recent French rheumatology guidelines support Mediterranean-type diet and weight management [12], the role of fasting remains controversial. Although historic trials show fasting's positive impact on RA activity for up to one-year [13 14], current evidence suggests that combining fasting with a subsequent plant-based diet may be more beneficial [15]. This combination can reduce inflammatory biomarkers and positively impact gut microbiota through modulation of the mTOR signaling pathway [16 17]. Certain nutrients, such as polyunsaturated fatty acids, may function as anti-inflammatory agents and antioxidants, but substances like salt and red meat can negatively impact RA development and progression through indirect mechanisms, such as altering gut microbiota and body composition [18]. High-fiber diets have been associated with improved T cell regulation and decreased bone erosion markers in RA patients [19], while adequate iron and calcium intake, shows positive correlations with bone health [20-22]. Additionally, adequate vitamin D levels have been linked to better disease management and reduced inflammation in patients with RA [23]. Furthermore, prebiotics, probiotics, and synbiotics may also exert beneficial effects on RA [24].

It is well-supported by substantial evidence that exercise is highly effective in treating RA in all clinical domains [2]. Certain physical activities function as a non-pharmacological treatment strategy due to their numerous benefits, including enhanced muscle mass, strength, and overall efficiency, particularly in patients with RA. During exercise, skeletal muscles release myokines, which exert direct anti-inflammatory effects with each activity [25]. Regular physical activity has been demonstrated to reduce disease activity scores, improve joint function, and promote a better quality of life among patients with RA [26].

Excess body weight appears to be another important environmental factor in the pathogenesis of RA. Obesity is associated with an increased risk of RA, which can be attributed to the secretion of adipokines from white adipose tissue. This increased risk can lead to heightened disease activity, thereby reducing the efficacy of treatment and the likelihood of achieving therapeutic targets [27 28]. Studies have demonstrated that RA patients who are overweight or obese experience heightened degrees of synovial inflammation, both at the time of disease onset and after achieving remission [29]. While the precise mechanisms through which obesity exerts its effects on joint damage remain multifaceted [30], the mechanical stress associated with excess weight appears to contribute to the acceleration of arthritis development in weight-bearing joints [31]. Consequently, effective weight management emerges as a modifiable risk factor in the prevention and management of RA.

Smoking and alcohol have been extensively studied as environmental factors in RA. Meta-analyses show smoking significantly increases RA risk, particularly in men and antibody-positive RA (Anti-citrullinated protein antibodies, ACPA), with nearly 30% of RA patients being smokers [32 33]. Beyond increasing risk, smoking reduces treatment efficacy, especially for anti-TNF-α drugs [34 35]. The relationship between alcohol consumption and RA remains controversial. Although some studies suggest an association between alcohol consumption and antibody-positive RA through downregulation of pro-inflammatory cytokines [36 37], others report no significant effects on disease activity [38]. Furthermore, evidence regarding alcohol's influence on radiological damage and disease progression remains inconsistent [39 40].

Limited data exist regarding the cumulative impact of unhealthy lifestyle factors in individuals with RA [41]. While several studies have assessed individual lifestyle factors, the combined effect of multiple lifestyle components on the odds of developing RA remains poorly understood [10]. Recent studies on various chronic diseases have indicated that the combined impact of lifestyle factors may be more significant than the effects of individual factors [42]. Additionally, preventive measures for rheumatic diseases should be implemented before individuals enter older age groups, emphasizing the importance of maintaining a healthy lifestyle [25]. Therefore, this study aims to investigate the significance of a CHLS in relation to RA among Iranian adults participating in the PERSIAN Dena Cohort Study (PDCS).

Material and methods

Participants

Data from the PDCS was used to conduct this case-control study [43]. To determine the contributing factors to non-communicable diseases in Iran, researchers have been conducting the PERSIAN Cohort Study since 2018, using the Dena PERSIAN cohort as a sub-cohort. The Dena cohort includes all individuals residing in Dena County (Sisakht region) near the city of Yasuj, aged between 35 and 70, excluding those unable to participate in interviews due to physical or mental health issues. The RA status of the participants (yes or no) was determined based on the results of biochemical tests and consultations with a rheumatologist. Additional information regarding the study design, participants, and data collection methods has been published previously [43]. The mean values of healthy life style score as key variable was obtained from Cristina de Oliveira et al. [44], was used to estimate the sample size. Considering the study power of 80%, a type I error of 5%, and the ratio of controls to cases as 2, we required 130 cases and 260 controls for this study. Participants with reported daily energy intakes below 800 kcal/day or above

4500 kcal/day were excluded from the study. The study was approved by the Ethics Committee of Yasuj University of Medical Sciences (ethics code: IR.YUMS.REC.1401.175).

Demographic, anthropometric, supplement intake, and lifestyle assessment

The data, which included demographic (age, sex, educational background, and marital status), anthropometric, medical, and lifestyle measurements, were collected according to the cohort protocol by trained interviewers. Height was measured using a stadiometer (Seca 755 1021994, Germany), ensuring that participants stood against a wall with their heels and buttocks in contact. Weight was measured using a calibrated standing scale (Seca 755 1021994, Germany), with participants wearing light clothing and no shoes. BMI was calculated by dividing the weight in kilograms by the square of height in meters. According to WHO classification, overweight is defined as BMI ≥ 25 kg/m² and obesity as BMI ≥ 30 kg/m² [45]. Smoking status was classified according to standard definitions: non-smokers (< 100 cigarettes in lifetime) and current smokers (≥ 100 cigarettes in lifetime and currently smoking) [46]. Supplement usage was defined as taking calcium and vitamin D supplements at least once a week for a minimum of six months. Physical activity levels were evaluated using the validated Iranian version of International Physical Activity Questionnaire (IPAQ). A daily activity questionnaire was utilized to measure the MET for all individuals' activities over a 24-hour period, with results expressed as Metabolic Equivalent-hours per week (MET-h/week) [47].

Dietary assessment

In this study, a validated 113-item Food Frequency Questionnaire (FFQ) and an additional 127-item FFQ specifically designed to include indigenous foods were used [48 49]. Participants reported the frequency and portion sizes of food items consumed on a daily, weekly, monthly, and annual basis over the past year. All portion sizes and household quantities were converted to grams per day. The energy and nutrient content of the foods were calculated using Nutritionist IV software (Version 7.0). Due to the incompleteness of the Iranian Food Composition Table (FCT), the USDA FCT was used for dietary analyses.

Assessment of combined healthy lifestyle score

Four lifestyle factors were used to determine the CHLS for individuals: smoking, diet quality, BMI, and physical activity. Diet quality assessed by Healthy Eating Index (HEI)-2020 diet score is used to evaluate the quality of individuals' diets. A maximum score of 100 points can be attained through the 13 components of HEI-2020, which consist of 4 moderation components and 9 adequacy components. The adequacy components—dairy, whole grains, and fatty acids—received scores of 10 and 0, respectively, indicating the highest and lowest levels of intake. For the other six adequacy components, the lowest and highest intakes were 0 and 5, respectively, for total fruits (including fruit, fruit juice, and canned fruit), whole fruits (excluding fruit juice), total vegetables, greens and beans, total protein foods, seafood, and plant proteins. Four moderation components—salt, refined grains, saturated fats, and added sugars—were assigned a maximum of 10 points for the lowest levels of consumption [50]. However, the highest intake of these components was scored as 0. Finally, participants were categorized into quintiles according to their HEI-2020 scores. Individuals in the upper two quintiles were assigned a score of 1 to indicate a higher level of adherence to a healthy diet [50]. The following characteristics were also assigned a score of 1: non-current smoking status, physically active or moderately active (highest and second-highest quartiles of MET-hours per week), BMI < 25 kg/m2, and placement in the upper two quintiles of the Alternative Healthy Eating Index 2020 (AHEI-2020) score. To calculate the overall CHLS, we summed the participants' scores across each lifestyle component. The scores range from 0 (indicating the lowest adherence to CHLS) to 4 (indicating the highest adherence to CHLS) [51].

Statistical analyses

The statistical analyses were performed using IBM SPSS Statistics version 25 (IBM Corp, Armonk, New York). Statistical significance was determined by p-values of less than 0.05. Qualitative variables were expressed as percentages, while quantitative variables were reported as mean ± standard deviation (SD). The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. The dietary intakes and general characteristics of the patients and controls were evaluated using the chi-square test for categorical variables and the independent samples t-test for continuous data. Additionally, one-way analysis of variance (ANOVA) was employed to analyze continuous variables, while chi-square tests were used for categorical variables to assess the general characteristics of study participants across the categories of the CHLS. Dietary intakes of study participants across categories of the CHLS were examined using analysis of covariance (ANCOVA), adjusting for age and sex in relation to energy intake, and further adjusting for age, sex, and energy intake for all other variables. The association between the CHLS and the odds of RA was evaluated using conditional logistic regression models. In the second model, adjustments were made for age, sex, vitamin D and calcium supplement use.

Patient and public involvement

None.

Results

The total number of participants who entered the study was 390. Table 1 compares the general characteristics of participants between RA cases (n = 130) and controls (n = 260), as well as across different categories of the CHLS, which ranges from 0 to 4. While there were no significant differences in the distribution of males and females between cases and controls, significant differences observed in their distribution across CHLS score categories. The mean BMI of RA cases was significantly higher compared to the control group (28.1 ± 5.2 vs. 26.8 ± 4.7 kg/m², *p* =

0.014). Furthermore, obesity, defined as a BMI ≥ 30 kg/m², was more prevalent among individuals with RA (33.8% vs. 23.1%, $p = 0.023$). In terms of healthy lifestyle scores, participants with a score of 0 exhibited the highest mean BMI (29.9 ± 2.9 kg/m²), while those with a score of 4 had the lowest mean BMI (22.6 ± 2.0 kg/m², $p < 0.001$). Similarly, the prevalence of obesity was significantly lower among participants with a score of 4 (0%) compared to those with a score of 0 (60.0%, p < 0.001). Additionally, higher waist circumference and weight were significantly associated with lower healthy lifestyle scores ($p < 0.001$ for both). Participants with a lifestyle score of 0 exhibited the highest waist circumference (101.7 ± 6.4 cm), whereas those with a score of 4 demonstrated the lowest waist circumference (88.9 ± 9.4 cm, $p < 0.001$). In this study, the difference between cases and controls was not statistically significant (97.5 ± 12.8 cm vs. 95.7 ± 10.8 cm, p = 0.141). Physical activity levels were positively associated with healthy lifestyle scores, increasing from 33.6 ± 4.2 MET-h/day in individuals with a score of 0 to 42.2 ± 5.0 MET-h/day in those with a score of 4 ($p < 0.001$).

Table 2 highlights the dietary intake of selected nutrients and food groups among RA cases, controls, and categories based on healthy lifestyle scores. Regarding energy and macronutrients, although energy intake did not differ significantly between cases and controls (p = 0.191) or across CHLS categories (p = 0.204), participants with a higher CHLS consumed significantly more protein ($p = 0.009$) and fat ($p = 0.039$). Significant differences were observed in the intake of several micronutrients across lifestyle scores. Participants with higher CHLS consumed significantly more vitamin A, vitamin C, vitamin E, zinc, and magnesium compared to those with lower scores (all $p < 0.001$). A statistically significant difference in mean vitamin B6 intakes was observed between cases and controls (13.7 ± 0.8 mg/d vs. 11.8 ± 0.4 mg/d, $p = 0.030$). Regarding food group consumption, individuals with higher score of CHLS showed a significantly greater intake of fruits ($p < 0.001$) and whole grains ($p = 0.038$), along with a notably lower consumption of refined grains ($p < 0.001$). Vegetable consumption was significantly lower in cases compared to controls (479 ± 17 vs. 546 ± 26 g/d, $p = 0.027$).

Figure 1 illustrates the crude and multivariable-adjusted odds ratios (ORs) for the odds of developing RA based on the CLHS. In the crude model, participants with a CLHS of 4 (the healthiest category) had significantly lower odds of developing RA compared to those with a CHLS score of 0 (OR = 0.127, 95% CI: 0.027–0.644, p-trend = 0.006). After adjusting for age (continuous), sex (male/female), and the use of vitamin D and calcium supplements (yes/no), the association remained significant (OR = 0.105, 95% CI: 0.024–0.461, p-trend = 0.001).

Discussion

Our study, a nested case-control investigation, found a significant inverse relationship between CHLS and the likelihood of RA in Iranian adults, even after adjusting for confounders. Specifically, individuals with the highest CHLS showed a reduced the odds of RA compared to those with the lowest scores.

RA pathogenesis is multifaceted, involving genetic predispositions and environmental triggers, as well as their interactions, which play a crucial role in determining susceptibility to RA [3]. Despite the strong role of genetics, numerous studies have primarily focused on single lifestyle factors, such as diet, physical activity, and body mass index (BMI), in relation to RA risk. However, given the interconnectivity of these lifestyle factors, considering them collectively provides a more holistic understanding of their influence on RA risk [11 52]. In past studies, comprehensive lifestyle indices like the Healthy Lifestyle Index Score (HLIS) from the Nurses' Health Study (NHS) have shown that maintaining multiple healthy lifestyle habits can reduce RA risk, especially in cases of seropositive RA. A recent cross-sectional study involving 17,532 adult Americans from the NHANES cohort showed that the Life's Simple 7 (LS7) score—developed according to the American Heart Association (AHA) guidelines to evaluate the cumulative effects of lifestyle risk factors for cardiovascular disease (CVD) through seven indicators: blood pressure, total cholesterol, HbA1c, smoking, BMI, physical activity, and diet exhibits a negative association with RA [42 53]. Our study expands on this by focusing on a synergy between healthy diet, BMI, physical activity, and smoking status as a unified CHLS and its connection to RA risk.

In terms of diet, the beneficial health effects of healthy dietary patterns have been established in relation to many chronic diseases, often by modulating levels of systemic inflammation [54 55]. The role of diet in RA risk is well-supported, particularly through its influence on systemic inflammation. Anti-inflammatory diets, like the AHEI-2010 and the Mediterranean diet, have demonstrated protective effects against RA. While some studies associate Mediterranean diet adherence with pain relief in RA patients, its role in preventing RA remains inconclusive [18 52]. The Nurses' Health Study (NHS), which tracked over 150,000 women and documented more than 1,000 new RA cases, found that sustained healthy eating habits were moderately linked to a lower RA risk, especially for women under 55 years [56]. The study used the AHEI-2010 to evaluate dietary quality, with healthy foods—such as fruits, vegetables, whole grains, nuts, long-chain fats, and polyunsaturated fatty acids (PUFAs), as well as moderate alcohol use—associated with a reduced risk of chronic diseases. In contrast, higher risk was linked to consuming sugar-sweetened drinks, red and processed meats, trans fats, and foods high in sodium [18]. Notably, in our study, we used the HEI-2020 to measure the nutritional quality of the diet, whereas the NHS study employed the AHEI-2010 version, which has minor differences in the scoring of dietary items. Additionally, several investigations have focused on the potential anti-inflammatory benefits of the Mediterranean diet—characterized by its abundance of fruits, vegetables, nuts, legumes, low-fat dairy, seafood, whole grains, and fiber, as well as its high content of antioxidant nutrients and low levels of red and processed meat, animal fat, sweets, and desserts—on the risk of RA. A systematic review assessed how the Mediterranean diet influences both the prevention and symptom management of RA in prospective studies involving humans. While findings suggested that the Mediterranean diet might help reduce pain and symptoms for individuals already diagnosed with RA, the evidence was not strong enough to confirm its role in preventing RA development [57]. Another population-based case-control study involving more than 5,000 participants demonstrated a significant reduction in the risk of seropositive RA among individuals with strong adherence to the Mediterranean diet; however, this effect was observed exclusively in male participants [58]. These findings suggest that a generally healthy diet, as part of a healthy lifestyle, may contribute to reduced odds of RA.

Previous research has suggested various biological mechanisms by which excess body weight could affect RA risk. Obesity is known to be an inflammatory state, marked by increased levels of pro-inflammatory cytokines released by fat cells, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), both of which are linked to RA development [58 59]. In our study, using BMI cut-off point of 25 kg/m^2, we found that higher BMI was associated with increased odds of RA, which aligns with previous findings. On the other hand, obesity is linked to relatively higher estrogen levels. Since RA is more common among females, this increase in estrogen might play a role in the disease's development and prevalence among women [60]. A systematic review encompassing 11 studies explored the relationship between BMI and RA risk, finding that obesity is notably associated with a higher RA risk compared to those without obesity [61]. Similarly, a later meta-analysis, which included 400,609 participants and identified 13,562 RA cases, found that obesity correlated with a relative risk (RR) of 1.21 for RA when compared to individuals with normal BMI. Additionally, for every 5 kg/m² increase in BMI, the RA risk rose by 13% [62]. These findings support our results showing the importance of maintaining normal BMI (< 25 kg/m²) as part of a healthy lifestyle pattern for reducing RA risk. However, these studies primarily examined BMI as a fixed category and did not assess the effects of weight or BMI fluctuations over time on RA risk.

Physical activity may contribute to the pathogenesis of RA through several mechanisms [63]. These mechanisms include energy consumption, the secretion of myokines (such as IL-6, IL-8, and IL-15), modulation of T helper 1/T helper 2 (Th1/Th2) cell levels, increased levels of natural killer (NK) cells, and the secretion of epinephrine and norepinephrine during exercise [64-66]. Together, these effects contribute to reducing systemic inflammation, providing a rationale for the idea that physical activity may protect against RA. Findings from the Swedish Mammography Cohort, which studied 30,112 women aged 54 to 89 years and identified 201 new RA cases, indicated that women who engaged in higher levels of physical activity (over 20 minutes of walking or bicycling daily and more than 1 hour of exercise weekly) had a significantly reduced risk of developing RA compared to those in the lowest physical activity category. These findings further support the potential protective role of regular physical activity in reducing RA risk [67]. Similarly, another prospective cohort study investigated the relationship between recreational physical activity and the risk of RA among women participating in the Nurses' Health Study II. This study utilized repeated measures of physical activity over 26 years and included 113,366 women, identifying 506 new cases of RA. The research focused on the correlation between levels of recreational physical activity and the risk of developing RA. The results indicated that a higher cumulative number of hours spent on recreational physical activities was associated with a significantly lower risk of developing RA compared to lower levels of physical activity. These findings underscore the potential protective effects of regular physical activity against the onset of RA, reinforcing the importance of incorporating physical activity into preventive health strategies [68]. Additionally, a recent meta-analysis, comprising four studies with a total of 255,365 women and 4,213 incident RA cases, identified an inverse relationship between physical activity and RA development. Notably, one study within the meta-analysis reported the progression of joint damage in large joints among individuals with existing extensive joint deterioration when engaging in high-intensity weight-bearing exercises [69]. However, all studies and meta-analyses regard resistance exercise as safe and beneficial for patients with RA [70-72]. Consequently, the European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) both strongly recommend physical activity in RA management [26 73]. EULAR recommends not only aerobic exercise but also specific muscle-strengthening exercises [26], and ACR similarly provides a strong recommendation for both types of exercise [73]. Guidelines from other regions such as Asia Pacific League of Associations for Rheumatology (APLAR) acknowledge the potential benefits of physical activity but note that evidence and resources for structured physical therapy are limited in many countries [74].

The present study has several notable strengths. First, to the best of our knowledge, it is the first study to investigate the relationship between the combined effects of four key healthy lifestyle factors, as represented by the CHLS, and the odds of RA. Second, the study utilized a large, nationally representative database with standardized data collection protocols, which helps minimize potential biases. All data were collected by expert and trained interviewers using reliable and validated questionnaires. Third, the nested case-control design of this study represents a significant strength compared to cross-sectional or traditional case-control designs. This approach offers superior computational efficiency for estimating odds ratios while reducing the risk of selection bias and recall bias.

However, this study also has certain limitations. First, the cross-sectional nature of the data limits the ability to infer causality. Second, as an observational study, it was not possible to fully control for all potential confounding factors and biases. Although the study adjusted for several covariates, unmeasured confounding factors may still exist. Additionally, lifestyle factors were assessed only during the baseline phase of the PDCS, whereas individuals' lifestyles are dynamic and can change over time. Fourth, despite the use of expert and trained interviewers, as well as validated questionnaires for dietary and physical activity assessments, some degree of measurement error is inevitable. These limitations should be considered when interpreting the findings, and future research should aim to address these gaps to further clarify the relationship between lifestyle factors and RA risk.

Additionally, the FFQ has several known limitations, including recall bias, seasonal variations in food intake, and the potential for over- or underestimation of portion sizes. Fifth, due to the incompleteness of the Iranian Food Composition Table (FCT), the USDA FCT was used for dietary analyses, which may introduce minor measurement errors in the calculations of macro- and micronutrient intake. Furthermore, the study lacked detailed body composition measurements beyond BMI, which could have provided more precise insights into the relationship between body composition and RA risk. Finally, we did not account for additional lifestyle factors such as sleep patterns, fatigue levels, stress, and alcohol consumption, despite their reported associations with RA in some studies. It is important to acknowledge that the findings of this study may not be generalizable beyond the specific sample of adults examined. Future research should aim to address these limitations to provide a more comprehensive understanding of the factors influencing RA risk.

Conclusion

In conclusion, the results of our population-based nested case-control study indicate that individuals with a higher CHLS have significantly lower odds of developing RA, even after adjusting for potential confounders. This finding suggests an inverse association between the healthy lifestyle behaviors represented by the CHLS and the incidence of RA. However, further prospective studies with long-term follow-up are necessary to confirm the causal relationship suggested by these results. Such research would provide deeper insights into the role of lifestyle modifications in RA prevention and management.

List of Abbreviations

AHEI: Alternative Healthy Eating Index

ACPA: Anti-citrullinated Protein Antibodies

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

BMI: Body Mass Index

CI: Confidence Interval

CVD: Cardiovascular Disease

EULAR: European League Against Rheumatism

ACR: American College of Rheumatology

APLAR :Asia Pacific League of Associations for Rheumatology

FCT: Food Composition Table

FFQ: Food Frequency Questionnaire

HEI: Healthy Eating Index

CHLS: Combined Healthy Lifestyle Score

HR: Hazard Ratio

IL: Interleukin

MET: Metabolic Equivalent of Task

NHS: Nurses' Health Study

NK: Natural Killer

OR: Odds Ratio

PDCS: PERSIAN Dena Cohort Study

PERSIAN: Prospective Epidemiological Research Studies in IrAN

PUFA: Polyunsaturated Fatty Acid

RA: Rheumatoid Arthritis

RR: Relative Risk

SD: Standard Deviation

SPSS: Statistical Package for the Social Sciences

TNF-α: Tumor Necrosis Factor-alpha

USDA: United States Department of Agriculture

Authorship Contributions

Conception and Design: F.A, J.H, M.J., S.H.S Acquisition of Data: S.A. Analysis and Interpretation of Data: S.H.S, F.A, J.H. Drafting the Manuscript: A.P, M.Z, F.K, V.M, M.J. Revising Manuscript for Intellectual Content: M.J, S.A., F.A. All authors read and approved the final manuscript. M.J. is the guarantor.

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Data Availability Statement

On reasonable request, the corresponding author will provide the datasets used and analyzed during the current work. Correspondence and requests for materials should be addressed to M.J.

Ethics statements

Patient consent for publication

Not applicable.

Ethics approval

The aims of the study were explained in detail, and written informed consent was obtained from all participants [43]. The study was approved by the Ethics Committee of Yasuj University of Medical Sciences (ethics code: IR.YUMS.REC.1401.175).

Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Figure 1. Crude and multivariable-adjusted ORs with 95% CIs for the odds of rheumatoid arthritis across the different categories of the combined healthy lifestyle score (n=390). (a) Crude model; (b) Adjusted for age (continuous), sex (male/female), vitamin D and calcium supplements use (yes/ no)

Table 1. General characteristics of participants by cases and controls as well as different categories of the combined healthy lifestyle score[a]

	Groups		p^b	Combined healthy lifestyle score				
	Cases (n= 130)	Controls (n= 260)		0 (n=5)	1 (n=61)	2 (n=159)	3 (n=94)	4 (n=71)
Sex, n(%)								
Males	29 (22.3)	60 (23.1)	0.865	5 (100.0)	26 (42.6)	35 (22.0)	14 (14.9)	9 (12.7)[c]
Females	101 (77.7)	200 (76.9)		0 (0.0)	35 (57.4)	124 (78.0)	80 (85.1)	62 (87.3)
Age (year)	49.8 ± 9.7	50.6 ± 9.3	0.484	45.8 ± 9.9	50.4 ± 10.1	50.8 ± 9.5	51.1 ± 9.0	48.4 ± 9.2
Weight (kg)	72.4 ± 13.1	70.2 ± 12.8	0.110	75.1 ± 8.8	75.8 ± 11.1	73.6 ± 12.6	69.9 ± 14.1	62.1 ± 8.8[c]
Height (cm)	164.2 ± 11.2	164.7 ± 10.1	0.649	176.4 ± 9.0	167.1 ± 12.0	163.5 ± 10.3	162.7 ± 9.2	166.1 ± 10.1
Waist circumference (cm)	97.5 ± 12.8	95.7 ± 10.8	0.141	101.7 ± 6.4	100.6 ± 10.3	98.4 ± 11.1	95.2 ± 12.0	88.9 ± 9.4[c]
BMI (kg/m^{2})	28.1 ± 5.2	26.8 ± 4.7	0.014	29.9 ± 2.9	29.9 ± 4.2	28.3 ± 4.6	26.9 ± 5.3	22.6 ± 2.0[c]
Obesity, n (%) [d]	44 (33.8)	60 (23.1)	0.023	3 (60.0)	29 (47.5)	45 (28.3)	27 (28.7)	0 (0.0)[c]
Educational level, n (%)								
Diploma and lower	122 (93.8)	223 (85.8)	0.019	5 (100.0)	57 (93.4)	148 (93.1)	76 (80.9)	59 (83.1)
University	8 (6.2)	37 (14.2)		0 (0.0)	4 (6.0)	11 (6.9)	18 (19.1)	12 (16.9)
Marital status, n (%)								
Married	122 (93.8)	223 (85.8)	0.912	5 (100.0)	49 (80.3)	133 (83.6)	89 (94.7)	68 (95.8)
Unmarried/divorced/widowed	8 (6.2)	37 (14.2)		0 (0.0)	12 (19.7)	26 (16.4)	5 (5.3)	3 (4.2)[c]
Vitamin D supplement use, n (%)	53 (40.8)	95 (36.5)	0.417	0 (0.0)	18 (29.5)	53 (33.3)	40 (42.6)	37 (52.1)[c]
Calcium supplement use, n (%)	27 (20.8)	30 (11.5)	0.015	0 (0.0)	6 (9.8)	20 (12.6)	23 (24.5)	8 (11.3)[c]
Physical activity (MET-h per day)	39.3 ± 6.1	40.3 ± 4.5	0.088	33.6 ± 4.2	37.2 ± 4.7	39.4 ± 4.1	40.9 ± 5.5	42.2 ± 5.0[c]
Current smoker, n (%)	18 (13.8)	34 (13.1)	0.833	5 (100.0)	24 (39.3)	16 (10.1)	7 (7.4)	0 (0.0)[c]

Abbreviations: BMI, body mass index; MET, metabolic equivalent

[a] All data are reported as means ± standard deviations unless indicated.

[b] Determined using the independent sample t-test or chi-square test, where appropriate.

[c] Significant difference with the lowest combined healthy lifestyle score ($p < 0.05$, determined using the one-way ANOVA test or chi-square test, where appropriate)

[d] Obesity was defined as BMI ≥ 30 kg/m^2

$p < 0.05$ was considered as statistically significant.

Table 2. Dietary intakes of selected nutrients and food groups of participants by cases and controls as well as different categories of the combined healthy lifestyle score[a]

	Groups			Combined healthy lifestyle score				
	Cases (n= 130)	Controls (n= 260)	p[b]	0 (n=5)	1 (n=61)	2 (n=159)	3 (n=94)	4 (n=71)
Energy (kcal/d)[d]	2380 ± 62	2486 ± 48	0.191	2645 ± 198	2369 ± 92	2374 ± 59	2585 ± 78	2498 ± 92
Nutrients								
Carbohydrate (g/d)	383 ± 10	407 ± 8	0.077	429 ± 41	384 ± 16	389 ± 110	415 ± 12	407 ± 16
Protein (g/d)	75.2 ± 2.2	77.8 ± 1.7	0.375	78.0 ± 5.6	73.1 ± 3.1	72.5 ± 2.0	83.3 ± 3.0	81.7 ± 3.3
Fat (g/d)	66.7 ± 2.0	66.5 ± 1.6	0.934	72.4 ± 7.6	63.4 ± 3.0	63.2 ± 1.8	72.7 ± 2.8	68.4 ± 3.1
Saturated fat (g/d)	25.3 ± 1.0	23.9 ± 0.7	0.224	21.5 ± 2.0	22.8 ± 1.3	25.1 ± 0.9	25.0 ± 1.0	23.6 ± 1.2
Trans fatty acids (g/d)	0.23 ± 0.02	0.26 ± 0.02	0.397	0.31 ± 0.11	0.24 ± 0.04	0.23 ± 0.02	0.31 ± 0.03	0.21 ± 0.02
Fiber (g/d)	28.3 ± 0.5	30.7 ± 0.4	0.346	28.1 ± 0.3	28.7 ± 0.3	29.1 ± 0.4	30.8 ± 0.9	30.2 ± 0.7
Vitamin A (RAE/d)	748 ± 57	710 ± 26	0.490	714 ± 131	638 ± 98	602 ± 26	904 ± 58	826 ± 48[c]
Vitamin C (mg/d)	130 ± 7	141 ± 6	0.247	93 ± 9	99 ± 8	122 ± 7	159 ± 10	179 ± 10[c]
Vitamin E (mg/d)	7.8 ± 0.3	8.2 ± 0.3	0.341	6.8 ± 0.6	6.5 ± 0.3	7.1 ± 0.2	9.1 ± 0.4	9.6 ± 0.5[c]
Folate (mcg/d)	546 ± 15	580 ± 13	0.109	612 ± 33	565 ± 24	560 ± 16	589 ± 22	563 ± 22
Vitamin B_6 (mg/d)	13.7 ± 0.8	11.8 ± 0.4	0.030	13.0 ± 4.4	11.0 ± 0.8	11.6 ± 0.6	13.6 ± 0.9	13.5 ± 0.9
Zinc (mg/d)	9.2 ± 0.3	9.4 ± 0.2	0.640	9.4 ± 0.6	8.7 ± 0.4	8.7 ± 0.2	10.2 ± 0.4	10.3 ± 0.4
Selenium (mg/d)	99 ± 4	104 ± 3	0.218	117 ± 7	106 ± 5	99 ± 3	107 ± 4	98 ± 5
Magnesium (mg/d)	335 ± 10	345 ± 8	0.468	311 ± 22	304 ± 12	318 ± 9	374 ± 13	384 ± 16[c]
Calcium (mg/d)	1164 ± 16	1179 ± 15	0.520	1125 ± 14	1156 ± 12	1190 ± 15	1206 ±23	1239 ±35
Iron (mg/d)	9.02 ± 0.23	9.26 ± 0.20	0.319	9.29 ± 0.21	8.94 ± 0.19	9.16 ± 0.12	9.30 ± 0.24	9.73 ± 0.23
Food groups								
Whole grains (g/d)	30.5 ± 5.4	24.4 ± 4.8	0.441	7.9 ± 1.2	14.1 ± 2.5	18.8 ± 2.4	44.6 ± 13.6	31.2 ± 6.4
Refined grains (g/d)	515 ± 19	524 ± 14	0.689	656 ± 62	571 ± 26	569 ± 20	457 ± 17	447± 23[c]
Fruits (g/d)	551 ± 35	558 ± 24	0.863	292 ± 41	375 ± 31	504 ± 26	613 ± 37	765 ± 61[c]
Vegetables (g/d)	479 ± 17	546± 26	0.027	621 ± 136	487 ± 34	479 ± 24	532 ± 31	510 ± 27
Legumes and nuts (g/d)	73.9 ± 4.0	67.4 ± 2.5	0.152	84.7 ± 17.8	59.9 ± 4.7	66.4 ± 3.5	75.6 ± 4.6	75.9 ± 4.4
Meats (g/d)	145 ± 7	136 ± 4	0.287	144 ± 27	129 ± 8	134 ± 6	151 ± 8	143 ± 8
Dairy products (g/d)	353 ± 24	304 ± 15	0.081	224 ± 76	293 ± 38	332 ± 23	316 ± 22	330 ± 25
Sugar-sweetened beverages (g/d)	125 ± 10	134 ± 9	0.585	188 ± 112	130 ± 18	140 ± 13	143 ± 15	92 ± 11

[a] All data are reported as means ± S.E.
[b] Determined using the independent samples *t*-test
[c] Significant difference with the lowest combined healthy lifestyle score ($p < 0.05$, determined using the ANCOVA test)
[d] Energy intake is adjusted for age and sex, all other values are adjusted for age, sex, and energy intake.
$p < 0.05$ was considered as statistically significant

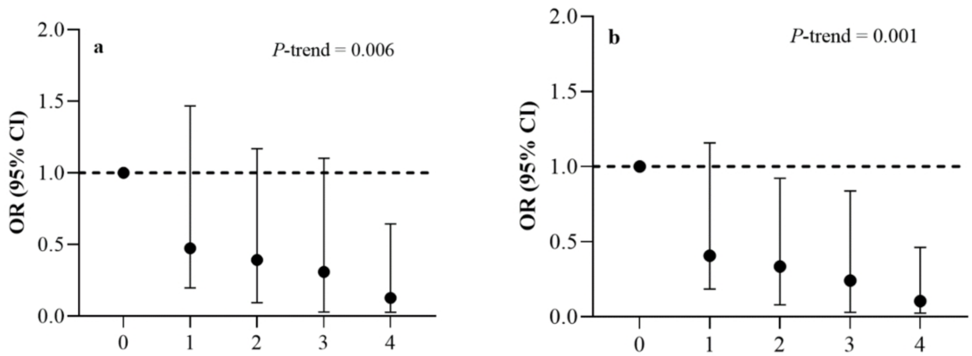

Figure 1. Crude and multivariable-adjusted ORs with 95% CIs for the odds of rheumatoid arthritis across the different categories of the combined healthy lifestyle score (n=390). (a) Crude model; (b) Adjusted for age (continuous), sex (male/female), vitamin D and calcium supplements use (yes/ no). P-trend values were determined by the Mantel-Hanszel extension χ2 test.

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