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Medical history risk factors in primary progressive multiple sclerosis: A case-control study

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Keywords
Primary Progressive Multiple Sclerosis; Medical History Taking; Risk Factors

Abstract

Background: The association between medical history and primary progressive multiple sclerosis (PPMS) development has not been well documented in the pertinent literature. The possible association between 23 medical diseases and PPMS occurrence was assessed in the present study.

Methods: In order to figure out the possible association between several medical histories and PPMS occurrence, the present population-based case-control study examined 143 PPMS cases in Tehran, Iran, from 2019 to 2020. Diagnosis of PPMS was confirmed by neurologists based on the 2017 McDonald criteria. Sex-matched healthy controls (n = 143) were selected using the random-digit dialing (RDD) technique. Face-to-face and telephone interviews were conducted for gathering the data. The conditional logistic regression model was used to calculate adjusted and unadjusted odds ratio (OR) at a 95% confidence interval (CI).

Results: A significant association was found between PPMS development and diseases like depression (OR = 3.12, 95% CI: 1.49-6.53), migraine (OR = 0.19, 95% CI: 0.05-0.67), infectious mononucleosis (OR = 13.16, 95% CI: 2.74-63.17), hypothyroidism (OR = 3.20, 95% CI: 1.23-8.30), and kidney failure (OR = 3.76, 95% CI: 1.41-9.99).

Conclusion: Lifetime history of depression, infectious mononucleosis, hypothyroidism, and kidney failure might increase the risk of PPMS development, while individuals with positive history of migraine disease are at lower risk for developing PPMS.

Introduction

Multiple sclerosis (MS) is the most common chronic neurological inflammatory disease in young adults worldwide.[1] MS disease has a rising trend with an estimated number of 2.3 million in

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2013.[2] Similarly, there is a significant rise in the prevalence and incidence of MS in Iranian population.[3] There are four main MS courses, which are relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and clinically isolated syndrome (CIS).[4] RRMS is the most common type affecting around 85% of patients with MS with a course of acute autoimmune attacks (relapse).[5] SPMS is the type with an initial relapsing-remitting pattern that converts to a progressive pattern worsening the disease lately.[4]

PPMS is the one with a progressive pattern from the beginning of the disease and affects around 10%-15% of the patients with MS.[4] Lastly, CIS is defined as the first episode of neurological symptoms that lasts more than 24 hours. CIS is caused by an inflammatory process that has not yet met the criteria of MS but may develop to MS in future.[4,6]

The exact cause of MS is still unidentified; however, it is believed that a combination of environmental and genetic risk factors makes some individuals susceptible to developing MS.[7-9] Many risk factors such as low sun exposure,[10] smoking,[7] Epstein-Barr virus (EBV),[7] etc. have been figured out to have a significant association with MS.

Although PPMS has been categorized as a subtype of MS, it has some significant differences with other types of MS. For instance, PPMS pathogenesis as compared to RRMS/SPMS mechanism is more likely due to neurodegeneration.[5] In addition, there is no significant difference between men and women in terms of the PPMS prevalence as compared to RRMS prevalence, which is significantly more common among female population.[11] The average age of onset for PPMS is around 40 years as compared to 30 years for RRMS, which indicates a difference of 10 years.[12]

All the mentioned differences may offer the involvement of totally different risk factors in patients with PPMS. There are many studies evaluating MS risk factors; however, they have mostly covered RRMS risk factors or all types of MS together without distinguishing MS types.[8] Therefore, there is no sufficient studies addressing PPMS risk factors with a special focus on the role of medical history in PPMS development.

Thus, the present study aimed at discovering a potential association between the positive history of diseases and PPMS development in a large sample of patients with PPMS.

Materials and Methods

Study subjects: The present population-based case-control study involved patients that were residents in Tehran, Iran, and referred to Sina Hospital as a tertiary care referral center in Tehran.

Overall, 143 cases and 143 controls were enrolled in the study using the census sampling method followed by matching individuals on the sex factor. Included cases were Tehran residents that have lived in Tehran for the last 2 years. The diagnosis of PPMS was performed by neurologists based on the 2017 McDonald criteria.[13]

Included controls were gathered from all 22 municipality zones of Tehran, aged between 18-50 years old, and should have lived in Tehran for the last 2 years. The controls had no history of any neurological disorders, were matched on sex with cases, and were from the same source of patient population.[14] The selection of the control group was performed randomly via random-digit dialing (RDD) using a standard RDD protocol.[15]

The excluded cases and controls were the ones that were pregnant, younger than 18 years old, and older than 69 years old. Moreover, subjects with a cognition disorder or memory dysfunction were also excluded.

Data collection protocol: An identical questionnaire was administered to cases and controls. Baseline characteristics and medical history data of each individual were collected by three trained interviewers using a face-to-face interview for cases and a telephone interview for controls. In both groups, data collection was conducted over a parallel period of time.

The study protocol was approved by the Institutional Review Board (IRB) at Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.1061).

Measurement: The questionnaire was designed by the MS research center of Sina Hospital to measure the association between medical histories and PPMS. The current study evaluated the association between the medical history of 23 diseases and PPMS according to the questionnaire designed for multinational case-control studies of environmental risk factors in MS (EnvIMS-Q).[16]

The validity and reliability of the Persian version of the questionnaire were already approved.[17] Both cases and controls were well aware of the main goals of the study. For the positive history of each disease, the diagnosis of a physician was required. Therefore, the subjects were questioned whether their disease was

diagnosed by a physician.[14] In order to reduce the effect of recall bias, each subject was requested to get help from his/her close relatives or family physicians about the questions that he/she did not know the answer, especially about the history of infectious diseases during childhood. To obtain more reliable reports, an interval of seven days was allowed to provide the definite answer.

Firstly, the questionnaire assessed each subject's demographic characteristics such as date of birth, marital status, current residential zone, self-rated health status, and ethnicity and educational level of patients' parents. These variables were examined to figure out whether they confounded or were causally related to outcomes. In order to address the association of the medical history with PPMS, the following medical histories were focused on: history of depression disorder, measles, rubella, mumps, hepatitis B virus, chickenpox, migraine, infection mononucleosis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), thyroid-related diseases (hyperthyroidism and hypothyroidism), Crohn's disease, ulcerative colitis (UC), type 1 diabetes mellitus (DM), celiac disease, psoriasis, leukemia, Hodgkin and non-Hodgkin lymphoma, melanoma, non-melanoma skin cancer, any kidney-related diseases, and head trauma history. The occurrence time of each of the mentioned diseases was also recorded to ensure that the mentioned diseases occurred before the onset of PPMS. Moreover, positive histories of MS in patients' first-degree relatives were questioned as well.[14]

Means and baseline characteristics of each subject were estimated. The chi-square test and independent samples t-test were used to analyze the association among variables. P-value < 0.05 was considered significant based on two-tailed tests. A large number of variables including age, marital status, self-rated health status, and parents' ethnicity and education level were examined to explore whether they played a confounding role in relation to the outcomes. Conditional logistic regression was used to estimate adjusted and unadjusted odds ratio (OR) at a 95% confidence interval (CI) using R-3.6.1 software.

Results

The characteristics of cases and controls are presented in table 1. Each of the case and control groups consisted of 143 participants with 83 women and 60 men in each group. The female-to-male ratio of controls and PPMS cases was 1.38:1 in both groups. The mean and standard deviation (SD) of age was 47.00 ± 9.57 years and 35.41 ± 8.95 years for cases and controls, respectively. Totally, 101 cases (70.6%) and 90 controls (62.9%) were married.

The most prevalent father ethnicity was Persian in 68 cases (47.6%) and 73 controls (51.0%). Similarly, Persian ethnicity in 73 cases (51.0%) and 80 controls (55.9%) was the dominant mother ethnicity in both groups.

As compared with 98 controls (69.0%), fewer patients, i.e., 39 (27.3%), were very satisfied or satisfied with their health condition.

Moreover, 12 cases (8.5%) versus 3 controls (2.1%) reported a history of familial MS among their first-degree relatives.

A significant difference was observed between the groups with respect to age (P < 0.0001), marital status (P < 0.0001), mother's education level (P = 0.039), and self-rated health status (P < 0.0001) (Table 1).

Table 2 summarizes the possible association between the medical history and PPMS according to applied conditional logistic regression. The significant association was observed between PPMS and depression (OR = 3.12, 95% CI: 1.49-6.53), migraine (OR = 0.19, 95% CI: 0.05-0.67), infectious mononucleosis (OR = 13.16, 95% CI: 2.74-63.17), hypothyroidism (OR = 3.20, 95% CI: 1.23-8.30), and kidney failure (OR = 3.76, 95% CI: 1.41-9.99).

There was no significant association between the development of PPMS and the history of measles (P = 0.652), mumps (P = 0.745), hepatitis B (P = 0.240), chickenpox (P = 0.490), RA (P = 0.159), hyperthyroidism (P = 0.314), UC (P = 0.835), type 1 DM (P = 0.095), psoriasis (P = 0.560), and head trauma (P = 0.548).

Moreover, as neither cases nor controls reported the positive history of SLE, Crohn's disease, celiac disease, leukemia, lymphoma, melanoma, and non-melanoma skin cancer, the mentioned diseases were not included in table 2.

Discussion

Regardless of the rapid increasing awareness provided by studies on MS risk factors, there is no sufficient information about PPMS risk factors. This study with its large sample size contributed to the current body of knowledge by addressing the medical histories association with the PPMS occurrence.

According to table 1, the mean age of the disease onset was 47 years among patients with PPMS. The mentioned mean age was higher than 40 years reported by a previous study.[12]

Table 1. Demographic characteristics of 143 multiple sclerosis (MS) cases and 143 controls

Variables	PPMS cases (n = 143)	Controls (n = 143)	P
Age (year) (mean ± SD)	47.00 ± 9.57	35.41 ± 8.95	< 0.0001
Gender [n (%)]			
Women	83 (58.0)	83 (58.0)	
Men	60 (42.0)	60 (42.0)	
Marital status [n (%)]			< 0.0001
Single	26 (18.2)	44 (30.8)	
Married	101 (70.6)	90 (62.9)	
Single due to death	5 (3.5)	5 (3.5)	
Single due to divorce	11 (7.7)	4 (2.8)	
Father ethnicity [n (%)]			0.2400
Persian	68 (47.6)	73 (51.0)	
Kurd	12 (8.4)	8 (5.6)	
Lor	7 (4.9)	9 (6.3)	
Turk	48 (33.6)	45 (31.5)	
Mazani	1 (0.7)	6 (4.2)	
Gilak	6 (4.2)	2 (1.4)	
Arab	1 (0.7)	0 (0)	
Mother ethnicity [n (%)]			0.5900
Persian	73 (51.0)	80 (55.9)	
Kurd	7 (4.9)	8 (5.6)	
Lor	10 (7.0)	8 (5.6)	
Turk	44 (30.8)	37 (25.9)	
Mazani	2 (1.4)	6 (4.2)	
Gilak	6 (4.2)	4 (2.8)	
Arab	1 (0.7)	0 (0)	
Education level [n (%)]			0.4600
Illiterate	3 (2.1)	1 (0.7)	
Primary school	10 (7.0)	6 (4.2)	
Secondary school	12 (8.4)	15 (10.5)	
High school	54 (37.8)	50 (35.0)	
Bachelor/associate's degree	53 (37.1)	52 (36.4)	
Master's degree and higher	11 (7.7)	19 (13.3)	
Father education level [n (%)]			0.0600
Illiterate	44 (30.8)	36 (25.2)	
Primary school	38 (26.6)	28 (19.6)	
Secondary school	18 (12.6)	19 (13.3)	
High school	30 (21.0)	30 (21.0)	
Bachelor/associate's degree	7 (4.9)	22 (15.4)	
Master's degree and higher	5 (3.5)	3 (3.5)	
Mother education level [n (%)]			0.0400
Illiterate	51 (35.7)	45 (31.5)	
Primary school	45 (31.5)	25 (17.5)	
Secondary school	17 (11.9)	24 (16.8)	
High school	23 (16.1)	29 (20.3)	
Bachelor/associate's degree	7 (4.9)	13 (9.1)	
Master's degree and higher	0 (0)	2 (1.4)	
Self-rated health [n (%)]			< 0.0001
Very unsatisfied	18 (12.6)	0 (0)	
Unsatisfied	29 (20.3)	13 (9.2)	
Neither unsatisfied nor satisfied	57 (39.9)	31 (21.8)	
Satisfied	34 (23.8)	81 (57.0)	
Very satisfied	5 (3.5)	17 (12.0)	
MS in family [n (%)]			0.0900
No	131 (91.6)	140 (97.9)	
Yes in mother	2 (1.4)	0 (0)	
Yes in sister/brother	9 (6.3)	3 (2.1)	
Yes in son/daughter	1 (0.7)	0 (0)	

Bold values indicate significant results

PPMS: Primary progressive multiple sclerosis; SD: Standard deviation; MS: Multiple sclerosis

Table 2. Medical history risk factors

Variables	Cases (n = 143) [n (%)]	Controls (n = 143) [n (%)]	Crude OR (95% CI)	Adjusted OR[#] (95% CI)	P
Depression					
Yes	67 (46.9)	29 (20.3)	3.20 (1.89-5.42)	3.12 (1.49-6.53)	0.003*
No	76 (53.1)	114 (79.7)	Reference	Reference	-
Measles					
Yes	57 (39.9)	51 (35.9)	1.23 (0.76-2.01)	1.19 (0.56-2.51)	0.652
No	86 (60.1)	91 (64.1)	Reference	Reference	-
Rubella					
Yes	7 (4.9)	15 (10.5)	0.45 (0.18-1.16)	0.27 (0.07-1.04)	0.059
No	136 (95.1)	128 (89.5)	Reference	Reference	-
Mumps					
Yes	39 (27.3)	43 (30.1)	0.98 (0.58-1.65)	0.77 (0.40-1.94)	0.745
No	104 (72.7)	100 (69.9)	Reference	Reference	-
Hepatitis B					
Yes	1 (0.7)	5 (3.5)	0.23 (0.03-2.12)	0.22 (0.01-3.50)	0.240
No	142 (99.3)	138 (96.5)	Reference	Reference	-
Chickenpox					
Yes	82 (57.3)	98 (68.5)	0.63 (0.39-1.03)	0.77 (0.36-1.63)	0.490
No	61 (42.7)	45 (31.5)	Reference	Reference	-
Migraine					
Yes	12 (8.4)	17 (11.9)	0.55 (0.25-1.21)	0.19 (0.05-0.67)	0.007*
No	131 (91.6)	126 (88.1)	Reference	Reference	-
Infectious mononucleosis					
Yes	2 (1.4)	15 (10.5)	8.28 (1.85-36.83)	13.16 (2.74-63.17)	0.001*
No	141 (98.6)	128 (89.5)	Reference	Reference	-
RA					
Yes	7 (4.9)	10 (7.0)	1.71 (0.49-5.98)	0.22 (0.03-1.78)	0.159
No	136 (95.1)	133 (93.0)	Reference	Reference	-
Hypothyroidism					
Yes	26 (18.2)	15 (10.5)	2.32 (1.12-4.80)	3.20 (1.23-8.30)	0.015*
No	117 (81.8)	128 (89.5)	Reference	Reference	-
Hyperthyroidism					
Yes	4 (2.8)	7 (4.9)	0.53 (0.15-1.87)	0.39 (0.06-2.58)	0.314
No	139 (97.2)	136 (95.1)	Reference	Reference	-
UC					
Yes	3 (2.1)	2 (1.4)	4.07 (0.67-24.61)	0.75 (0.05-10.79)	0.835
No	140 (97.9)	141 (98.6)	Reference	Reference	-
Diabetes type 1					
Yes	2 (1.4)	4 (2.8)	0.96 (0.13-6.89)	0.08 (0-1.81)	0.095
No	141 (98.6)	139 (97.2)	Reference	Reference	-
Psoriasis					
Yes	1 (0.7)	1 (0.7)	1.34 (0.12-14.86)	7.38 (0.01-6.96)	0.560
No	142 (99.3)	142 (99.3)	Reference	Reference	-
Kidney failure					
Yes	7 (4.9)	23 (16.1)	3.72 (1.54-8.98)	3.76 (1.41-9.99)	0.008*
No	136 (95.1)	120 (83.9)	Reference	Reference	-
Head trauma					
Yes	26 (18.2)	26 (18.2)	1.47 (0.88-2.48)	1.31 (0.54-3.16)	0.548
No	117 (81.8)	117 (81.8)	Reference	Reference	-

[#]Adjusted for age, sex, marital status, and self-rated health; *Significant results
RA: Rheumatoid arthritis; UC: Ulcerative colitis; OR: Odds ratio; CI: Confidence interval

In addition, the mentioned value was 17 years higher than the mean age of 30 years reported for patients with RRMS.[12] Overall, it can be stated that patients with PPMS had higher onset age, tended to

have mothers with a lower educational level, and were more likely to be married which was probably due to their older age in comparison with controls.

The female-to-male ratio was 1.38:1, which was not as high as that of the other forms of MS. Similarly, Tremlett et al. study revealed that despite other types of MS, women with a female-to-male ratio of 1.13:1 were not dominant in PPMS.[11]

Based on the results of this study, parent's ethnicity distribution was not significantly different between cases and controls. However, Abdollahpour et al. recent study revealed that Lor ethnicity as compared with other Iranian ethnicities was the most prone ethnic group to developing MS. Interestingly, this study indicated that subjects with heterogeneity in parental ethnicity were more likely to develop MS.[18]

Regarding self-rated health status, ratings of patients with PPMS were lower than healthy controls. However, Abdollahpour et al. study indicated that self-rated health status was not significantly different between patients with MS and controls.[18] As it was expected, these findings suggest that PPMS as the progressive and severe type of MS affects the individual's health status more and leads to a lower self-rated health status.

The current study evaluated the possible association between PPMS risk and medical history of 23 diseases among Tehran resident patients. As the obtained findings indicated, five diseases of depression, migraine, infectious mononucleosis, hypothyroidism, and kidney failure had a strong association with PPMS risk.

According to the results of this study, depression history had a strong association with PPMS. Since the patients provided information about their depression diagnosis before PPMS onset, we can consider depression as a risk factor for PPMS occurrence. There are few studies that evaluated depression as a possible risk factor for MS. Generally, based on previous studies, depression has been mostly mentioned as the upcoming complication after MS development in up to 50% of patients with MS[19] rather than a risk factor for MS development. Based on the findings of another study, depression was more prevalent among patients with MS (OR = 2.30, 95% CI: 1.60-3.30); however, it was not implied whether depression was diagnosed before MS development.[20] However, in line with our findings, another case-control study revealed that depression prevalence was higher among patients with MS before the MS diagnosis, although the significance of the relation was not reported.[21]

The present study did not support measles, rubella, and mumps infections as risk factors for PPMS. However, there are various studies supporting measles infection as a possible risk factor for MS.[22,23] Ahlgren et al. claim that anti-measles antibodies in serum and cerebrospinal fluid (CSF) increase as MS disease progresses.[22] However, based on Ahlgren et al. cohort study, after mass measles, mumps, and rubella (MMR) vaccination of Swedish population, no effect was observed on the MS incidence, suggesting the fact that a decrease in measles, rubella, and mumps infections in the future will not decrease the MS incidence. Hence, it was concluded that there might be no association between the mentioned diseases and the MS development.[24]

Similar to previous studies, this study did not figure out any significant association between hepatitis B and PPMS.[7]

The present study did not find a significant association between chickenpox infection and PPMS occurrence. Previous studies addressing this subject have presented controversial findings. However, mostly there is not much evidence supporting a significant association between these two diseases.[23]

Interestingly, as the findings of this study indicated, migraine headache can be considered as a protective factor for PPMS and makes individuals less likely to develop PPMS. Contrary to our unexpected finding, most studies found migraine or MS as a risk factor of each other[23,25] or even considered migraine as a probable symptom of MS due to the presence of MS plaques in midbrain area of the brain.[26] Pakpoor et al. explain that the role of migraine in MS occurrence might be overestimated due to the fact that patients with MS are more likely to be visited by a neurologist. Therefore, as compared with the general population, migraine disease of patients with MS is more likely to be diagnosed by neurologists.[25] Another explanation for this association might be due to the increased permeability of the blood-brain barrier (BBB) in patients with migraine. The mentioned level of permeability can lead to the infiltration of immune cells that can initiate neuro-inflammatory processes.[27] However, as none of these studies have specifically focused on patients with PPMS, this drastic difference highlights the necessity of conducting further investigations that may help to decipher PPMS pathophysiology.

In line with previous studies which mostly

support infectious mononucleosis as a risk factor for MS,[7,8] the present study also found a strong association between EBV infection and PPMS development. According to a recent meta-analysis study addressing the interaction of EBV and other MS risk factors, individuals carrying certain genotypes [human leukocyte antigen (HLA)-DRB1*1501] were most likely to develop MS after EBV infection.[28] The mentioned claim may suggest targeted therapy for EBV infection in these certain carriers in the near future.

This study did not find any significant association between PPMS and some autoimmune diseases such as RA, UC, type 1 DM, psoriasis, SLE, Crohn's disease, and celiac disease. However, according to a nationwide Danish cohort study conducted in 2008, patients with MS were more likely to develop certain autoimmune diseases like UC and pemphigoid and were less likely to develop RA and temporal arteritis.[29] Based on a systematic review about autoimmune comorbidities in patients with MS, psoriasis and thyroid-related diseases were the most common comorbidities among patients with MS.[30]

In addition, our results revealed that hypothyroidism had a significant association with PPMS risk. The reason for this association might be due to the autoimmunity base of both diseases or the application of different disease-modifying therapies (DMTs).[31]

Another study claimed that alemtuzumab could increase the occurrence of autoimmune diseases through lymphopenia and increased level of interleukin 21 (IL-21), which can lead to the development of self-reactive T cells.[32] However, all the mentioned associations should be regarded as upcoming MS complications rather than being risk factors for MS.

Kidney failure was more common among patients with PPMS with OR of 3.76. This significant result indicates kidney failure as a risk factor for PPMS, though there is not much evidence supporting kidney failure as a risk factor for MS. Perhaps, in contrast with our hypothesis, kidney failure has occurred before PPMS and has become clinically evident due to related bladder dysfunctions of PPMS, which can possibly lead to the upper urinary tract (UUT) involvement.[33-36] However, new studies have shown that the rate of renal involvement in patients with MS with neurogenic bladder dysfunction after 79 months of follow-up was as low as 3%.[37] Another explanation for this significant association is probably due to the older age of patients with PPMS as compared to controls since the older age is a risk factor for kidney deterioration.[38,39] According to Fletcher et al. study, clinically-stable patients with MS are at a lower risk for UUT involvement.[38] However, patients with abnormal detrusor muscle compliance and advanced age are at the risk of renal deterioration.[38] According to Betts et al. study, lower degree of UUT involvement of patients with MS is probably due to relapse and remission phenomena of most common MS types, which lead to the fluctuation of neurogenic bladder dysfunction that decreases the chance of future UUT involvement.[40] However, it is not the case for the progressive nature of PPMS disease.

The current study did not find a significant association between head trauma and PPMS development. Based on an umbrella review of systematic reviews and meta-analyses, head trauma association with MS development was either very small or non-existent.[7] However, a recent study indicated that the childhood head trauma history requiring a 24-hour hospital admission had a significant association with MS.[23] In another study, traumatic brain injury accompanied with a diagnosis of concussion in adulthood seemed to increase the risk of MS through the infiltration of myelin-antigen specific T cells to the central nervous system (CNS).[41]

As one of the strengths of the present study, it can be stated that this study is one of the first studies investigating the association between the medical history and PPMS risk. One of the prominent obstacles that this study faced was the small number of cases, which was due to the rareness of PPMS disease. The mentioned point made it difficult to find a sufficient number of patients with PPMS for the case group. Furthermore, the small sample size weakened our evaluations with respect to the association of rare diseases with PPMS. Another limitation of the present study was related to the recall bias, which can be problematic especially with regard to the history of childhood diseases that can lead to the inaccuracy of the results. To resolve the mentioned problem, the patients were requested to consult their parents or family physician about the presence of the disease if they were unsure about the answer.

Conclusion

The results of this study indicated that diseases like depression, migraine, infectious mononucleosis, hypothyroidism, and kidney failure were

significantly associated with PPMS development. However, further studies are required to provide more accurate and robust conclusions in this regard.

Conflict of Interests

The authors declare no conflict of interest in this study.

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