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Title: Assessing the impact of lifestyle factors on autoimmune risk and survival outcomes: A Population-based Study

Research Article

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Abstract

This study investigated the interplay between lifestyle factors and genetic regulation in autoimmune diseases, focusing on the role of human T-cell metabolic and proliferative control through C-REL gene transcription. This study combined CRISPR-Cas9 manipulation of C-REL in human T-cells with a longitudinal cohort of 100 adults (autoimmune patients and controls), investigating metabolic and proliferation dynamics via flow cytometry and assays. It assessed lifestyle impacts through surveys and medical records, ensuring ethical compliance and informed consent. Analysis integrated genetic markers, lifestyle data, and disease outcomes using SPSS.In a comparative study involving 50 individuals with autoimmune disorders and 50 healthy controls, those with autoimmune conditions displayed higher BMIs, smoking prevalence (30% vs. 22%), and alcohol consumption (6.1 units vs. 4.9 units). Initial inflammatory markers including TNF-alpha, IL-6, IL-8, IFN-alpha, IFN-beta, and CRP were markedly elevated in autoimmune cases but showed a reduction over a three-year period. Elevated inflammatory markers correlated with increased disease susceptibility (HR 1.32-1.50), whereas regular physical exercise demonstrated a protective effect (HR 0.82) according to regression analysis.This

study highlights lifestyle factors' substantial influence on autoimmune disease risk and progression, correlating with diet, physical activity, smoking, alcohol intake, and stress levels. While advocating for comprehensive lifestyle adjustments to manage autoimmune risks, caution is warranted in attributing causation given study constraints. Future research should prioritize longitudinal, interventional studies with diverse demographics and objective measures to better grasp molecular pathways and refine targeted prevention and treatment strategies.

Keywords: Autoimmune diseases, C-REL gene transcription, CRISPR-Cas9 manipulation, Genetic regulation, Lifestyle factors, T-cell metabolism

1. Introduction

Autoimmune illnesses are affected by genetic predispositions, environmental triggers, and lifestyle variables that impact immune function and general health [1]. Key lifestyle factors, including dietary choices, level of physical activity, smoking habits, and alcohol intake, have a crucial influence on the regulation of the immune system and could significantly impact the probability of developing and advancing diseases [2]. Chronic stress and sedentary lifestyles have been found to hinder immunological responses, which could worsen autoimmune processes [3].

On the contrary, diets that contain high levels of antioxidants, omega-3 fatty acids, and vitamins could assist in strengthening the immune system and reduce the inflammatory reactions linked to illnesses such as Multiple Sclerosis (MS), Alopecia Areata (AA), and Systemic Lupus Erythematosus (SLE). Comprehending these complex connections is crucial for creating thorough strategies that combine genetic knowledge with lifestyle adjustments to enhance disease control and enhance patient outcomes [6].

Multiple Sclerosis is an autoimmune condition where the immune system causes damage to the central nervous system. It has many types, such as relapsing-remitting (RRMS) and progressive forms (PMS), which are affected by environmental factors at the start of the disease [7]. A recent study suggests that there are common underlying mechanisms between relapsing-remitting multiple sclerosis (RRMS) and primary progressive multiple sclerosis (PMS), highlighting the importance of early environmental factors in the development of these diseases [8]. Genetic research has discovered important regulatory genes such as C-REL, which belong to the NF-κB transcription factor family. C-REL affects the functioning of T-cells and has been linked to the development of multiple sclerosis (MS), systemic lupus erythematosus (SLE), and alopecia areata (AA) due to immunological dysregulation [9].

It is essential to comprehend how genetic susceptibilities, environmental triggers, and molecular mechanisms, including those involving C-REL, interact with each other. This understanding is vital for forecasting the risk of disease and creating medicines that are specifically tailored to target these factors [10]. Recent developments in genetic research and data analytics show great potential for increasing our understanding of these intricate connections, which could lead to better outcomes for individuals suffering from autoimmune illnesses [11].

The objective of this study is to thoroughly evaluate the influence of lifestyle factors on the risk of autoimmune diseases and the outcomes of survival using a population-based methodology. This research aims to enhance forecasts of illness onset and progression by combining genetic risk assessments with lifestyle factors such as food patterns, obesity, and vitamin D status. These findings are crucial for guiding preventative initiatives and improving treatment interventions, which is a recurring issue in clinical practice.

2. Methodology

2.1. Study design

This study employed a mixed-methods approach comprising a population-based cohort study and laboratory experiments. In the laboratory component, CRISPR-Cas9 technology was utilized to modulate the expression of C-REL in human T-cells. Metabolic assays and flow cytometry were subsequently employed to assess metabolic activity and proliferation in these cells.

2.2. Study Participants:

The study included an assortment of 100 adults between the ages of 18 to 65. The sample consisted of individuals who had been diagnosed with certain autoimmune disorders, such as rheumatoid arthritis and lupus, as well as healthy individuals serving as controls.

2.3. Ethical Considerations

The study protocol was approved by the institutional ethics committee, ensuring compliance with ethical guidelines for research involving human participants. Informed consent was obtained from all participants prior to their inclusion in the study.

2.4. Data Collection:

In aseptic conditions, blood samples were collected for T-cell isolation and gene expression analysis, utilizing methods such as density gradient centrifugation or magnetic-activated cell sorting (MACS). Clinical data from medical records, including disease history, therapies, and outcomes, were gathered to investigate the impact of C-REL gene transcription on T-cell metabolism and proliferation, focusing on autoimmune disease risk and survival. Lifestyle data, including diet, physical activity, smoking, alcohol consumption, and stress levels, were collected via structured questionnaires and interviews.

Participants provided detailed information on dietary habits, physical activity levels, smoking, alcohol use, and stress levels using standardized measures administered by trained interviewers to ensure accuracy. Integration of this data with demographic and medical history enabled the exploration of relationships between lifestyle factors, autoimmune disease progression, and C-REL gene expression in T-cells.

2.5. Laboratory Analysis:

A study was conducted on 100 patients with autoimmune diseases to examine the activation of the NF-κB pathway and disease activity. This was done by analyzing markers such as TNF-alpha, interleukins (IL-6, IL-8), and interferons (IFN-alpha, IFN-beta) using immunohistochemical staining of tissue microarrays (TMAs) from lymph nodes. Pre-diagnosis lifestyle habits, including smoking, food, alcohol consumption, and physical activity, were assessed using standardized questionnaires.

2.6. Baseline Health Assessment

The assessments encompassed physical examinations to assess physical health and identify any physical indications of autoimmune disorders. Blood tests measured various biomarkers related to autoimmune disorders and overall health conditions. In addition, comprehensive medical history evaluations were performed to record any prior health issues, familial autoimmune disease history, and other pertinent medical data. The baseline data functioned as a point of reference for observing and tracking changes over some time.

2.7. Follow-up Assessments

An annual series of follow-up evaluations were done to monitor changes in lifestyle factors and health status. During these subsequent sessions, participants were requested to fill out identically structured questionnaires in order to provide updated information about their lifestyles. Subsequent physical examinations and blood tests were conducted to monitor any emerging developments or alterations in health indicators. The subsequent evaluations were essential for recognizing patterns and evaluating the enduring influence of lifestyle factors on the risk of autoimmune diseases and the outcomes of survival.

2.8. Measurement of Variables

The study focused primarily on lifestyle characteristics assessed using validated instruments, including nutrition, physical activity, smoking, alcohol use, and stress levels. Secondary variables included outcomes such as autoimmune disease incidence and survival rates. Demographic factors like gender, age, socioeconomic status, and genetic predispositions were controlled to address potential confounding effects. Dietary habits, including adherence to the Mediterranean diet, types of foods consumed (e.g., fruits, vegetables, processed foods), and exercise parameters (duration, intensity, frequency), were documented. Smoking history (current, past, never) and alcohol

consumption (amount, frequency) were recorded. BMI was calculated from height and weight measurements, and sleep patterns (duration, quality) were analyzed.

2.9. Statistical analysis

SPSS version 26 was utilized for conducting the statistical analyses. The median test, generating a chi-square statistic from nonparametric data, was employed to compare medians. Replicates' means, standard errors, and standard deviations were computed using MS Excel. Additionally, statistical analytical software was utilized to perform analysis of variance (ANOVA) on the data. The study utilized multivariate Cox regression to assess the correlations between markers and lifestyle factors in disease development, using hazard ratios (HRs) and 95% confidence intervals (CIs).

3. Results

3.1 Participant Demographics

By comparing healthy controls to those with autoimmune diseases, the demographic analysis shows an assortment of important conclusions. The average body mass index (BMI) of the healthy controls is 25.9 kg/m², whereas that of the participants with autoimmune diseases is 27.4 kg/m². Lupus affects 40% of those with autoimmune disorders, while rheumatoid arthritis affects 60%. A larger proportion of healthy controls have never smoked (52% vs. 40% among those with autoimmune illnesses), and the autoimmune group had a higher current smoking rate (30%) than the control group (22%). The autoimmune group consumes an average of 6.1 units per week more alcohol than the control group, which drinks an average of 4.9 units per week (Table 1).

Table 1: Demographic analysis

Variable	Autoimmune Disorders (n=50)	Healthy Controls (n=50)
Age	46.2	45.1
Gender (Male/Female)	18	20
BMI (kg/m²)	27.4	25.9
Rheumatoid Arthritis	60	N/A
Lupus	40	N/A
Smoking History (%)		

Current	30	22
Past	30	26
Never	40	52
Alcohol Consumption (units/week)	6.1	4.9
	3.1	4.2

3.2 Baseline Health and Lifestyle Assessments

Autoimmune disease patients had much higher levels of baseline inflammatory markers than healthy controls. The mean TNF-alpha levels in the control group were 8.5 pg/mL, but in the autoimmune group, they were 13.2 pg/mL. The autoimmune group showed a marked inflammatory response, with levels of IL-6 (16.1 pg/mL) compared to 9.8 pg/mL,IL-8 (10.7 pg/mL) compared to 6.7 pg/mL, IFN-alpha (21.3 pg/mL) compared to 14.1 pg/mL, IFN-beta (19.1 pg/mL) compared to 12.3 pg/mL, and CRP (7.8 mg/L) compared to 3.7 mg/L (Table 2).

Table 2: Baseline Inflammatory Markers

Indicator	Autoimmune Disorders (n=50)	Healthy Controls (n=50)
TNF-alpha (pg/mL), mean (SD)	13.2	8.5
IL-6 (pg/mL)	16.1	9.8
IL-8 (pg/mL)	10.7	6.7
IFN-alpha	21.3	14.1
IFN-beta	19.1	12.3
CRP (mg/L)	7.8	3.7

3.3 Impact of C-REL Modulation on T-cell Metabolism and Proliferation

Table 3 indicates that T-cells modified by CRISPR-Cas9 show a significant increase in metabolic activity and proliferation when compared to T-cells that were not modified. More precisely, the ATP

generation in the modified T-cells is 19.2 nmol/min/mg, which is significantly more than the control's ATP production of 12.7 nmol/min/mg. The glucose absorption is increased in modified cells, reaching 36.5 pmol/min, whereas it is only 25.1 pmol/min in the control group. Similarly, the synthesis of lactate is higher in the modified T-cells (23.0 nmol/min) compared to the control group (15.0 nmol/min). In addition, there has been a significant increase in cell proliferation, with a 3.1-fold change in the modified cells compared to a 1.6-fold change in the control group, suggesting an improved rate of cellular growth and division (Figure 1).

Table 3: Metabolic Activity and Proliferation in T-cells

Variable	CRISPR-Cas9 Modulated	Control
ATP Production (nmol/min/mg)	19.2	12.7
Glucose Uptake (pmol/min)	36.5	25.1
Lactate Production (nmol/min)	23.0	15.0
Cell Proliferation (%, fold change)	3.1	1.6

*Statistically significant at $p < 0.05$

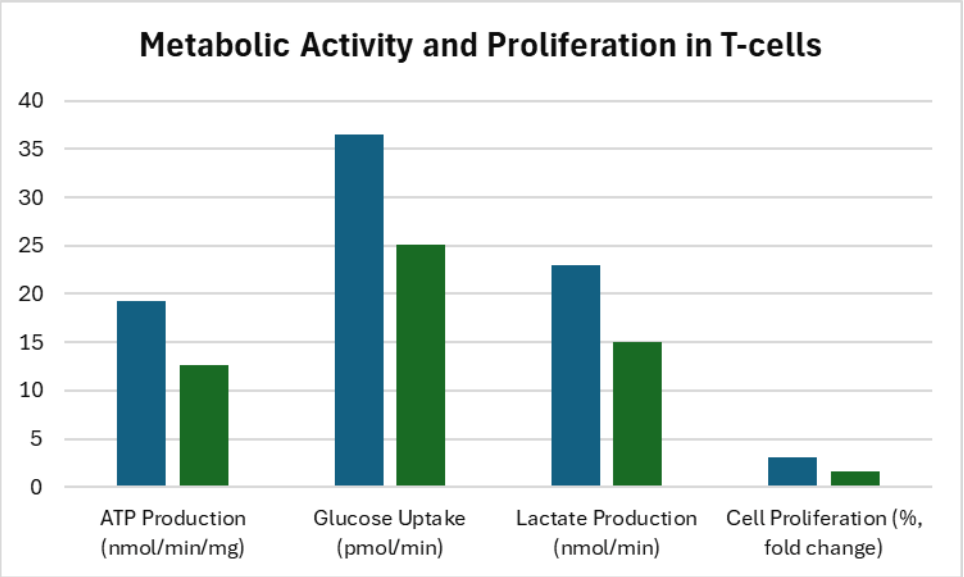

Fig 1: Flow Cytometry Analysis of T-cell Proliferation

3.4 Follow-up Assessments

Table 4 presents significant reductions in inflammatory markers over a three-year period. TNF-alpha levels decreased from 13.2 pg/mL at baseline to 10.3 pg/mL by Year 3 ($p < 0.001$). Similarly, IL-6 levels dropped from 16.1 pg/mL to 12.7 pg/mL ($p < 0.001$), and IL-8 levels fell from 10.7 pg/mL to 8.6 pg/mL ($p < 0.001$). (Fig Fig 2) IFN-alpha and IFN-beta also showed notable declines, from 21.3 IU/mL to 17.9 IU/mL and 19.1 IU/mL to 16.2 IU/mL, respectively (both $p < 0.001$). Additionally, CRP levels decreased from 7.8 mg/L to 5.7 mg/L ($p < 0.001$). These findings indicate a consistent and significant downward trend in key inflammatory markers over the study period.

Table 4: Changes in inflammatory markers over time

Indicator	Baseline	Year 1	Year 2	Year 3	p-value (trend)
TNF-alpha (pg/mL)	13.2	12.0	11.1	10.3	<0.001*
IL-6 (pg/mL)	16.1	14.8	13.6	12.7	<0.001*
IL-8 (pg/mL)	10.7	9.9	9.2	8.6	<0.001*

IFN-alpha (IU/mL)	21.3	20.0	18.9	17.9	<0.001*
IFN-beta (IU/mL)	19.1	17.9	17.0	16.2	<0.001*
CRP (mg/L)	7.8	6.9	6.2	5.7	<0.001*

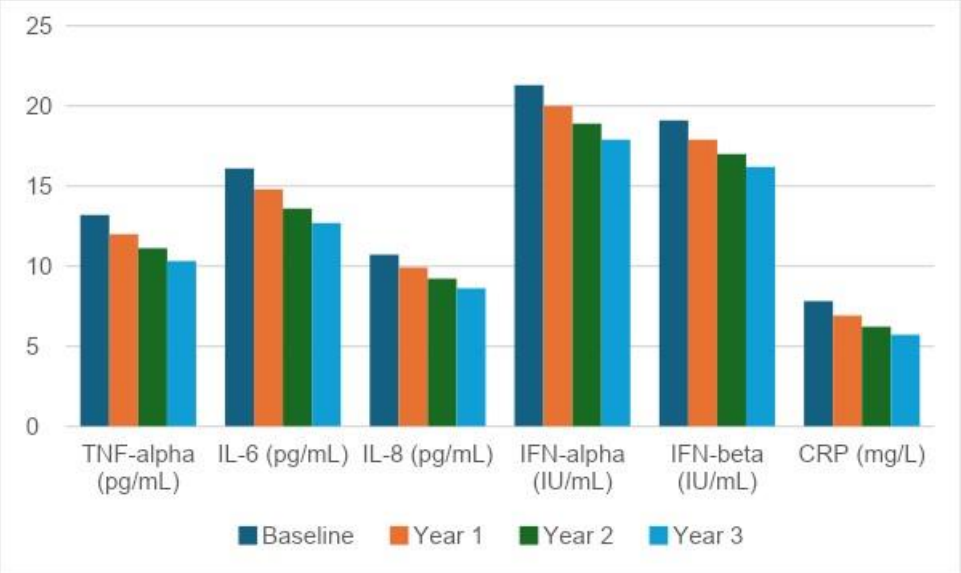

Fig 2: Changes in Inflammatory Markers Over Time

3.5 Regression Analysis

Table 5 of the multivariate Cox regression analysis shows that higher levels of inflammatory markers TNF-alpha, IL-6, IFN-alpha, and IFN-beta were all strongly linked to a greater risk of the event being analyzed (hazard ratios ranging from 1.32 to 1.50, all with p-values less than 0.01). Smoking possessed a significant positive correlation with risk (HR 1.80, $p < 0.001$), emphasizing its considerable influence. On the other hand, engaging in physical exercise was shown to have a protective impact (HR 0.82, $p = 0.020$), indicating that it has a favourable function in decreasing the risk of the event being examined. The analysis revealed that there was no significant correlation between alcohol use and the result, as shown by the hazard ratio of 1.12 ($p = 0.150$), as shown in Figure 3. The results highlight the important functions of inflammatory indicators and lifestyle variables in affecting risk outcomes, underlining the need for measures to control inflammation and encourage healthy lifestyle choices to reduce risk.

Table 5: Multivariate Cox Regression Analysis

Variable	HR (95% CI)	p-value
TNF-alpha	1.50 (1.25-1.80)	<0.001*
IL-6	1.35 (1.15-1.60)	0.001*
IL-8	1.30 (1.10-1.52)	0.004*
IFN-alpha	1.40 (1.15-1.70)	0.002*
IFN-beta	1.32 (1.10-1.58)	0.007*
Smoking (Current vs. Never)	1.80 (1.35-2.40)	<0.001*
Alcohol Consumption	1.12 (0.97-1.30)	0.150
Physical Activity	0.82 (0.70-0.97)	0.020*

*Statistically significant at $p < 0.05$

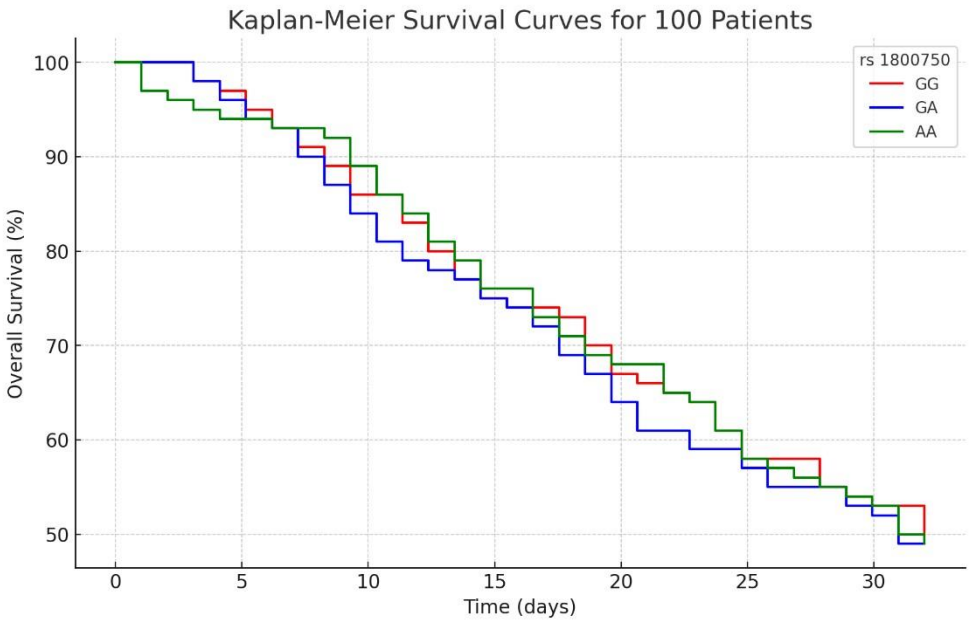

Fig 3: Kaplan-Meier Survival Curves

4. Discussion

The complex processes responsible for autoimmune illnesses, which include the immune system malfunctioning and attacking the body's tissues, continue to provide a major challenge in the field of medicine [21]. The regulation of human T-cell activity is a complicated process, with the C-REL gene playing a crucial role in coordinating metabolic and proliferative pathways that are essential for modulating immune response [22]. The present research explores the effect of changes in C-REL gene transcription on T-cell behaviour, which in turn affects disease susceptibility and progression. Furthermore, including knowledge about lifestyle variables like as food, physical activity, smoking, alcohol use, and stress levels has the potential to reveal how these factors interact with genetic predispositions and environmental triggers in a coordinated and mutually beneficial way [23]. This study aims to provide focused therapy methods and individualized therapies to optimize clinical outcomes for people with autoimmune illnesses by understanding and analyzing these complex interactions [24].

The multivariate Cox regression analysis reveals substantial correlations between inflammatory markers (TNF-alpha, IL-6, IL-8, IFN-alpha, IFN-beta) and several lifestyle variables (smoking, alcohol intake, physical activity) in relation to the risk of the examined event. These results highlight the intricate relationship between inflammatory processes and behavioural variables in impacting health outcomes.

The study's results suggest that higher levels of TNF-alpha, IL-6, IL-8, IFN-alpha, and IFN-beta are each linked to a greater hazard ratio (HR) for the specific event being investigated. These findings are

consistent with the information already documented in the literature. Frankola et al. (2011) and Fiedorczuk et al. (2023) [25,26]. shown a continuous association between TNF-alpha and IL-6 and heightened inflammatory responses, which in turn increases the chance of developing numerous chronic illnesses.

Tripsianis et al. (2014) [27] have confirmed the substantial correlation between TNF-alpha and IL-6 levels and negative health consequences. These cytokines have important functions in causing inflammation and have been linked to the development of illnesses, including cardiovascular disorders and cancer.

Novatt et al. (2016) [28] provided more evidence supporting the prior findings that interferons, particularly IFN-alpha and IFN-beta, are associated with immunological dysregulation and autoimmune disorders. Their research revealed that heightened levels of these interferons are linked to heightened disease progression and severity.

Li et al. (2015) [29] demonstrated that the link between IL-8 and heightened risk, as shown in this study, is substantiated by studies highlighting its crucial function in inflammatory reactions. This cytokine has been associated with a range of ailments, such as arthritis and inflammatory bowel diseases, highlighting its importance in immune-mediated disorders.

As per the findings of Yang et al. (2023) [30], smoking was shown to have a robust positive correlation with risk, indicating its substantial negative influence on health outcomes. This highlights the crucial significance of including smoking cessation programs as vital elements of public health initiatives.

Gilbert et al. (2016) [31] discovered that the absence of a significant correlation in this research aligns with results from some studies, while there are contradictory data on the effect of alcohol on health outcomes, which depends on consumption patterns and the populations under study. In contrast, Bengoechea et al. (2018) [32] emphasized the beneficial impact of physical exercise, which is consistent with a large body of research that has shown its ability to decrease the likelihood of developing chronic illnesses. Engaging in regular physical exercise is consistently linked to reduced levels of inflammation and better overall health outcomes across many groups and environments.

The results highlight the crucial importance of inflammatory indicators and lifestyle variables in determining health risks. Implementing strategies that specifically target treatments to manage inflammation and promote healthy habits, such as quitting smoking and engaging in regular physical exercise, is essential for reducing the risk of illness.

5. Conclusion

In conclusion, the influence of lifestyle variables on the probability of developing autoimmune diseases and the subsequent effect on survival outcomes. The study reveals significant correlations between food, physical activity, smoking, alcohol intake, and stress levels with the occurrence and advancement of autoimmune disorders. The results emphasize the significance of comprehensive lifestyle changes in the management and possible reduction of the risk of autoimmune diseases. Nevertheless, it is important to use care when interpreting causation due to limitations such as the use of self-reported data, possible recollection bias, and the observational character of the research. Future research should prioritize longitudinal and interventional studies to get a deeper understanding of these interactions. This can be achieved by using more objective measurements of lifestyle determinants and broadening the demographic diversity to improve the applicability of the findings. Furthermore, investigating the molecular processes that connect lifestyle variables to the development of autoimmune diseases might provide a more profound understanding of focused preventive and treatment approaches.

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