DR. JEFFREY A. SPARKS (Orcid ID : 0000-0002-5556-4618)

Article type : Original Article

Effectiveness of a web-based personalized rheumatoid arthritis risk tool with or without a health educator for knowledge of RA risk factors

Maria G. Prado, MPH[1]
Maura D. Iversen, PT, DPT, SD, MPH[1,2,3,4]
Zhi Yu, MS[1]
Rachel Miller Kroouze, MA[1]
Nellie A. Triedman, BA[1]
Sarah S. Kalia, ScM[5]
Bing Lu, DrPH[1,2]
Robert C. Green, MD, MPH[2,6,7]
Elizabeth W. Karlson, MD, MS[1,2]
Jeffrey A. Sparks, MD, MMSc[1,2]

[1]Department of Medicine, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA
[2]Harvard Medical School, Boston, MA
[3]Department of Physical Therapy, Movement and Rehabilitation Sciences, Northeastern University, Boston, MA
[4]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden
[5]Harvard T.H. Chan School of Public Health, Boston, MA
[6]Department of Medicine, Division of Genetics, Brigham and Women's Hospital, Boston, MA
[7]Broad Institute, Cambridge, MA

Funding/Support: This work was supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) under award number P60 AR047782. Dr. Sparks is supported by NIAMS under award numbers K23 AR069688 and L30 AR066953 as well as the Rheumatology Research Foundation Scientist Development Award. Dr. Karlson is supported by NIAMS under award numbers R01 AR049880, P30 AR070253, and P30 AR069625. Dr. Green is supported by U01 HG006500, U19 HD077671, R01 HG005092, U01 HG008685, and U41 HG006834. The funders had no role in study design, data collection, analysis, decision to publish, or preparation of the manuscript. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Running head: Personalized RA risk disclosure and RA risk factor knowledge

Keywords: personalized medicine, rheumatoid arthritis, risk factors, patient education, health behaviors

Correspondence and reprint requests:

Jeffrey A. Sparks, MD, MMSc
Department of Medicine
Division of Rheumatology, Immunology and Allergy
Brigham and Women's Hospital
60 Fenwood Road, #6016U
Boston, MA 02115
Phone: 617-525-1038
Fax: 617-713-3030
Email: jsparks@bwh.harvard.edu

SIGNIFICANCE & INNOVATIONS

- We analyzed data from a randomized controlled trial to test whether personalized educational strategies increased RA risk factor knowledge.
- Despite prior research identifying modifiable RA risk factors, first-degree relatives (FDRs) had low baseline knowledge of these behaviors.
- After receiving web-based disclosure of personalized RA risk, FDRs significantly increased their knowledge of RA risk factors over 12 months of follow-up compared to the standard strategy of RA education.
- We developed a web-based personalized RA education tool that successfully increased RA risk factor knowledge and could be widely implemented.

ABSTRACT

Objective: To assess knowledge of rheumatoid arthritis (RA) risk factors among unaffected first-degree relatives (FDRs) and to study whether a personalized RA education tool increases risk factor knowledge.

Methods: We performed a randomized controlled trial assessing RA educational interventions among 238 FDRs. The web-based Personalized Risk Estimator for RA (PRE-RA) tool displayed personalized RA risk results (genetics, autoantibodies, demographics, and behaviors) and educated about risk factors. Subjects were randomly assigned to: Comparison arm (standard RA education, n=80), PRE-RA arm (PRE-RA alone, n=78), or PRE-RA Plus arm (PRE-RA and a one-on-one session with a trained health educator, n=80). The RA Knowledge Score (RAKS, the number of 8 established RA risk factors identified as related to RA) was calculated at baseline and post-education (immediate/6 weeks/6 months/12 months). We compared RAKS and its components at each post-education point by randomization arm.

Results: At baseline before education, few FDRs identified behavioral RA risk factors (15.9% for dental health, 31.9% for smoking, 47.5% for overweight/obesity, and 54.2% for diet). After education, RAKS increased in all arms, higher in PRE-RA and PRE-RA Plus than Comparison at all post-education points ($p<0.05$). PRE-RA were more likely to identify risk factors than those that received standard education (proportion agreeing smoking is a risk factor at 6 weeks: 83.1% in PRE-RA Plus arm, 71.8% in PRE-RA, and 43.1% in Comparison arms, $p<0.05$ for PRE-RA vs. Comparison).

Conclusion: Despite being both familiar with RA and at increased risk, FDRs had low knowledge about RA risk factors. A web-based personalized RA education tool successfully increased RA risk factor knowledge.

Health behaviors, such as diet, smoking, and exercise, are important modifiable risk factors for many chronic diseases, including rheumatic diseases such as rheumatoid arthritis (RA) (1-5). As medical care shifts its focus from treatment to prevention and early detection of chronic diseases, clearly communicating and contextualizing factors that may affect disease risk becomes crucially important. Therefore, understanding and measuring these qualities of health literacy in at-risk populations is an essential first step to providing effective education that promotes positive health behavior changes (6, 7).

RA is a chronic autoimmune disease that affects about 1% of the population (8). While the etiology of RA is not yet fully understood, previous studies have identified several risk factors to be associated with the development of RA. The contribution of genetic factors to RA risk has been estimated to be as high as 50% in twin studies (9). Other non-modifiable risk factors include the presence of RA-related auto-antibodies, rheumatoid factor (RF), and cyclic citrullinated peptide (CCP) (10, 11). Modifiable risk factors such as smoking, obesity, low fish consumption, and poor dental health also increase risk for developing RA (5, 12-15). Modifiable factors may account for up to 41% of the risk of developing RA (16). Despite this progress, it is unclear whether those at risk for RA know about these modifiable risk factors, particularly those who are at increased susceptibility due to positive family history.

Health education has been shown to enhance knowledge and help individuals modify lifestyle behaviors that place them at risk for disease (6). Health education can be delivered in a variety of modes including in person through one-on-one and group sessions with health educators and virtually, either through written materials or through interactive web-based platforms. Information may be standardized or personalized to an individual's risk factor profile. Incorporating a personalized medicine approach, such as individualized genetic and biomarker testing to disclose personalized genetic risk, into health education about lifestyle and behavioral factors may be an effective method to influence behaviors (17, 18). Another educational approach, motivational interviewing (MI) is a goal-oriented, person-centered approach that aims

to support behavior change by identifying a patient's readiness and ambivalence for behavior change. MI uses techniques such as asking open-ended questions, providing affirmations, and using reflective listening (19). A systematic review of 72 studies found that MI outperformed traditional advice in 80% of studies (20). MI can encourage weight loss in overweight and obese patients and may be efficacious for smoking cessation (21, 22). While MI has primarily been used to facilitate behavior change, greater knowledge can be obtained or reinforced during the interaction which may ultimately contribute to improved downstream clinical outcomes (23).

This study tested the effectiveness of RA educational interventions using a randomized controlled trial that allocated unaffected first-degree relatives (FDR) of patients with RA to personalized RA risk education or standard RA education. The primary analysis from the Personalized Risk Estimator for RA (PRE-RA) Family Study reported that disclosure of RA risk personalized with genetic, biomarker and behavioral risk factor results increased motivation to improve RA risk-related behaviors compared to non-personalized education, ClinicalTrials.gov identifier NCT02046005) (24).

In this secondary analysis of the PRE-RA Family Study, we aimed to describe the baseline knowledge of RA risk factors among FDRs prior to RA education and to investigate which educational intervention most effectively improves RA risk factor knowledge. We focused on FDRs because they are at increased risk for RA and are familiar with RA due to interaction with their RA-affected relatives. We performed this randomized controlled trial using three strategies of RA education: 1) Comparison arm that received standard education; 2) PRE-RA arm that received an interactive web-based RA risk tool personalized using demographics, behaviors, biomarkers, and genetics; and 3) PRE-RA Plus arm that received the same interactive web-based RA risk tool and additionally received a one-on-one session with a health educator trained in MI techniques. We hypothesized that subjects who received personalized RA risk information would demonstrate greater knowledge of RA risk factors after the educational intervention than subjects receiving standard RA education. Further, we

hypothesized that subjects in the PRE-RA Plus arm who received one-on-one health education with a health educator using MI techniques would demonstrate greater knowledge of RA risk factors and retain this knowledge longer than subjects in the PRE-RA arm.

METHODS

Study population

We recruited FDRs of patients with RA at a large tertiary care medical center (Brigham and Women's Hospital, Boston, MA). Adult FDRs aged <70 years without diagnosis of RA or other systemic rheumatic disease were eligible. Past or current inflammatory arthritis was assessed during eligibility screening by using a modified version of the Connective Tissue Disease Screening Questionnaire (25). Those who had a positive screen had a complete joint examination by a study rheumatologist (JAS). Anyone with inflammatory arthritis on examination was excluded. We also excluded non-English-speaking individuals, since the study materials and interventions were developed in English. All aspects of the study were approved by the Partners HealthCare Institutional Review Board.

Study design

We performed a randomized controlled trial of RA educational interventions. All subjects completed demographic and RA risk factor knowledge information at baseline, prior to intervention. Subjects were then randomly allocated to one of three educational interventions using permuted block randomization. RA risk factor knowledge was assessed at the following time points after educational intervention: immediately, 6 weeks, 6 months, and 12 months. Data were collected at in-person study visits at baseline, immediately following RA education intervention, and after the 6-month booster RA education visit. Assessments at 6-week and 12-month time points were collected using mailed questionnaires. The study was performed from 2013 to 2016. The study flow of recruitment and follow-up is shown in **Figure 1**.

PRE-RA tool

The PRE-RA web-based educational intervention is an interactive educational tool adapted from Your Disease Risk (http://www.yourdiseaserisk.wustl.edu), which was customized for the PRE-RA Family Study to incorporate personalized genetic and biomarker information and RA-specific material (26). The PRE-RA tool collects data on age, sex, family history of RA and autoimmune diseases in FDRs, and RA risk-related behaviors (height, weight, physical activity, diet including fish and fish oil supplements, dental health, and smoking) (27-30). Individuals received personalized genetic results (positive defined as any shared epitope, or negative), autoantibody results (RF and/or CCP positive or both negative), and an interactive webpage with a thermometer graphic that displayed non-modifiable risk factors, and modifiable risk factors, where clicking on an individual risk factor raised or lowered the height of the thermometer based on its presence and strength of association with RA (**Figure 2**). Risk factor education was also provided throughout the PRE-RA tool with links to personalized educational tips, text, and websites. Individuals also received quantitative lifetime risk estimates for RA as a graphic representation with a proportion of 100 pictographs shaded to represent their personal lifetime risk of developing RA (along with text showing the percent likelihood of developing RA).

Interventions and study arms

Comparison arm. Subjects randomized to the Comparison arm received standard, non-personalized education about RA conveyed in a one-on-one lecture format. The RA education consisted of RA signs and symptoms, treatment, screening, pathophysiology, and epidemiology. RA education in the Comparison arm was geared towards the general population, not patients with RA. Detailed information on RA behavioral risk factors, genetics, and autoantibodies were not presented, as is typical for standard care.

PRE-RA arm. Subjects randomized to the PRE-RA study arm received personalized RA health education via the PRE-RA web-based tool. Information provided included genetic and autoantibody results, and personalized relative risk (through graphic display) and lifetime risk (in percent) of developing RA.

PRE-RA Plus arm. Subjects randomized to the PRE-RA Plus arm received education via the web-based tool plus a one-on-one session with a health educator using MI techniques. The MI session consisted of an interactive session tailored to the subject's behaviors and individual results attained from the PRE-RA tool. The session included interpretation of genetic and autoantibody results as well as education of how behaviors might increase or decrease the risk for developing RA.

6-month booster education. At the conclusion of the 6-month post-education visit, all subjects received another session of RA education according to the original assignment of study arm. The education portion of the study occurred after surveys were obtained that measured RA risk factor knowledge.

Outcomes

RA Knowledge Score (RAKS). The primary outcome of this study was RA risk factor knowledge, measured by RAKS. We collected whether subjects agreed or disagreed that risk factors were related to RA development using the previously validated Illness Perception Questionnaire that was modified for RA (31). This questionnaire consists of a list of possible RA risk factors that range from modifiable factors such as smoking or high caffeine intake, to non-modifiable factors such as heredity. Subjects indicated their beliefs about whether each risk factor is related to RA risk using a 5-point Likert scale with possible answers of: "strongly disagree," "disagree," "neither agree nor disagree," "agree," or "strongly agree." **Table 1** shows the items on this questionnaire. From this list of possible risk factors, we chose 8 established risk factors for RA (aging, altered immunity, being overweight/obese, diet or eating habits,

genetics or heredity, my own behavior, poor dental health, and smoking) to calculate RAKS (32-34). RAKS was the sum of the number of these 8 RA risk factors that a subject either agreed or strongly agreed was related to RA, with a possible range of 0-8, and higher scores indicating more RA risk factor knowledge. Other items on the questionnaire were not considered in the score. We assessed RAKS at baseline among the entire study sample. We then compared responses between subjects allocated to the Comparison, PRE-RA, and PRE-RA Plus arms immediately post-education intervention, through mail-in surveys at 6 weeks post-education, prior to the 6 month booster education, and at the conclusion of the 12 month trial.

Individual components of RAKS. In addition to the overall RAKS score, we evaluated the proportion of subjects agreeing that the components of RAKS were related to RA risk (left column of **Table 1**). We calculated the proportion of the entire study sample at baseline prior to RA education that agreed that each item was a risk factor for RA. We then analyzed each post-education time point and arm separately to evaluate the change over time for knowledge of each risk factor.

Statistical analysis

We used descriptive statistics to characterize the study sample by study arm at baseline and describe knowledge of individual RA risk factors. We calculated the continuous RAKS scores at baseline and each post-education time point by study arm and plotted these scores over time to evaluate for trend before and after each educational intervention. Similarly, we reported the proportion of subjects in each arm that agreed each RA risk factor in RAKS was related to RA risk. Since characteristics were balanced across study arms prior to randomization, we reported the baseline proportion of those that agreed RAKS components were RA risk factors among the entire study at baseline for ease of interpretation.

For our primary analysis, we used linear regression comparing study arms at each post-intervention time point where RAKS was the dependent variable and the study arms were the

independent variables, adjusted for baseline RAKS. We made the following between-arm comparisons at each post-intervention time point: PRE-RA Plus vs. Comparison, PRE-RA vs. Comparison, and PRE-RA Plus vs. PRE-RA at each post-education study time point. We compared the PRE-RA Plus and PRE-RA arms to investigate whether the health educator offered additional benefit beyond the web-based PRE-RA tool.

In the secondary analysis investigating the 8 individual components of RAKS, we compared the percentage of those who agreed or strongly agreed to the RA risk factors by study arm at each time point using chi-square tests. Similar to the primary analysis, we performed the following between-arm comparisons for each component at each post-education time point: PRE-RA Plus vs. Comparison, PRE-RA vs. Comparison, and PRE-RA Plus vs. PRE-RA.

We considered a two-sided p value <0.05 as statistically significant. All analyses were performed using SAS v9.4 (Cary, NC).

RESULTS

Study subject characteristics

The study sample included 238 subjects who were randomized to the Comparison arm (n=80), the PRE-RA arm (n=78), or the PRE-RA Plus arm (n=80). The study flow showing recruitment, enrollment, and follow-up is summarized in **Figure 1**. A total of 206 subjects (87%) completed 12 months of follow-up and this high follow-up rate was similar in all arms.

Baseline characteristics of randomized subjects assigned to each study arm are summarized in **Table 2**. The majority of subjects were female (79% in the Comparison arm, 80% in the PRE-RA arm, and 71% in the PRE-RA Plus arm). Study subjects were also highly educated, with 88% having greater than high school education. There were no statistically significant differences between the study arms regarding any of the baseline characteristics, as expected in this randomized controlled trial.

Primary outcome: RA knowledge score (RAKS)

At baseline prior to the educational intervention, RAKS was similarly low in all study arms (4.4, SD 1.9 for the Comparison arm; 4.5, SD 1.9 for the PRE-RA arm; and 4.0, SD 1.9 for the PRE-RA Plus arm) as shown in **Figure 3**. Immediately after the educational intervention, there were statistically significant improvements in RAKS in both the PRE-RA and PRE-RA Plus arms compared to the Comparison arm (p<0.05). The PRE-RA arm had mean RAKS of 7.0 (SD 1.2) and the PRE-RA Plus arm had mean RAKS of 7.2 (SD 0.8) compared to the Comparison arm, which had a mean RAKS of 5.3 (SD 1.7). While the RAKS score decreased at subsequent time points, it remained higher than at baseline in all arms. RAKS remained significantly higher in the PRE-RA arm (at 6 weeks: 6.0, SD 1.7; at 6 months: 6.1, SD 1.6) and PRE-RA Plus arm (at 6 weeks: 6.5, SD 1.6; at 6 months: 6.4, SD 1.6) compared to the Comparison arm (at 6 weeks: 5.1, SD 2.2; at 6 months: 4.8, SD 2.0) (p<0.05 for all comparisons). Overall, the increased RAKS in the PRE-RA and PRE-RA Plus arms was maintained during the entire study 1-year follow-up period.

We also compared the PRE-RA Plus and PRE-RA arms to investigate whether the health educator offered additional benefit in RA knowledge beyond the web-based PRE-RA tool. Subjects in the PRE-RA Plus arm had slightly higher RAKS than those in the PRE-RA arm at all post-education time points. However, this difference was only statistically significant at 6 weeks and 12 months post-education (p<0.05).

Individual RA risk factor knowledge

Knowledge of specific risk factors was measured by the proportion of subjects who correctly identified each of the 8 risk factors of RAKS, by indicating that they agreed or strongly agreed that the risk factor was related to RA (**Table 3**). At baseline, combining all three arms, nearly all subjects (96.2%) agreed that heredity or genetics is related to RA risk. However, only

15.6% agreed or strongly agreed that poor dental health is related to RA. Smoking, one of the most well-established modifiable risk factors for RA, was not perceived as a risk factor by the majority of FDRs at baseline, with only 31.9% agreeing or strongly agreeing that smoking is related to RA risk. Similarly, FDRs had low knowledge about other modifiable RA risk factors: my own behavior (43.7%), being overweight/obese (47.5%), and diet (54.2%).

After the RA educational intervention, a significantly greater percentage of subjects in the PRE-RA arm relative to the Comparison arm identified that the following 3 risk factors were related to RA at the 6 week study time point: poor dental health (86.8% vs. 37.3%), smoking (69.1% vs. 48.0%), diet or eating habits (77.9% vs. 56.0%) (p<0.05 for all comparisons). The statistically significant difference between the PRE-RA and Comparison arms persisted at 6 months and 12 months post-education.

Subjects in the PRE-RA Plus arm identified even more of the 8 risk factors at 6 weeks post-education compared to the Comparison arm: poor dental health (91.6% vs. 37.3%), smoking (78.9% vs. 48.0%), my own behavior (74.7% vs. 53.3%), being overweight/obese (83% vs. 52%), diet or eating habits (83% vs. 56%) (p<0.05 for all comparisons). At 6 months and 12 months post-educational intervention, the statistically significant differences between these groups regarding these 5 risk factors persisted.

When comparing PRE-RA Plus and PRE-RA arms, a greater percentage of subjects in the PRE-RA Plus arm agreed that the following risk factors were related to RA: my own behavior (74.7% vs. 55.9%, p<0.05) and being overweight/obese (83.1% vs. 66.2%, p<0.05). At 6 months, more subjects in the PRE-RA Plus arm than the PRE-RA arm agreed that overweight/obese (81.7% vs. 63.4%, p<0.05) was an RA risk factor. At 12 months, the only risk factor that had higher knowledge in PRE-RA Plus arm was poor dental health (98.5% vs. 86.8%, p<0.05). There were no other differences when comparing the PRE-RA Plus and PRE-RA arms.

DISCUSSION

In this randomized controlled trial performed among FDRs without RA, we found that the baseline knowledge of RA risk factors was low but increased significantly following a personalized RA educational intervention. Personalized health education with disclosure of RA risk via the web-based tool in the PRE-RA and PRE-RA Plus arms led to significantly higher RAKS at all post-education time points when compared to the Comparison arm that received standard, non-personalized education. Overall, the health educator provided only modest excess benefit beyond the web-based PRE-RA tool, suggesting that the web-based platform alone could be sufficient to educate FDRs about RA risk factors.

A systematic review of health education interventions demonstrated improved health literacy for a variety of illnesses in the primary care setting (6). Some studies found that providing personalized risk estimates alone is insufficient to change behaviors (18, 35, 36). MI was found to effectively motivate behavior change, and outperformed traditional strategies in the treatment of behavioral problems and diseases (20). In our study, the PRE-RA arm (personalized RA risk factor education) had a similar increase in RAKS as the PRE-RA Plus arm (personalized RA risk factor education with health educator using MI techniques). This suggests that viewing personalized risk information for RA increases health literacy regardless of using MI techniques through a health educator. MI techniques may be more useful for individuals with a disease, rather than those who were at risk for a disease, such as our study population of FDRs unaffected with RA. However, there were some modest improvements in RA risk factor knowledge in the PRE-RA Plus arm compared to PRE-RA alone.

Epidemiologic studies show strong associations between smoking and increased RA risk (5), moderate associations between overweight/obesity and increased RA risk (37-40) and periodontitis and increased RA risk (13, 29), and modest protective associations of fish/omega-3 fatty acid consumption (14, 15, 41, 42). Despite this extensive literature, risk factor knowledge for modifiable lifestyle and behavioral risk factors was low among FDRs in our study even

though they were motivated to participate in this study. Particularly concerning was the lack of knowledge about well-established risk factors for RA, such as smoking. While few subjects were active smokers, most subjects disagreed, rather than agreed, that smoking was a risk factor for RA. Since this is one of the most well established behavioral RA risk factors, our findings suggest that more work needs to be done in educating those at risk for developing RA before there can be any potential for behavior change or pharmacologic intervention that might result in preventing or delaying the onset of RA. These results are particularly pertinent now that multiple pharmacologic studies for RA prevention are actively enrolling subjects based on risk factor profiles, autoantibody positivity, arthralgias, or subclinical synovitis (34, 43).

We used data from a randomized controlled trial using a novel web-based interactive tool for personalized RA education, so these results are unlikely to be confounded by other factors. We modeled our tool based on Your Disease Risk, a standard web-based risk calculator that has already been widely implemented for 12 cancers and 6 other chronic diseases (44). We used disclosure techniques of risk incorporating several quantitative and qualitative approaches after extensive literature review (45). All study health educators underwent standardized training for MI techniques. We recruited family members of patients seen at our center who were known to have RA and did not rely solely on self-report of family history. We did not enroll any subjects who had early or undiagnosed inflammatory arthritis. Other strengths of our study include: 12 months of follow-up, which is relatively lengthy for a behavioral intervention study; ability to detect a difference between study arms; and high rates of follow-up.

Our study has several limitations. Although there is some evidence that changing smoking behavior can reduce RA risk (46, 47), there are less data showing that behavior change for diet, physical activity, weight loss, and dental care actually reduce RA risk. While RAKS was developed based on a validated survey instrument (31), its validity in capturing RA risk factors has not been established. Further, we created RAKS through expert consensus but alternative definitions of RA knowledge are possible and may have affected results. However, when

analyzing the individual components of RAKS, such as smoking, we observed similar effects as the overall score. Therefore, we find it unlikely that our results are due to the derivation of RAKS. While we used a randomized controlled trial, this was a secondary analysis so should be considered as hypothesis-generating and not as confirmatory. Further, we were unable to blind subjects or study staff to allocation of arms due to the nature of the study which may have affected results. While we observed the greatest difference in knowledge attainment between PRE-RA Plus arm and the Comparison arm, we only included two brief sessions with the health educator. Other more intense approaches using MI techniques may have resulted in even greater differences. We did observe that subjects in the Comparison arm had an increase in RA knowledge over time likely due to participation in the study and interest in RA prevention. However, we were still able to detect differences between both PRE-RA arms and the Comparison arm throughout the study. While the PRE-RA tool could be widely implemented based only on questionnaires, our study used genetics and autoantibody results which may have motivated FDRs to participate. It is unclear how well the PRE-RA tool might perform without these components. Because our study population was highly educated (88% had more than a high school education) and were mostly white, our results may not be widely generalizable. Despite this high level of education, the baseline knowledge of RA risk factors in our study was very low. This suggests that enacting this intervention in more diverse and less educated populations might have an even greater impact on increasing knowledge of RA risk factors which could result in positive health behavior changes and ultimately lower the risk for RA.

In conclusion, our results suggest that a web-based tool using personalized RA risk disclosure may be effective in educating unaffected FDRs about RA risk factors. Our study suggests that the PRE-RA web-based tool may be a helpful public health resource for providing personalized risk disclosure and increasing RA risk knowledge, particularly among FDRs without RA. Since we found similar results when comparing the PRE-RA Plus and PRE-RA

arms, this suggests that even without in-person facilitation, the PRE-RA tool could be widely implemented to educate about RA risk factors and motivate healthy behavior change.

ACKNOWLEDGMENTS

We thank Graham Colditz, MD, DrPH and Hank Dart, MSc for their assistance in creating the web-based PRE-RA tool, based on Your Disease Risk (http://www.yourdiseaserisk.wustl.edu/).

The authors thank Michelle L. Frits, BA, Christine K. Iannaccone, MPH, Taysir G. Mahmoud, BA, J. Adebukola Awosogba, MA, Jessica Brandano, BA, Jonathan C. Karlson, BA, David J. Kreps, MS, Elisabeth Smith, Beatrice Pan, MPH, and the Massachusetts chapter of the Arthritis Foundation for assistance in recruitment and data collection. Finally, we thank the patients, families, staff, and physicians at the Brigham Orthopaedic and Arthritis Center at Brigham and Women's Hospital, the Arthritis and Orthopedic Center at Brigham and Women's Faulkner Hospital, the 850 Boylston Arthritis Center, the Fish Center at 850 Boylston, and the BWH Arthritis Center at Braintree.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published. Dr. Sparks had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Prado, Iversen, Miller Kroouze, Triedman, Karlson, Sparks

Acquisition of data. Prado, Iversen, Miller Kroouze, Triedman, Kalia, Karlson, Sparks

Analysis and interpretation of data. Prado, Iversen, Yu, Miller Kroouze, Triedman, Kalia, Lu, Green, Karlson, Sparks

REFERENCES

1. Byrne DW, Rolando LA, Aliyu MH, McGown PW, Connor LR, Awalt BM, et al. Modifiable Healthy Lifestyle Behaviors: 10-Year Health Outcomes From a Health Promotion Program. Am J Prev Med. 2016;51(6):1027-37.
2. Ford ES, Bergmann MM, Kroger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. Arch Intern Med. 2009;169(15):1355-62.
3. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. JAMA. 2004;291(10):1238-45.
4. Hu Y, Sparks JA, Malspeis S, Costenbader KH, Hu FB, Karlson EW, et al. Long-term dietary quality and risk of developing rheumatoid arthritis in women. Ann Rheum Dis. 2017;76(8):1357-64.
5. Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, et al. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2010;69(1):70-81.
6. Taggart J, Williams A, Dennis S, Newall A, Shortus T, Zwar N, et al. A systematic review of interventions in primary care to improve health literacy for chronic disease behavioral risk factors. BMC Fam Pract. 2012;13:49.
7. Kok G, van den Borne B, Mullen PD. Effectiveness of health education and health promotion: meta-analyses of effect studies and determinants of effectiveness. Patient Educ Couns. 1997;30(1):19-27.

8. Gabriel SE, Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. Arthritis Rheum. 1999;42(3):415-20.

9. MacGregor AJ, Snieder H, Rigby AS, Koskenvuo M, Kaprio J, Aho K, et al. Characterizing the quantitative genetic contribution to rheumatoid arthritis using data from twins. Arthritis Rheum. 2000;43(1):30-7.

10. Rantapaa-Dahlqvist S, de Jong BA, Berglin E, Hallmans G, Wadell G, Stenlund H, et al. Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. Arthritis Rheum. 2003;48(10):2741-9.

11. Nielen MM, van Schaardenburg D, Reesink HW, van de Stadt RJ, van der Horst-Bruinsma IE, de Koning MH, et al. Specific autoantibodies precede the symptoms of rheumatoid arthritis: a study of serial measurements in blood donors. Arthritis Rheum. 2004;50(2):380-6.

12. Wesley A, Bengtsson C, Elkan AC, Klareskog L, Alfredsson L, Wedren S, et al. Association between body mass index and anti-citrullinated protein antibody-positive and anti-citrullinated protein antibody-negative rheumatoid arthritis: results from a population-based case-control study. Arthritis Care Res (Hoboken). 2013;65(1):107-12.

13. Chen HH, Huang N, Chen YM, Chen TJ, Chou P, Lee YL, et al. Association between a history of periodontitis and the risk of rheumatoid arthritis: a nationwide, population-based, case-control study. Ann Rheum Dis. 2013;72(7):1206-11.

14. Rosell M, Wesley AM, Rydin K, Klareskog L, Alfredsson L, group Es. Dietary fish and fish oil and the risk of rheumatoid arthritis. Epidemiology. 2009;20(6):896-901.

15. Di Giuseppe D, Crippa A, Orsini N, Wolk A. Fish consumption and risk of rheumatoid arthritis: a dose-response meta-analysis. Arthritis Res Ther. 2014;16(5):446.

16. Sparks JA, Chen CY, Hiraki LT, Malspeis S, Costenbader KH, Karlson EW. Contributions of familial rheumatoid arthritis or lupus and environmental factors to risk of rheumatoid arthritis in women: a prospective cohort study. Arthritis Care Res (Hoboken). 2014;66(10):1438-46.

17. McBride CM, Bowen D, Brody LC, Condit CM, Croyle RT, Gwinn M, et al. Future health applications of genomics: priorities for communication, behavioral, and social sciences research. Am J Prev Med. 2010;38(5):556-65.

18. McClure JB. Are biomarkers useful treatment aids for promoting health behavior change? An empirical review. Am J Prev Med. 2002;22(3):200-7.

19. Lundahl B, Moleni T, Burke BL, Butters R, Tollefson D, Butler C, et al. Motivational interviewing in medical care settings: a systematic review and meta-analysis of randomized controlled trials. Patient Educ Couns. 2013;93(2):157-68.

20. Rubak S, Sandbaek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract. 2005;55(513):305-12.

21. Armstrong MJ, Mottershead TA, Ronksley PE, Sigal RJ, Campbell TS, Hemmelgarn BR. Motivational interviewing to improve weight loss in overweight and/or obese patients: a systematic review and meta-analysis of randomized controlled trials. Obes Rev. 2011;12(9):709-23.

22. Heckman CJ, Egleston BL, Hofmann MT. Efficacy of motivational interviewing for smoking cessation: a systematic review and meta-analysis. Tob Control. 2010;19(5):410-6.

23. Christie D, Channon S. The potential for motivational interviewing to improve outcomes in the management of diabetes and obesity in paediatric and adult populations: a clinical review. Diabetes Obes Metab. 2014;16(5):381-7.

24. Sparks JA, Iversen MD, Yu Z, Triedman NA, Prado MG, Miller Kroouze R, et al. Disclosure of personalized rheumatoid arthritis risk using genetics, biomarkers, and lifestyle factors to motivate health behavior improvements:A randomized controlled trial. Arthritis Care Res (Hoboken). 2017.

25. Karlson EW, Sanchez-Guerrero J, Wright EA, Lew RA, Daltroy LH, Katz JN, et al. A connective tissue disease screening questionnaire for population studies. Ann Epidemiol. 1995;5(4):297-302.

26. Sparks JA, Iversen MD, Miller Kroouze R, Mahmoud TG, Triedman NA, Kalia SS, et al. Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA) Family Study: rationale and design for a randomized controlled trial evaluating rheumatoid arthritis risk education to first-degree relatives. Contemp Clin Trials. 2014;39(1):145-57.

27. Rifas-Shiman SL, Willett WC, Lobb R, Kotch J, Dart C, Gillman MW. PrimeScreen, a brief dietary screening tool: reproducibility and comparability with both a longer food frequency questionnaire and biomarkers. Public Health Nutr. 2001;4(2):249-54.

28. Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol. 1985;122(1):51-65.

29. Dietrich T, Stosch U, Dietrich D, Kaiser W, Bernimoulin JP, Joshipura K. Prediction of periodontal disease from multiple self-reported items in a German practice-based sample. J Periodontol. 2007;78(7 Suppl):1421-8.

30. Colditz GA, Atwood KA, Emmons K, Monson RR, Willett WC, Trichopoulos D, et al. Harvard report on cancer prevention volume 4: Harvard Cancer Risk Index. Risk Index Working Group, Harvard Center for Cancer Prevention. Cancer Causes Control. 2000;11(6):477-88.

31. Weinman J, Petrie KJ, Moss-Morris R, Horne R. The Illness Perception Questionnaire: A new method for assessing the cognitive representation of illness. Psychol Health. 1996;11(3):431-45.

32. Deane KD. Preclinical rheumatoid arthritis (autoantibodies): an updated review. Curr Rheumatol Rep. 2014;16(5):419.

33. Lahiri M, Morgan C, Symmons DP, Bruce IN. Modifiable risk factors for RA: prevention, better than cure? Rheumatology (Oxford). 2012;51(3):499-512.

34. Karlson EW, van Schaardenburg D, van der Helm-van Mil AH. Strategies to predict rheumatoid arthritis development in at-risk populations. Rheumatology (Oxford). 2016;55(1):6-15.

35. Hollands GJ, French DP, Griffin SJ, Prevost AT, Sutton S, King S, et al. The impact of communicating genetic risks of disease on risk-reducing health behaviour: systematic review with meta-analysis. BMJ. 2016;352:i1102.

36. Marteau TM, Lerman C. Genetic risk and behavioural change. BMJ. 2001;322(7293):1056-9.

37. Lu B, Solomon DH, Costenbader KH, Karlson EW. Alcohol consumption and risk of incident rheumatoid arthritis in women: a prospective study. Arthritis Rheumatol. 2014;66(8):1998-2005.

38. Symmons DP, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DG, et al. Blood transfusion, smoking, and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum. 1997;40(11):1955-61.

39. Voigt LF, Koepsell TD, Nelson JL, Dugowson CE, Daling JR. Smoking, obesity, alcohol consumption, and the risk of rheumatoid arthritis. Epidemiology. 1994;5(5):525-32.

40. Qin B, Yang M, Fu H, Ma N, Wei T, Tang Q, et al. Body mass index and the risk of rheumatoid arthritis: a systematic review and dose-response meta-analysis. Arthritis Res Ther. 2015;17:86.

41. Linos A, Kaklamanis E, Kontomerkos A, Koumantaki Y, Gazi S, Vaiopoulos G, et al. The effect of olive oil and fish consumption on rheumatoid arthritis--a case control study. Scand J Rheumatol. 1991;20(6):419-26.

42. Gan RW, Demoruelle MK, Deane KD, Weisman MH, Buckner JH, Gregersen PK, et al. Omega-3 fatty acids are associated with a lower prevalence of autoantibodies in shared epitope-positive subjects at risk for rheumatoid arthritis. Ann Rheum Dis. 2017;76(1):147-52.

43. Deane KD. Can rheumatoid arthritis be prevented? Best Pract Res Clin Rheumatol. 2013;27(4):467-85.

44. http://www.yourdiseaserisk.wustl.edu/. Accessed on September 24, 2017.

45. Lautenbach DM, Christensen KD, Sparks JA, Green RC. Communicating genetic risk information for common disorders in the era of genomic medicine. Annu Rev Genomics Hum Genet. 2013;14:491-513.

46. Costenbader KH, Feskanich D, Mandl LA, Karlson EW. Smoking intensity, duration, and cessation, and the risk of rheumatoid arthritis in women. Am J Med. 2006;119(6):503 e1-9.

47. Di Giuseppe D, Orsini N, Alfredsson L, Askling J, Wolk A. Cigarette smoking and smoking cessation in relation to risk of rheumatoid arthritis in women. Arthritis Res Ther. 2013;15(2):R56.

FIGURE LEGENDS

Figure 1. Flow diagram indicating recruitment, randomization, and follow-up of participants. PRE-RA = Personalized Risk Estimator for Rheumatoid Arthritis; RA = rheumatoid arthritis.

Figure 2. Example of the results pages of web-based PRE-RA risk tool personalized with demographics, genetics, RA-related autoantibodies, and behaviors using A) an interactive relative RA risk display and B) a pictogram displaying absolute lifetime RA risk.

Figure 3. RA Knowledge Score of 8 RA risk factors at each study time point according to randomly assigned RA educational intervention.

Table 1. Items included in RA risk factor knowledge questionnaire given to participants at all study visits.

8 components of RA Knowledge Score (RAKS)	Other items included in questionnaire
Aging	Accident or injury
Altered immunity	Alcohol
Being overweight/obese	Chance or bad luck
Diet or eating habits	Feeling down, lonely, or empty
Genetics or Heredity*	High caffeine intake
My own behavior	Infection
Poor dental health	Low calcium intake
Smoking	My mental attitude
	Overwork
	Pollution in the environment
	Poor medical care in my past
	Stress or worry

Possible answers were: strongly disagree, disagree, neither agree nor disagree, agree, or strongly agree.

* Heredity and genetics were asked separately but combined when calculating the RA Knowledge Score.

RAKS is the sum of 8 items in the left column that a subject either agreed or strongly agreed is a risk factor for RA. Items in the right column were not considered. Possible scores range from 0-8 with higher scores indicating more RA risk factor knowledge.

RA = rheumatoid arthritis; RAKS = RA Knowledge Score

Table 2. Baseline characteristics of subjects according to randomized RA educational intervention (n=238).

	Comparison arm n=80	**PRE-RA arm n=78**	**PRE-RA Plus arm n=80**
Mean age, years (SD)	43.4 (14.7)	45.0 (14.9)	48.3 (13.7)
Female, n (%)	63 (78.8)	62 (79.5)	57 (71.3)
Education >high school, n (%)	72 (90.0)	68 (87.2)	69 (86.3)
White, n (%)	69 (86.3)	65 (83.3)	73 (91.3)
BMI category, n (%)*			
Underweight (<18.5 kg/m^2)	0 (0.0)	0 (0.0)	2 (2.6)
Normal weight (18.5-24.9 kg/m^2)	28 (45.9)	37 (48.7)	25 (32.9)
Overweight (25-29.9 kg/m^2)	16 (26.2)	17 (22.4)	25 (32.9)
Obese (≥30 kg/m^2)	17 (27.9)	22 (29.0)	24 (31.6)
Mean RAKS (SD)	4.4 (1.9)	4.5 (1.9)	4.0 (1.9)
Type of relative with RA, n (%)			
Parent only	55 (68.8)	53 (70.7)	47 (66.2)
Sibling only	9 (11.2)	13 (17.3)	16 (22.5)
Offspring only	7 (8.8)	9 (12.0)	8 (11.3)
More than one type of relative with RA	9 (11.3)	3 (3.9)	9 (11.3)
Perceived RA severity of relative with RA, n (%)			
Mild	11 (13.8)	9 (12.3)	7 (9.0)
Moderate	44 (55.0)	50 (68.5)	43 (55.1)
Severe	21 (26.3)	12 (16.4)	26 (33.3)
Unsure	4 (5.0)	7 (9.0)	4 (5.0)
HLA-DRB1 shared epitope alleles present, n (%)			
None	40 (50.0)	39 (50.0)	45 (56.3)
1	35 (43.8)	34 (43.6)	24 (30.0)
2	5 (6.3)	5 (6.4)	11 (13.8)

Positive CCP2, n (%)	0 (0.0)	2 (2.6)	0 (0.0)
Positive RF, n (%)	4 (5.0)	4 (5.1)	3 (3.8)
Positive CCP2 or RF, n (%)	4 (5.0)	4 (5.1)	3 (3.8)

* Body mass index data were available on 61 in the comparison arm, 76 in the PRE-RA arm, and 76 in the PRE-RA Plus arm. There were no missing data for any other variables.

** Only current smokers were assessed by the smoking ladder (n=15).

CCP2 = cyclic citrullinated peptide, 2nd generation; PRE-RA = Personalized Risk Estimator for RA; RA = rheumatoid arthritis; RAKS = RA Knowledge Score

Table 3. Proportion of subjects who agreed that each RAKS component was related to RA risk at each study time point according to RA educational intervention.

	Baseline	6 weeks post-education			6 months post-education			12 months post-education		
Component of RAKS	**Overall[1]**	**Comparison arm**	**PRE-RA arm**	**PRE-RA Plus arm**	**Comparison arm**	**PRE-RA arm**	**PRE-RA Plus arm**	**Comparison arm**	**PRE-RA arm**	**PRE-RA Plus arm**
Poor dental health	15.6%	37.3%	86.8%*	91.6%*	51.4%	88.7%*	94.4%*	50.7%	86.8%*	98.5%*†
Smoking	31.9%	48.0%	69.1%*	78.9%*	43.1%	71.8%*	83.1%*	46.6%	73.5%*	86.2%*
My own behavior	43.7%	53.3%	55.9%	74.7%*†	40.3%	54.9%	69.0%*	53.4%	60.3%	70.8%*
Being overweight/obese	47.5%	52.0%	66.2%	83.1%*†	47.2%	63.4%	81.7%*†	57.5%	64.7%	76.9%*
Diet or eating habits	54.2%	56.0%	77.9%*	83.1%*	52.8%	88.7%*	73.2%*†	57.5%	79.4%*	87.7%*
Aging	58.4%	80.0%	67.7%	60.6%*	63.9%	71.8%	63.4%	57.5%	61.8%	58.5%
Altered immunity	79.4%	81.3%	76.5%	84.5%	84.7%	70.4%*	77.5%	86.3%	77.9%	80.0%
Heredity or Genetics	96.2%	98.7%	98.5%	97.2%	98.6%	100.0%	98.6%	97.3%	97.1%	98.5%

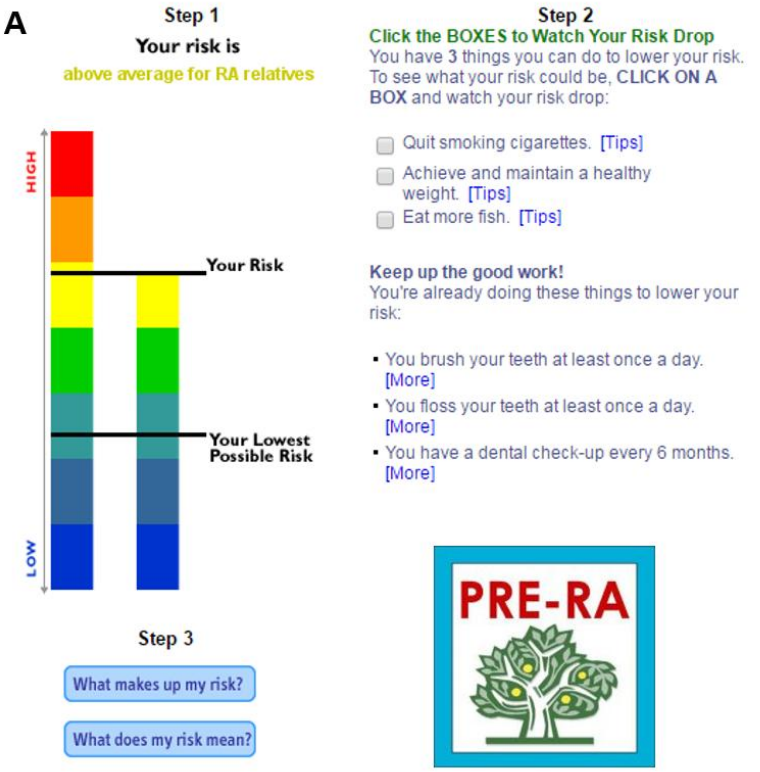
* $p<0.05$ in PRE-RA Plus arm or PRE-RA arm compared to the Comparison arm

† $p<0.05$ in PRE-RA Plus arm compared to the PRE-RA arm

[1] The proportion of subjects at baseline prior to randomization for educational intervention was similar in all 3 study arms so the overall percentage of the total study sample is presented.

RA = rheumatoid arthritis; RAKS = RA Knowledge Score

A



B