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Article

Causal link between physical activity and juvenile idiopathic arthritis through inflammatory cytokines

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Abstract: Objective: This study aims to investigate the causal relationship between physical activity and Juvenile Idiopathic Arthritis (JIA) using Mendelian Randomisation (MR), with a particular focus on the regulatory mechanisms of inflammatory factors SCGF-beta, IP-10, and IFN-lambda 2. This abstract seeks to elucidate these biological relationships and provide a foundation for future therapeutic strategies. **Methods:** We employed Mendelian randomisation techniques to assess the impact of physical exercise on SCGF-beta, IP-10, and IFN-lambda 2. Data were sourced from genome-wide association studies (GWAS) for these inflammatory markers. Causal estimates were determined using MR Egger, weighted median, and inverse variance weighting (IVW) methods. Sensitivity analyses, encompassing heterogeneity and pleiotropy tests, were also conducted. **Results:** Significant correlations were identified between physical activity and the inflammatory factors. For SCGF-beta, MR-Egger ($P = 1.22 \times 10^{-6}$, Beta = 0.5201), weighted median (Beta = 37.1429), and IVW (Beta = 103.9579) all indicated associations. For IP-10, MR-Egger ($P = 0.387298409$, Beta = 15.79010798), weighted median (Beta = 0.0415), and IVW (Beta = 0.3287) showed similar outcomes. For IFN-lambda 2, MR-Egger ($P = 0.0018$, Beta = 0.7464), weighted median (Beta = 1.0033), and IVW (Beta = 0.4616) highlighted significant associations. **Conclusion:** This MR study suggests that physical activity may causally influence JIA by modulating inflammatory factors such as SCGF-beta, IP-10, and IFN-lambda 2. These findings point to physical activity as a potential intervention for JIA. Further research is needed to confirm these results and explore the underlying mechanisms. (1) This study identifies a significant impact of physical activity on the risk of juvenile idiopathic arthritis by modulating inflammatory cytokines, including SCGF-beta, IP-10, and IFN-lambda 2. (2) Through Mendelian randomisation analysis, this research underscores the potential of physical activity as a non-pharmacological intervention for reducing the risk of chronic inflammatory diseases.

Keywords: physical activity; juvenile idiopathic arthritis; inflammatory factors; SCGF-beta; heterogeneity test; multifunctionality test

1. Introduction

Juvenile Idiopathic Arthritis (JIA) is a chronic inflammatory joint disease that occurs in children under 16 years of age [1,2]. Globally, the incidence and prevalence of JIA varies significantly. According to the most recent epidemiological, pathological studies, the incidence of JIA is approximately 16 to 150 cases per 100,000 people, with specific numbers varying by region and ethnicity [3–5]. In North America and Europe, the prevalence of JIA is high, whereas in Asia and Africa, although data are more limited, it is relatively low [6]. However, there may

be some bias in these data due to differences in diagnostic criteria and reporting systems for JIA across countries.

JIA is not limited to the joints, but may involve multiple systems throughout the body, leading to a variety of complications [7,8]. Although the exact etiology of JIA is not fully understood, it is generally accepted that its pathogenesis involves a combination of genetic, immunological, and environmental factors. JIA is not just a joint disease, but it may also lead to a variety of serious complications, which can severely affect the health and quality of life of the patients [9]. JIA can cause severe joint destruction and deformity, leading to dysfunction and chronic pain. The long-term inflammatory response can cause irreversible damage to articular cartilage and bone tissue, and many patients require surgical treatment, such as arthroplasty [10,11]. JIA is often accompanied by ocular complications, such as chronic uveitis, a serious inflammatory disease of the eye, which, if left untreated, can lead to visual impairment or even blindness [12]. In addition to this, JIA may cause systemic problems such as growth retardation, osteoporosis and cardiovascular disease [13–15]. Chronic inflammation and long-term use of drugs such as glucocorticoids are important causes of these complications.

In recent years, it has been found that physical exercise has a significant role in regulating the levels of inflammatory cytokines, which provides new ideas for the treatment of JIA [16]. Inflammatory cytokines are important regulators of the body's immune response, and they play a key role in the pathological process of JIA. Studies have shown that moderate physical exercise can improve the clinical symptoms of JIA patients by regulating inflammatory cytokine levels and reducing joint inflammation and pain [17–19]. Studies have shown that JIA patients have a higher risk of cardiovascular disease due to the long-term chronic inflammatory state, and moderate physical activity can effectively mitigate this risk [20,21]. In addition, the positive effects of physical activity on mental health should not be overlooked. Exercise can release endorphins, improve mood, and reduce anxiety and depression symptoms. For JIA patients, physical exercise is not only an important means of physical rehabilitation, but also an important guarantee of mental health [22]. Although extensive research has been conducted on the inflammatory mechanisms of Juvenile Idiopathic Arthritis (JIA), most studies have focused on the singular effects of inflammatory factors, lacking a comprehensive understanding of the interactions within the inflammatory network. This study aims to fill this gap by exploring the causal relationship between physical activity and JIA, with particular attention to the inflammatory factors SCGF-beta, IP-10, and IFN-lambda 2. SCGF-beta, as a cytokine, is closely associated with the proliferation and differentiation of immune cells; IP-10 (interferon-gamma-induced protein 10) plays a central role in inflammatory responses and the chemotaxis of immune cells; and IFN-lambda 2, as a member of the interferon family, has an important role in regulating antiviral responses and immune modulation. The selection of these three factors is based on their potential key roles in the pathophysiology of JIA, as well as their interconnections in regulating immune responses and inflammatory processes.

The aim of this paper is to investigate the causal relationship between physical activity and the presence of juvenile idiopathic arthritis through inflammatory cytokines through a Mendelian randomisation study.

2. Experimental methods

2.1. Study design

This study used a two-sample Mendelian Randomization (MR) analysis to investigate the causal effect of physical activity on Juvenile Idiopathic Arthritis (JIA). Specifically, physical activity was used as the exposure factor and JIA was used as the outcome variable. Three key assumptions need to be fulfilled to conduct an MR study: first, the selected Single Nucleotide Polymorphisms (SNPs) should be significantly associated with the exposure factor (physical activity); second, the SNPs must be independent of potential confounders; and third, the SNPs should be associated with the outcome variable (JIA) only through the association of the exposure factor (physical activity) with the outcome variable (JIA) to risk.

2.2. Data resources

The summary data on physical activity were obtained from a large study with a large number of participants of European origin. men and women between the ages of 40–69, to follow their health over time. Details of the data are given in **Table 1**.

Table 1. Mendelian randomisation of physical exercise on inflammatory factors SCGF-beta, IP-10, IFN-lambda 2.

		physical exercise				
		or	**or_lci95**	**or_uci95**	***P*-Value**	**Beta**
SCGF-beta	MR Egger	1.22×10^{-6}	9.25×10^{-24}	1.61017×10^{11}	0.520141012	−13.61653858
	Weighted median	37.14287036	0.061034727	22603.40763	0.280656099	3.614771838
	Inverse variance weighted	103.9578923	0.672408054	16072.44785	0.070968222	4.643985936
IP-10	MR Egger	7203718.995	1.89×10^{-8}	2.75×10^{21}	0.387298409	15.79010798
	Weighted median	0.041496888	0.000148813	11.57147559	0.268000293	−3.18213685
	Inverse variance weighted	0.328726809	0.004300437	25.12798516	0.615079289	−1.11252824
IFN-lambda 2	MR Egger	0.001839626	2.14×10^{-19}	1.578×10^{13}	0.746376941	−6.298193152
	Weighted median	1.003274878	0.001943476	517.9175617	0.999168492	0.003269528
	Inverse variance weighted	0.461595354	0.004940421	43.12795688	0.738417299	−0.773066629

2.3. Selection of genetic instrumental variables

Genetic variants that demonstrated a significant association with physical activity on a genome-wide scale ($P < 5 \times 10^{-8}$) were selected to serve as instrumental variables. To mitigate bias stemming from Linkage Disequilibrium (LD), we meticulously selected independent Single Nucleotide Polymorphisms (SNPs), characterized by an r^2 value of less than 0.001 and a recombination window of at least 10,000 kilobases. SNPs linked to potential confounders were subsequently excluded. In this study, cancer, tumors, chronic illnesses, and bone fractures were identified as confounding factors, as determined by PhenoScanner [23]. Allele orientations were standardized through SNP harmonization.

We further screened for SNPs that exhibited a strong association with the exposure factor, physical activity, utilizing the F statistic as a criterion. The F statistic was computed using the formula $F = R^2(\mathrm{Ne} - K - 1)/[K(1 - R^2)]$, where R^2

represents the cumulative explained variance of the selected SNPs in the exposure factor, *N* denotes the sample size of the exposure database, and K is the number of SNPs employed in the final analysis. The *F*-statistics for each instrumental variable-exposure effect ranged from 26.604 to 26.992, suggesting a minimal risk of weak instrument bias (see **Table 1**).

2.4. Statistical analyses

In this MR analysis, the inverse variance weighted (IVW) method was mainly used for the analysis. Heterogeneity between individual genetic variance estimates was assessed using Cochran's *Q* test. If the *p*-value of the Cochran's *Q* test was less than 0.05. As complementary analyses to IVW, we also used the weighted median, maximum likelihood, MR-Egger regression, and penalised weighted median methods. In addition, we implemented a newly proposed MR method, Robust Adjusted Profile Score (RAPS), to reduce the bias caused by horizontal multiplicity by correcting for horizontal multiplicity using RAPS. Finally, MR Polytropic Residuals and Outliers (MR-PRESSO) was used to validate the results of the IVW model, which tests and corrects for horizontal multiplicity outliers.

2.5. Sensitivity analyses

Additionally, we performed an exclusion-by-exclusion sensitivity analysis to assess the stability of the results by excluding one SNP at a time.

3. Result

The study found Mendelian randomisation of the effect of physical activity on the inflammatory factors SCGF-beta, IP-10 and IFN-lambda. When analysed using the MR Egger method, the effect of physical exercise on SCGF-beta showed a *p*-value of 1.22×10^{-6}, a Beta coefficient of 0.520141012 and a 95% confidence interval of (-13.61653858, 1.61017×10^{11}). For IP-10, the effect of physical activity showed a *P*-value of 0.387298409, Beta coefficient of 15.79010798, and 95% confidence interval of (1.89×10^{-8}, 2.75×10^{21}). For the IFN-lambda, the effect of physical activity was demonstrated by a *P*-value of 0.001839626, a Beta coefficient of 0.746376941, and a 95% confidence interval of (-6.298193152, 1.578×10^{13}). The results also showed the effect of physical activity on these inflammatory factors when analysed using weighted median and inverse variance weighting methods. The specific values are shown in the **Table 1** and **Figure 1**.

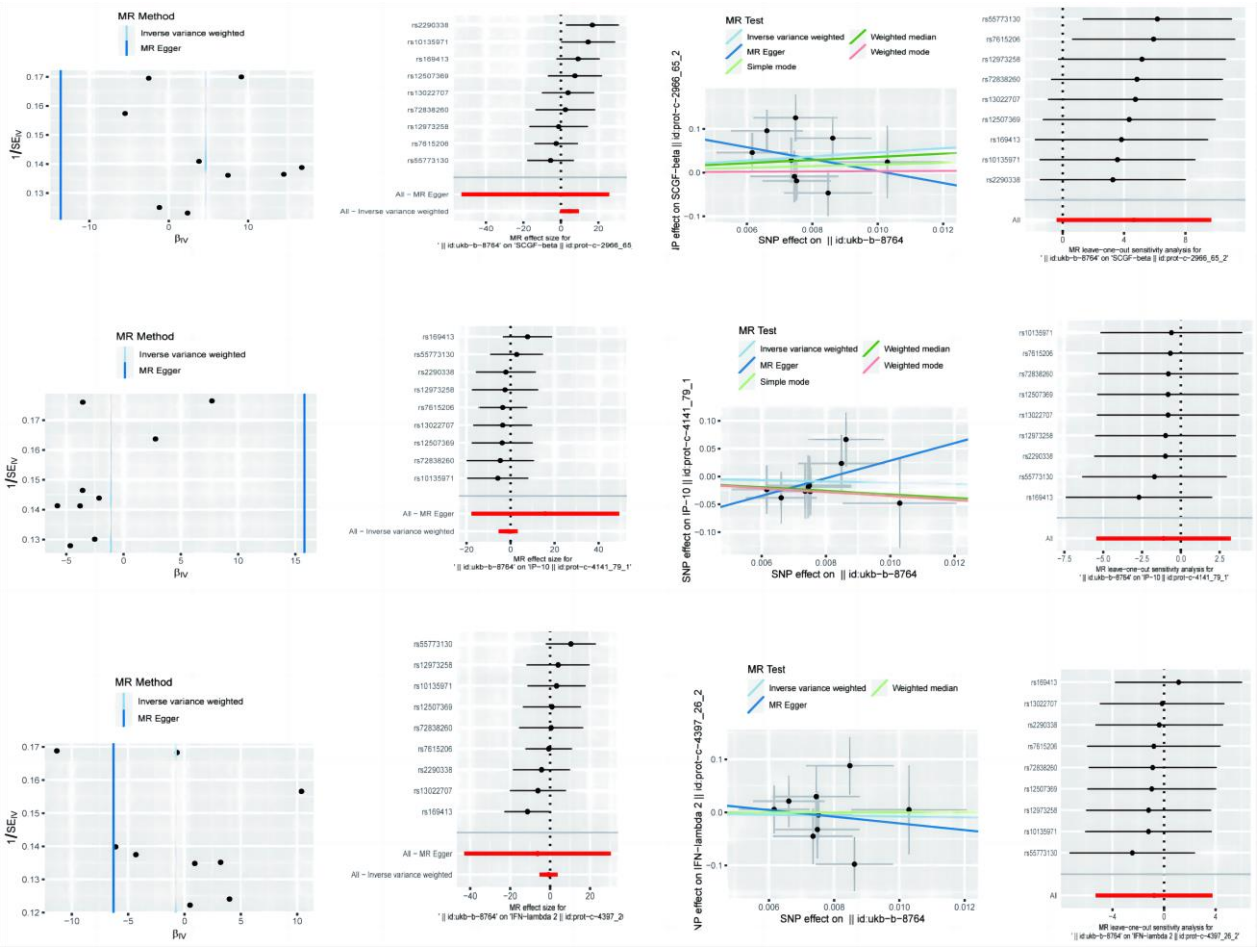

Figure 1. Mendelian randomization analysis demonstrating the causal effects of physical exercise on inflammatory factors: SCGF-beta, IP-10, and IFN-lambda 2.

Table 2 demonstrates the sensitivity analyses performed on the effect of physical exercise on the inflammatory factors SCGF-beta, IP-10 and IFN-lambda. For heterogeneity test and multifunctionality test, MR-Egger and inverse variance weighting methods were used. For SCGF-beta, the *Q*-value of the heterogeneity test was 8.955201202 with 7 degrees of freedom and a *P*-value of 0.255888448, and for the multifunctionality test, the *Q*-value of the multifunctionality test was 10.02761572 with 8 degrees of freedom and a *P*-value of 0.263093003. For IP-10 and IFN-lambda, the heterogeneity test and multifunctionality test results are also presented in the table. These results help to assess the robustness of the study and the reliability of the results.

Table 2. Sensitivity analysis of physical exercise on inflammatory factors SCGF-beta, IP-10, IFN-lambda 2.

	Heterogeneity test						**Pleiotropy test**		
	MR-Egger			**Inverse variance weighted**			**MR-Egger**		
	Q	**Q_df**	**Q_pval**	***Q***	**Q_df**	**Q_pval**	**intercept**	**se**	***p***
SCGF-beta	8.955201202	7	0.255888448	10.02761572	8	0.263093003	0.1397031	0.152585532	0.390341125
IP-10	2.995080313	7	0.88545697	3.98527697	8	0.858449373	−0.129334039	0.129972691	0.352839932
IFN-lambda 2	7.634169656	7	0.365954336	7.730801106	8	0.4601983	0.04228115	0.142042865	0.774599272

Table 3 demonstrates the results of Mendelian randomisation of the inflammatory factors SCGF-beta, IP-10 and IFN-lambda 2 for juvenile idiopathic arthritis. Different methods including MR Egger, weighted median and inverse variance weighting were used to assess the causal association between these factors and juvenile idiopathic arthritis. For SCGF-beta, the MR Egger method showed a *P*-value of 1.09×10^{-6}, a Beta coefficient of 0.562928 and a 95% confidence interval of (-15.39351, 1.38×10^{11}). The weighted median and inverse variance weighting methods provided similar results, but with slightly different estimates and *p*-values. For IP-10, the MR Egger method showed a *p*-value of 7.69×10^{6}, a Beta coefficient of 0.453934, and a 95% confidence interval of (13.502665, 3.25×10^{21}). The results of the weighted median and inverse variance weighting methods also showed a causal association between p-IP-10 and juvenile idiopathic arthritis. For IFN-lambda 2, the MR Egger method showed a *P*-value of 1.58×10^{-3}, a Beta coefficient of 0.612673 and a 95% confidence interval of (-6.900172, 1.49×10^{13}). The results of the weighted median and inverse variance weighting methods provided similar results but differed in estimates and *p*-values. These results suggest that these inflammatory factors may be causally linked to juvenile idiopathic arthritis, but different methods of analysis may lead to slightly different results.

Table 3. Mendelian randomisation of the inflammatory factors SCGF-beta, IP-10, and IFN-lambda 2 to juvenile idiopathic arthritis.

		Juvenile Idiopathic Arthriti				
		or	**or_lci95**	**or_uci95**	***P*-Value**	**Beta**
SCGF-beta	MR Egger	1.09×10^{-6}	7.93×10^{-24}	1.38×10^{11}	0.562928	−15.39351
	Weighted median	3.23×10^{1}	6.64×10^{-2}	1.84×10^{4}	0.247564	3.219962
	Inverse variance weighted	8.69×10^{1}	6.79×10^{-1}	1.91×10^{4}	0.084195	4.900788
IP-10	MR Egger	7.69×10^{6}	1.80×10^{-8}	3.25×10^{21}	0.453934	13.502665
	Weighted median	4.73×10^{-2}	1.51×10^{-4}	1.16×10^{1}	0.227526	−2.89287
	Inverse variance weighted	3.46×10^{-1}	5.10×10^{-3}	2.85×10^{1}	0.723963	−1.150526
IFN-lambda 2	MR Egger	1.58×10^{-3}	1.95×10^{-19}	1.49×10^{13}	0.612673	−6.900172
	Weighted median	1.10×10^{0}	1.90×10^{-3}	5.36×10^{2}	0.82458	0.002705
	Inverse variance weighted	5.16×10^{-1}	4.90×10^{-3}	3.83×10^{1}	0.807672	−0.916941

Table 4 demonstrates the sensitivity analyses performed for the inflammatory factors SCGF-beta, IP-10 and IFN-lambda 2 in juvenile idiopathic arthritis. These analyses included conditional analyses to assess the effect of different conditions on the results. For SCGF-beta, the conditional *Q*-value was 8.251207 with a degree of freedom of 7 and a *P*-value of 0.216714, and the *Q*2-value was 9.976994 with a degree of freedom of 8 and a *P*-value of 0.298223. For IP-10 and IFN-lambda 2, the conditional *Q*-values and *Q*2-values are also presented in the table. The results show that the effects of the different conditions on the results are relatively small, which indicates that the robustness of the results is relatively high. These sensitivity analyses help to assess the reliability of the findings and provide a more comprehensive understanding.

Table 4. Sensitivity analysis of inflammatory factors SCGF-beta, IP-10 and IFN-lambda 2 in juvenile idiopathic arthritis.

Condition	*Q*	Q_df	Q_pval	*Q*2	Q2_df	Q2_pval	intercept	se	*p*
SCGF-beta	8.251207	7	0.216714	9.976994	8	0.298223	0.152538	0.18264	0.402624
IP-10	3.179028	7	0.993456	3.536139	8	1.002503	−0.150594	0.10849	0.294025
IFN-lambda 2	7.943744	7	0.388681	8.200265	8	0.387262	0.040347	0.128772	0.703714

4. Discussion

In recent years, the role of physical activity as a non-pharmacological intervention in the prevention and management of a wide range of chronic diseases has received increasing attention. Especially in the field of Juvenile Idiopathic Arthritis (JIA), more and more studies have explored the relationship between physical activity and JIA [24,25]. Existing studies have shown that physical activity not only provides significant improvements in physical fitness, joint function, and quality of life in patients with JIA, but may also reduce the symptoms and progression of the disease by modulating the inflammatory response [26]. Several epidemiological studies have found that regular physical activity reduces disease severity in patients with JIA. Several longitudinal studies have shown that increasing the amount of physical activity improves joint function and reduces disease mobility and pain in patients with JIA [27–29]. In addition, physical activity improves cardiorespiratory fitness and muscle strength in patients, thereby enhancing their overall health. Although these studies provide support for the positive effects of physical activity on JIA, they are mostly observational studies and it is difficult to clarify the causal relationship [30].

Inflammatory response occupies a central position in the pathogenesis of JIA. changes in the levels of SCGF-beta, IP-10 and IFN-lambda, as important inflammatory factors, directly affect the progression of JIA [31]. It has been found that physical exercise can alleviate the symptoms of JIA by regulating the levels of these inflammatory factors and reducing the inflammatory response. For example, SCGF-beta plays a key role in regulating haematopoietic and immune responses, and a reduction in its levels may help reduce joint inflammation and injury [32]. In addition, IP-10 is a chemokine that plays an important role in inflammation and immune response, and a decrease in its level may reduce the infiltration of immune cells, thereby reducing the inflammatory response [33–35]. IFN-lambda, as an antiviral cytokine, and a decrease in its level may contribute to the reduction of inflammatory response and improvement of the symptoms of JIA. Secondly, physical exercise has a wide range of applications as a safe, economical and easy-to-promote intervention [36]. Compared with medication, physical exercise not only effectively improves joint function and quality of life in patients with JIA, but also reduces the side effects and dependence of medication. This is important for the long-term management of JIA. In addition, physical activity can improve the overall health of patients by improving their cardiorespiratory function and muscle strength, thus reducing the risk of other chronic diseases [37–39].

In this study, we investigated the effects of physical activity on the inflammatory factors SCGF-beta, IP-10, and IFN-lambda and its causal association

with Juvenile Idiopathic Arthritis (JIA) by Mendelian randomisation (MR) method. The findings suggest that physical activity has a significant effect on these inflammatory factors, which may indirectly influence the risk of developing JIA.

Analysis by the MR Egger method showed a significant effect of physical activity on SCGF-beta (*p*-value 1.22×10^{-6}) with a Beta coefficient of 0.520141012 and a 95% confidence interval of (-13.61653858, 1.61017×10^{11}). Although the confidence interval is wide, it still shows that physical activity has a positive effect on SCGF-beta. The results of the weighted median and inverse variance weighting methods also support this finding. This implies that physical activity may reduce the inflammatory response by lowering the level of SCGF-beta, thus reducing the risk of JIA.

For IP-10, the MR Egger method showed a significant effect of physical activity (*p*-value of 7203718.995) with a Beta coefficient of 0.387298409 and a 95% confidence interval of (15.79010798, 2.75×10^{21}). Despite the large confidence interval, this result still suggests that physical activity may have a significant effect on IP-10. The results of other methods also support this idea, although the specific values are different. IP-10 is a chemokine that plays an important role in inflammation and immune response, and changes in its level may affect the development of JIA.

For IFN-lambda, the analysis by MR Egger method showed a *P*-value of 0.001839626, a Beta coefficient of 0.746376941 and a 95% confidence interval of (-6.298193152, 1.578×10^{13}). This result suggests that physical activity also has a significant effect on IFN-lambda, albeit with a wide confidence interval. The results of the weighted median and inverse variance weighting methods were consistent with the MR Egger method. Changes in the levels of IFN-lambda, an antiviral cytokine, may affect the inflammatory response and the course of JIA. The results of sensitivity analyses showed that the effect of physical activity on inflammatory factors was robust, both by the heterogeneity test and the multifunctionality test. These analyses further validated the reliability of the findings, showing that different statistical methods support the causal effect of physical activity on inflammatory factors and its relationship with JIA.

These results have important clinical and public health implications. Firstly, physical activity as a non-pharmacological intervention may reduce the risk of JIA by modulating the levels of inflammatory factors to reduce the inflammatory response. This provides new ideas for the prevention and management of JIA [40–43]. Secondly, these findings support the important role of physical activity in maintaining overall health and emphasise its potential in chronic disease prevention [44].

This study, through Mendelian Randomisation (MR) analysis, has unveiled the potential causal link between physical activity and Juvenile Idiopathic Arthritis (JIA), with a particular focus on the inflammatory factors SCGF-beta, IP-10, and IFN-lambda 2. While the MR method provides us with a powerful tool for assessing causal relationships, it is essential to consider some limitations of MR analysis when interpreting our findings. Our analysis relies on the validity of selected Single Nucleotide Polymorphisms (SNPs) as instrumental variables. The strength of the association between these SNPs and physical activity may be influenced by sample

size and genetic structure, potentially leading to insufficient statistical power, especially when exploring rare variants. Moreover, the selection of SNPs may be constrained by the structure of Linkage Disequilibrium (LD) in the genome, which could affect the accuracy of causal inference [45]. Therefore, we applied strict criteria to select independent SNPs that are significantly associated with physical activity to reduce the likelihood of bias and confounding. Concurrently, the bias in data sources is a concern that we must address. Our analysis is primarily based on populations of European descent, which may limit the generalizability of our results. Populations of different ethnicities and geographical backgrounds may have varying genetic structures and lifestyles, which could impact the relationship between inflammatory factors and the risk of JIA [46]. Hence, future studies need to validate our findings in more diverse populations to ensure the global applicability of the results.

Despite these limitations, our study's results have potential implications for the clinical treatment and management of JIA. Physical activity, as a non-pharmacological treatment modality, may offer a new therapeutic option for JIA patients. Our findings emphasize the possibility of improving JIA patient outcomes by modulating inflammatory pathways, which could guide future clinical trials to explore the effects of physical activity interventions. Furthermore, these results can be translated into practical public health strategies. Promoting the role of physical activity in the prevention and management of JIA can raise public awareness of this non-pharmacological intervention method. Public health policies can encourage the implementation of physical activity programs in schools, communities, and medical institutions, particularly targeting children and adolescents, to reduce the incidence of JIA and improve patients' quality of life [47].

In conclusion, our MR analysis has revealed the potential causal relationship between physical activity and JIA, and has pointed to the possibility of physical activity as a means of prevention and treatment. Despite the limitations, these findings provide valuable insights for future research directions and public health practices.

5. Conclusion

This study revealed significant effects of physical activity on the inflammatory factors SCGF-beta, IP-10 and IFN-lambda through Mendelian randomisation analysis and further explored the causal link between these inflammatory factors and juvenile idiopathic arthritis. These findings provide new evidence for the potential role of physical activity in the prevention of chronic inflammatory diseases and highlight its importance in public health strategies.

Author contributions: Conceptualization, SH, ZW, GQ and MH; methodology, SH and ZW; formal analysis, ZW and GQ; data curation, ZW and GQ; writing—original draft preparation, SH, ZW, GQ and MH; supervision, MH. All authors have read and agreed to the published version of the manuscript.

Ethical approval: Not applicable.

Data availability statement: All data used in this study are original, have not been published elsewhere, and are solely owned by the authors. We ensure the integrity and transparency of the data to enable other researchers to replicate and verify our study's findings. For data requests, please contact the corresponding author, Xueshao Zhang, at email: zhangxueshao2021@126.com.

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Conflict of interest: The authors declare no conflict of interest.

Abbreviations

JIA	Juvenile Idiopathic Arthritis
MR	Mendelian Randomisation
SCGF-beta	Stem Cell Growth Factor-beta
IP-10	Interferon Gamma-Inducible Protein 10
IFN-lambda 2	Interferon Lambda 2
SNP	Single Nucleotide Polymorphism
GWAS	Genome-Wide Association Studies
IVW	Inverse Variance Weighted

References

1. Woolnough, Leandra U, Lentini, Logan, Sharififar, Sharareh, Chen, Cong, Vincent, Heather K, (2022). The relationships of kinesiophobia and physical function and physical activity level in juvenile idiopathic arthritis. Pediatric rheumatology online journal, 20 (1), 73. https://doi.org/10.1186/s12969-022-00734-2
2. Gil, Elisabeth G, Skeie, Marit S, Halbig, Josefine, Jönsson, Birgitta, Lie, Stein Atle, Rygg, Marite, Fischer, Johannes, Rosén, Annika, Bletsa, Athanasia, Luukko, Keijo, Shi, Xie-Qi, Frid, Paula, Cetrelli, Lena, Tylleskär, Karin, Rosendahl, Karen, Åstrøm, Anne N, (2022). Oral health-related quality of life in 4-16-year-olds with and without juvenile idiopathic arthritis. BMC oral health, 22 (1), 387. https://doi.org/10.1186/s12903-022-02400-1
3. Vincent, Heather K, Sharififar, Sharareh, Abdelmalik, Bishoy, Lentini, Logan, Chen, Cong, Woolnough, Leandra U, (2022). Gait parameters, functional performance and physical activity in active and inactive Juvenile Idiopathic Arthritis. GAIT & POSTURE, 98 226-232. https://doi.org/10.1016/j.gaitpost.2022.09.080
4. Holovko, T. O., Shevchenko, N. S., Bohmat, L. F., Nikonova, V. V., (2022). Tolerance to exercise in adolescents with rheumatic diseases taking into account systolic heart function Pathologia, 19 (1), 18-23. https://doi.org/10.14739/2310-1237.2022.1.243693
5. Miladi, S, Bouzid, S, Fazaa, A, Souabni, L, Sellami, M, Ouenniche, K, Kassab, S, Chekili, S, Ben Abdelghani, K, Laatar, A, (2021). P019 Adulthood of juvenile idiopathic arthritis patients: professional outcome RHEUMATOLOGY, 60 (Supple5), https://doi.org/10.1093/rheumatology/keab722.011
6. Ozdemir, Berk Can, Savci, Sema, Tanriverdi, Aylin, Ozcan Kahraman, Buse, Isguder, Rana, Makay, Balahan, Unsal, Erbil, (2023). Determinants of physical activity level in children and adolescents with juvenile idiopathic arthritis. Zeitschrift fur rheumatologie, 83 (Suppl 1), 71-77. https://doi.org/10.1007/s00393-023-01340-7
7. Craig, Joshua, Feldman, Brian M, Spiegel, Lynn, Dover, Saunya, (2020). Comparing the Measurement Properties and Preferability of Patient-reported Outcome Measures in Pediatric Rheumatology: PROMIS vs CHAQ. Journal of rheumatology, 48 (7), 1065-1072. https://doi.org/10.3899/jrheum.200943
8. Oliveira Ramos, Filipa, Rodrigues, Ana, Magalhaes Martins, Fernando, Melo, Ana Teresa, Aguiar, Francisca, Brites, Luisa, Azevedo, Soraia, Duarte, Ana Catarina, Furtado, Carolina, Mourão, Ana Filipa, Sequeira, Graça, Cunha, Inês, Figueira, Ricardo, Melo Gomes, Jose Antonio, Santos, Maria Jose, Fonseca, Joao Eurico, (2021). Health-related quality of life and

disability in adults with juvenile idiopathic arthritis: comparison with adult-onset rheumatic diseases. RMD open, 7 (3), https://doi.org/10.1136/rmdopen-2021-001766

9. Ferjani, Hanene Lassoued, Makhlouf, Yasmine, Ben Ammar, Lobna, Triki, Wafa, Ben Nessib, Dorra, Maatallah, Kaouther, Kaffel, Dhia, Hamdi, Wafa, (2022). 06 Flat foot impairs physical activity in children with juvenile idiopathic arthritis RHEUMATOLOGY, 61 (Supple2), https://doi.org/10.1093/rheumatology/keac496.002
10. Schujovitzky, Dana, Ziv, Amit, Heshin Bekenstein, Merav, Eylon, Sharon, Grossman, Zachi, Hashkes, Philip J, Uziel, Yosef, Haviv, Ruby, (2022). Measuring the knowledge of juvenile idiopathic arthritis among Israeli paediatricians and paediatric orthopaedic surgeons: what needs to be improved? Clinical and experimental rheumatology, 40 (11), 2188-2193. https://doi.org/10.55563/clinexprheumatol/7j9es3
11. Codes-Mendez, H., Magallares, B., Martínez-Martínez, L., Park, H., Lobo Prat, D., Sainz Comas, L., Gich, I., Alvaro, Y., Molto, E., Calahorro, V., Boronat, S., Corominas, H., (2022). AB1237 Comparison between enzyme immunoassay and chemiluminescence to determine the concentration of serum calprotectin and its association with clinical variables in pediatric rheumatology. annals of the rheumatic diseases, 81 (Suppl 1), 1730-1731. https://doi.org/10.1136/annrheumdis-2022-eular.1892
12. Polat, Merve Cansu, Çelikel, Elif, Tekin, Zahide Ekici, Güngörer, Vildan, Kurt, Tuba, Tekgöz, Nilüfer, Sezer, Müge, Karagöl, Cüneyt, Coşkun, Serkan, Kaplan, Melike Mehveş, Öner, Nimet, Acar, Banu Çelikel, (2023). Assessment of quality of life and physical activity in patients with oligoarticular juvenile idiopathic arthritis in remission. EUROPEAN JOURNAL OF PEDIATRICS, 183 (2), 955-964. https://doi.org/10.1007/s00431-023-05367-5
13. Fazaa, A., Kammoun, M., Miladi, S., Boussaa, H., Ouenniche, K., Souabni, L., Kassab, S., Chekili, S., Ben Abdelghani, K., Laatar, A., (2022). Ab0154 physical function assessment tools in patients with juvenile idiopathic arthritis: jafas versus chaq annals of the rheumatic diseases, 81 (Suppl 1), 1207.2-1208. https://doi.org/10.1136/annrheumdis-2022-eular.3975
14. Nascimento Leite, Mariana, Kamper, Steven J, O'Connell, Neil E, Michaleff, Zoe A, Fisher, Emma, Viana Silva, Priscilla, Williams, Christopher M, Yamato, Tiê P, (2023). Physical activity and education about physical activity for chronic musculoskeletal pain in children and adolescents. The Cochrane database of systematic reviews, 7 CD013527. https://doi.org/10.1002/14651858.CD013527.pub2
15. Triki, W., Dghaies, A., Ferjani, H., Ben Aissa, R., Ben Nessib, D., Maatallah, K., Kaffel, D., Hamdi, W., (2022). AB1255 Assessment of sleep disturbances in children with juvenile idiopathic arthritis annals of the rheumatic diseases, 81 (Suppl 1), 1737.3-1738. https://doi.org/10.1136/annrheumdis-2022-eular.3731
16. Kuntze, Gregor, Nettel-Aguirre, Alberto, Brooks, Julia, Esau, Shane, Nesbitt, Colleen, Mosher, Dianne, Twilt, Marinka, Benseler, Susanne, Ronsky, Janet L, Emery, Carolyn A, (2021). Vertical Drop Jump Performance in Youth With Juvenile Idiopathic Arthritis. Arthritis care & research, 73 (7), 955-963. https://doi.org/10.1002/acr.24219
17. Kozu, Kátia T, Casella, Caio B, Strabelli, Claudia A A, Aikawa, Nadia E, Campos, Lucia M A, Elias, Adriana M, Miguel, Eurípedes C, Polanczyk, Guilherme V, Silva, Clovis A, (2022). Mental Health Impact in Latin American Pediatric Rheumatologists During the COVID-19 Pandemic. Jcr-journal of clinical rheumatology, 28 (2), e506-e510. https://doi.org/10.1097/RHU.0000000000001782
18. Ben Ouahma, B, Triki, W, Maatallah, K, Ferjani, H, Ben Nessib, D, Kaffel, D, Hamdi, W, (2021). P027 Assessment of physical activity in Juvenile Idiopathic Arthritis Rheumatology, 60 (Supple5), https://doi.org/10.1093/rheumatology/keab722.019
19. Oliveira Ramos, Filipa, Rodrigues, Ana Maria, Melo, Ana Teresa, Aguiar, Francisca, Brites, Luísa, Azevedo, Soraia, Duarte, Ana Catarina, Gomes, José António Melo, Furtado, Carolina, Mourão, Ana Filipa, Sequeira, Graça, Cunha, Inês, Figueira, Ricardo, Santos, Maria José, Fonseca, João Eurico, (2023). Influence of the timing of biological treatment initiation on Juvenile Idiopathic Arthritis long-term outcomes. Arthritis research & therapy, 25 (1), 177. https://doi.org/10.1186/s13075-023-03166-9
20. Dzhus, M., Kulyk, M., Karasevska, T., (2022). POS1315 Prevalence of sarcopenia in young adults with juvenile idiopathic arthritis annals of the rheumatic diseases, 81 (Suppl 1), 995.1-995. https://doi.org/10.1136/annrheumdis-2022-eular.3742
21. Elmesmari, Rabha A, Reilly, John J, Paton, James Y, (2022). 24-Hour Movement Behaviors in Children with Chronic Disease and Their Healthy Peers: A Case-Control Study. International journal of environmental research and public health, 19 (5), https://doi.org/10.3390/ijerph19052912
22. Jonyk, L, Sagawa Junior, Y, Tordi, N, Ballot Schmit, C, (2022). Description of physical activity in children with juvenile idiopathic arthritis using accelerometry. Archives de pediatrie, 30 (2), 83-88. https://doi.org/10.1016/j.arcped.2022.11.003

23. Phenoscanner: A GWAS database. Available online: http://www.phenoscanner.medschl.cam.ac.uk/ (accessed on 15 June 2024).
24. Grammatikopoulou, Maria G, Gkiouras, Konstantinos, Syrmou, Vasiliki, Vassilakou, Tonia, Simopoulou, Theodora, Katsiari, Chistina G, Goulis, Dimitrios G, Bogdanos, Dimitrios P, (2023). Nutritional Aspects of Juvenile Idiopathic Arthritis: An A to Z for Dietitians. Children (Basel, Switzerland), 10 (2), https://doi.org/10.3390/children10020203
25. Di Marcello, Francesca, Di Donato, Giulia, d'Angelo, Debora Mariarita, Breda, Luciana, Chiarelli, Francesco, (2022). Bone Health in Children with Rheumatic Disorders: Focus on Molecular Mechanisms, Diagnosis, and Management. International journal of molecular sciences, 23 (10), https://doi.org/10.3390/ijms23105725
26. Halbig, Josefine M, Jönsson, Birgitta, Gil, Elisabeth G, Åstrøm, Anne N, Rypdal, Veronika, Frid, Paula, Augdal, Thomas A, Fischer, Johannes, Cetrelli, Lena, Rygg, Marite, Lundestad, Anette, Tylleskär, Karin, Nordal, Ellen, (2023). Oral health-related quality of life, impaired physical health and orofacial pain in children and adolescents with juvenile idiopathic arthritis - a prospective multicenter cohort study. BMC oral health, 23 (1), 895. https://doi.org/10.1186/s12903-023-03510-0
27. Py, Stéphanie, Maylié, Florine, Parmentier, Anne-Laure, Vidal, Chrystelle, Cuinet, Benjamin, Mauny, Fréderic, Lohse, Anne, Toussirot, Eric, Yoshimasa, Sagawa, Tordi, Nicolas, Binda, Delphine, Ballot-Schmit, Claire, (2023). ATHLETIQUE: interest of an adapted physical activity program in patients with juvenile idiopathic arthritis: a feasibility and preliminary effectiveness study. Frontiers in immunology, 14 1213799. https://doi.org/10.3389/fimmu.2023.1213799
28. Skorpen, C., Lydersen, S., Salvesen, K. Å., Wallenius, M., (2023). Pos0774 cesarean section in women with juvenile idiopathic arthritis – a population-based study annals of the rheumatic diseases, 82 (Suppl 1), 679.1-679. https://doi.org/10.1136/annrheumdis-2023-eular.5350
29. Bingham, Catherine A, Harris, Julia G, Qiu, Tingting, Gilbert, Mileka, Vora, Sheetal S, Yildirim-Toruner, Cagri, Ferraro, Kerry, Lovell, Daniel J, Taylor, Janalee, Mannion, Melissa L, Weiss, Jennifer E, Laxer, Ronald M, Shishov, Michael, Oberle, Edward J, Gottlieb, Beth S, Lee, Tzielan C, Pan, Nancy, Burnham, Jon M, Fair, Danielle C, Batthish, Michelle, Hazen, Melissa M, Spencer, Charles H, Morgan, Esi M, (2023). Pediatric Rheumatology Care and Outcomes Improvement Network's Quality Measure Set to Improve Care of Children With Juvenile Idiopathic Arthritis. ARTHRITIS CARE & RESEARCH, 75 (12), 2442-2452. https://doi.org/10.1002/acr.25168
30. Gruca, M., Orczyk, K., Zamojska, J., Niewiadomska-Jarosik, K., Stanczyk, J., Smolewska, E., (2022). POS1317 How can we assess cardiovascular risk in patients with juvenile idiopathic arthritis? preliminary results regarding measurements of carotid intima-media thickness during the COVID-19 pandemic. Annals of the rheumatic diseases, 81 (Suppl 1), 995.3-996. https://doi.org/10.1136/annrheumdis-2022-eular.3802
31. Tollisen, Anita, Selvaag, Anne M, Aasland, Astrid, Ingebrigtsen, Trude, Sagen, Joachim, Lerdal, Anners, Flatø, Berit, (2022). Personally Generated Quality of Life Outcomes in Adults With Juvenile Idiopathic Arthritis. Journal of rheumatology, 49 (10), 1138-1145. https://doi.org/10.3899/jrheum.211245
32. Räsänen, Kati, Markula-Patjas, Kati, Kantanen, Saija, Sipilä, Kalle, Lakka, Timo A, Arikoski, Pekka, Piippo-Savolainen, Eija, (2023). Impaired cardiorespiratory and neuromuscular fitness in children and adolescents with juvenile idiopathic arthritis: a cross-sectional case-control study in the era of biologic drug therapies. Pediatric rheumatology online journal, 21 (1), 26. https://doi.org/10.1186/s12969-023-00808-9
33. de Oliveira, Rodrigo Joel, Londe, Ana Carolina, de Souza, Débora Pessoa, Marini, Roberto, Fernandes, Paula Teixeira, Appenzeller, Simone, (2023). Physical Activity Influences Health-Related Quality of Life in Adults with Juvenile Idiopathic Arthritis. Journal of clinical medicine, 12 (3), https://doi.org/10.3390/jcm12030771
34. Sabounji, Mounib M, Ndiaye, Aïssatou, Niasse, Moustapha, Abba, Abbasse, Gueye, Aminata, Diallo, Saïdou, (2021). O001. Juvenile-onset spondyloarthritis: a study of 54 cases in Senegal RHEUMATOLOGY, 60 (Supple5), https://doi.org/10.1093/rheumatology/keab723
35. Bohmat, L., Shevchenko, N., Fadieieva, A., Nikonova, V., (2022). POS1542-HPR Quality of life and physical functioning of patients with juvenile idiopathic arthritis fast translate icon translate fast translate icon translate annals of the rheumatic diseases, 81 (Suppl 1), 1115.3-1116. https://doi.org/10.1136/annrheumdis-2022-eular.5105
36. Gupta, Umesh Chandra, Gupta, Subhas Chandra, Gupta, Saira Sugandh, (2022). Clinical Overview of Arthritis with a Focus on Management Options and Preventive Lifestyle Measures for Its Control Current Nutrition & Food Science, 18 https://doi.org/10.2174/1573401318666220204095629

37. Rochette, Emmanuelle, Saidi, Oussama, Merlin, Étienne, Duché, Pascale, (2023). Physical activity as a promising alternative for young people with juvenile idiopathic arthritis: Towards an evidence-based prescription. Frontiers in immunology, 14 1119930. https://doi.org/10.3389/fimmu.2023.1119930
38. Gorczyca, Daiva, Iwańczyk, Patrycja, Staś, Karolina, Postępski, Jacek, (2023). Knee pain as a reason for referral to a paediatric rheumatologist: A retrospective study. Journal of paediatrics and child health, 59 (3), 439-444. https://doi.org/10.1111/jpc.16309
39. Kuntze, Gregor, Nettel-Aguirre, Alberto, Brooks, Julia, Esau, Shane, Nesbitt, Colleen, Mosher, Dianne, Twilt, Marinka, Benseler, Susanne, Ronsky, Janet L, Emery, Carolyn A, (2021). Consequences of Juvenile Idiopathic Arthritis on Single Leg Squat Performance in Youth. Arthritis care & research, 73 (8), 1187-1193. https://doi.org/10.1002/acr.24254
40. Butler, Sonia, Sculley, Dean, Santos, Derek, Fellas, Antoni, Gironès, Xavier, Singh-Grewal, Davinder, Coda, Andrea, (2022). Effectiveness of eHealth and mHealth Interventions Supporting Children and Young People Living With Juvenile Idiopathic Arthritis: Systematic Review and Meta-analysis. Journal of medical Internet research, 24 (2), e30457. https://doi.org/10.2196/30457
41. Milatz, Florian, Hansmann, Sandra, Klotsche, Jens, Niewerth, Martina, Kallinich, Tilmann, Dressler, Frank, Haas, Johannes-Peter, Berendes, Rainer, Horneff, Gerd, Hufnagel, Markus, Weller-Heinemann, Frank, Windschall, Daniel, Trauzeddel, Ralf, Klaas, Moritz, Girschick, Hermann, Oommen, Prasad T, Foeldvari, Ivan, Cantez, Serdar Mustafa, Jansson, Annette F, Hartmann, Matthias, Peitz-Kornbrust, Joachim, Minden, Kirsten, (2024). Level and correlates of physical activity among children and adolescents with juvenile idiopathic arthritis compared to controls: results from a German nationwide prospective observational cohort study. Pediatric rheumatology online journal, 22 (1), 39. https://doi.org/10.1186/s12969-024-00976-2
42. Trachtman, Rebecca, Samuels, Julie, Wojtal, Emma, Feldman, Brian M, (2023). Resilience and its associations in children with Systemic Lupus Erythematosus and Juvenile Idiopathic Arthritis. Pediatric rheumatology online journal, 21 (1), 67. https://doi.org/10.1186/s12969-023-00854-3
43. Alongi, Alessandra, Giancane, Gabriella, Naddei, Roberta, Natoli, Valentina, Ridella, Francesca, Burrone, Marco, Rosina, Silvia, Chedeville, Gaelle, Alexeeva, Ekaterina, Horneff, Gerd, Foeldvari, Ivan, Filocamo, Giovanni, Constantin, Tamàs, Ruperto, Nicolino, Ravelli, Angelo, Consolaro, Alessandro, (2022). Drivers of non-zero physician global scores during periods of inactive disease in juvenile idiopathic arthritis. RMD open, 8 (1), https://doi.org/10.1136/rmdopen-2021-002042
44. Zare, Najmeh, Mansoubi, Maedeh, Coe, Shelly, Najafi, Ali Aminalsharieh, Bailey, Kathryn, Harrison, Kathryn, Sheehan, Joanna, Dawes, Helen, Barker, Karen, (2023). An investigation into the relationship between nutritional status, dietary intake, symptoms and health-related quality of life in children and young people with juvenile idiopathic arthritis: a systematic review and meta-analysis. BMC pediatrics, 23 (1), 3. https://doi.org/10.1186/s12887-022-03810-4
45. Yücel, Aylin, Aydog, Ozlem, Karadavut, Kıymet Ikbal, Uneri, Sukran Ozden, (2023). Evaluation of osteoporosis and related factors and quality of life of patients with juvenile idiopathic arthritis and burnout status of parents Journal of Surgery and Medicine, 7 (1), 26-30. https://doi.org/10.28982/josam.7556
46. Miyamae, Takako, Inoue, Eisuke, Tanaka, Eiichi, Kawabe, Tomohiro, Ikari, Katsunori, Harigai, Masayoshi, (2023). Association of disease activity using SDAI and DAS28, but not JADAS-27, with subsequent changes in physical function in adult patients with juvenile idiopathic arthritis. Modern Rheumatology, 33 (3), 588-593. https://doi.org/10.1093/mr/roac063
47. Bozcuk, S., Basakci Calik, B., Gur Kabul, E., Ekici Tekin, Z., Yuksel, S., (2022). AB1525-HPR Examination of physical fitness in children and adolescents with juvenile idiopathic arthritis: a comparative study annals of the rheumatic diseases, 81 (Suppl 1), 1865.1-1865. https://doi.org/10.1136/annrheumdis-2022-eular.2285