

# Pediatric multiple sclerosis: current perspectives on health behaviors

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**Purpose:** Pediatric-onset multiple sclerosis (POMS) accounts for ~5% of all multiple sclerosis cases, and has a prevalence of ~10,000 children in the USA. POMS is associated with a higher relapse rate, and results in irreversible disability on average 10 years earlier than adult-onset multiple sclerosis. Other manifestations of POMS include mental and physical fatigue, cognitive impairment, and depression. We believe that the health behaviors of physical activity, diet, and sleep may have potential benefits in POMS, and present a scoping review of the existing literature.

**Methods:** We identified papers by searching three electronic databases (PubMed, GoogleScholar, and CINAHL). Search terms included: pediatric multiple sclerosis OR pediatric onset multiple sclerosis OR POMS AND health behavior OR physical activity OR sleep OR diet OR nutrition OR obesity. Papers were included in this review if they were published in English, referenced nutrition, diet, obesity, sleep, exercise, or physical activity, and included pediatric-onset multiple sclerosis as a primary population.

**Results:** Twenty papers were identified via the literature search that addressed health-promoting behaviors in POMS, and 11, 8, and 3 papers focused on diet, activity, and sleep, respectively. Health-promoting behaviors were associated with markers of disease burden in POMS. Physical activity participation was associated with reduced relapse rate, disease burden, and sleep/rest fatigue symptoms. Nutritional factors, particularly vitamin D intake, may be associated with relapse rate. Obesity has been associated with increased risk of developing POMS. POMS is associated with better sleep hygiene, and this may benefit fatigue and quality of life.

**Discussion:** Participation in health behaviors, particularly physical activity, diet, and sleep, may have benefits for POMS. Nevertheless, there are currently no interventions targeting promotion of these behaviors and examining the benefits of managing the primary and secondary manifestations of POMS.

**Keywords:** POMS, health promotion, physical activity, diet, sleep

## Introduction

Multiple sclerosis (MS) is an immune-mediated disease of the central nervous system that was once considered an adult disease, but can also occur in children and adolescents (i.e., pediatric-onset MS or POMS).<sup>1</sup> Indeed, an estimated 3%–5% of adults with MS report experiencing initial symptomatic episodes before the age of 18 years.<sup>2,3</sup> We further note that an estimated 10,000 children and adolescents in the USA have been diagnosed with MS, and an additional 15,000 have had symptoms indicative of an MS diagnosis.<sup>4</sup>

POMS typically presents as a relapsing–remitting clinical course.<sup>5</sup> POMS has a slower progression rate than adult-onset MS, but earlier onset does not necessarily

portend better long-term prognosis.<sup>6</sup> POMS typically transitions into a secondary-progressive clinical course, on an average, 10 years earlier in chronological age than adult-onset MS, presumably based on the earlier disease onset.<sup>5,7</sup> We further note that POMS is associated with higher relapse rates than observed in adults with MS,<sup>8</sup> and those with POMS reach irreversible and permanent disability earlier in adult life than those with adult-onset MS.<sup>5</sup> POMS has many symptomatic manifestations such as mental and physical fatigue,<sup>9,10</sup> depression,<sup>11</sup> and cognitive impairment.<sup>12–15</sup> Such manifestations might have considerable impact on academic performance, social interaction and development, and ultimately quality of life in POMS.

There is a focus on early initiation of treatment after first symptom occurrence of POMS, as this is seemingly associated with better long-term outcomes.<sup>16</sup> The first line of treatment for POMS includes injectable therapy with interferon- $\beta$  and glatiramer acetate.<sup>17</sup> The application of these disease-modifying drugs reduces relapse rate and delays disease progression,<sup>17</sup> but upward of 30% of children experience breakthrough disease activity and residual symptoms.<sup>18</sup> Based on a US cohort of POMS patients evaluated in specialty clinics, over one-fourth of patients prescribed interferon- $\beta$  discontinued usage because of poor tolerance.<sup>19</sup> Since 2010, 3 oral, disease-modifying drugs have been approved as first-line agents for adults with MS, but clinical trials of these agents for POMS are either in process of enrollment (teriflunimide, dimethyl fumarate) or nearing completion (fingolimod). Importantly, no pharmacological treatment, to date, has been approved by the US Food and Drug Administration for POMS. Furthermore, there is a paucity of data on disease-modifying drugs effect on functional and symptomatic outcomes in POMS.<sup>19</sup>

We believe it is time that researchers and clinicians focus on health behaviors as an approach for managing the manifestations, and perhaps course, of POMS. This argument is based on evidence from clinical trials that health behaviors exert beneficial effects on dysfunction, symptoms, and participation outcomes and perhaps disease progression among adults with MS.<sup>20</sup> “Health behavior” is defined as specific actions an individual performs for health management, maintenance, and restoration combined with the determinants, correlates, and consequences of those actions.<sup>21</sup> Health behavior can be described as participation in directly observable actions that broadly influence health status (i.e., state of physical, mental, and social well-being). Health behavior can be separated into 2 distinct categories, namely health-promoting and health-compromising behaviors.<sup>22</sup> Health-promoting behaviors

benefit or improve health, and health-compromising behaviors weaken health in either the short or long term. Health-promoting behaviors typically involve physical activity, including exercise; healthy diet, including weight control; and sleep hygiene, including consistent bedtime routines.<sup>22</sup>

We undertook a scoping review of health behaviors in POMS, as it provided an overview or landscape of current evidence and identified future directions for health behavior research in this population. We limited our focus on the health behaviors of diet, physical activity, and sleep as these 3 health behaviors are most commonly studied in POMS, and further represent appropriate targets for future health promoting, behavioral interventions. Obesity is included in diet, as obesity is frequently an outcome of health-compromising behaviors, such as overeating. This scoping review is a necessary first step in 1) establishing a research agenda for health behavior participation, 2) developing health promotion programs, and 3) creating population-specific interventions targeting health behavior engagement (i.e., physical activity, nutrition, and sleep) within POMS.

## Methods

Papers related to health behavior participation in youth with POMS were identified by searching 3 electronic databases (i.e., PubMed, GoogleScholar, and CINAHL) using scoping review procedures.<sup>23,24</sup> The papers were included from the timeframe of 1984 (i.e., date of the earliest known published paper on POMS)<sup>25</sup> through October of 2017.

## Eligibility

Studies were included in this review based on the following criteria: 1) POMS was a primary population of interest; 2) nutrition, diet, obesity, physical activity, exercise, or sleep were identified as focal health behaviors; and 3) the paper was published in English. Two abstracts were included as both provided novel information with regard to health behavior in POMS and have been cited in systematic and scoping reviews. Book chapters were excluded.

## Data extraction

The preliminary literature search was undertaken in August 2017, with a follow-up search in October 2017. One author (EMS) conducted the search and retrieved the papers from databases. Searches were conducted by using the following search phrases: pediatric multiple sclerosis OR pediatric onset multiple sclerosis OR POMS AND health behavior OR physical activity OR sleep OR diet OR nutrition OR obesity. Duplicate records were excluded. Studies were

included based on a review of the Abstract, Introduction, and Discussion sections. One author (EMS) manually searched reference lists for identifying additional papers not captured in the electronic literature search.

## Data synthesis/analysis

Papers were coded into categories by 1 author (EMS) after review. Papers were categorized as investigating nutrition/diet/obesity, exercise/physical activity, or sleep. Two papers discussed 2 of the health behaviors and were sorted into 2 categories. Subcategories within each category emerged during the coding process. For example, sodium intake emerged as a subcategory of nutrition/diet/obesity because it was identified in several papers within this category. Title, author, primary results, and targeted health behavior data were extracted and synthesized into tables. Tables 1–3 contain specific information for diet, exercise, and sleep, respectively.

## Results

One reviewer (EMS) identified 66 relevant papers through the electronic literature search and manual inspection of

references. Of those, 20 papers remained after duplicates were removed via title search performed in Microsoft Word (Figure 1). Of the papers identified during this review, 11 involved diet, nutrition, or obesity; 8 physical activity; and 3 sleep.

## Diet/nutrition

Most papers in this category were case–control studies (6 of 11).<sup>26–31</sup> Three were retrospective observational studies<sup>32–34</sup> and 2 prospective longitudinal studies.<sup>35,36</sup>

Factors associated with nutrition comprised 7 of the 11 papers included in this section. Four papers investigated vitamin D status and its association with POMS.<sup>31–33,36</sup> One reported no difference in the prevalence of insufficiency ( $p=0.98$ ) or deficiency ( $p=0.81$ ) in vitamin D between children with POMS and adults with MS.<sup>32</sup> Two papers suggested that vitamin D levels were associated with relapse rate ( $p=0.03$  and  $p=0.02$ )<sup>33,36</sup> such that higher levels of vitamin D were associated with fewer relapses in POMS. One of those papers reported that the association between vitamin D and relapse rate is mediated by a known genetic

**Table 1** Papers investigating diet/nutrition/obesity

Reference number	Author, year	Purpose	Results
26	McDonald et al, 2016	Determine if salt intake is associated with POMS risk	No association between salt intake and POMS risk
27	Pakpoor et al, 2017	Determine association between dietary factors and POMS	POMS vs controls: POMS are less likely to have insufficient iron No difference in fat, protein, carbohydrates, sugars, fruits, or vegetables
28	Chitnis et al, 2016	Evaluate contribution of BMI and puberty for risk and age of onset of POMS	POMS had earlier puberty and higher BMI
29	Langer-Gould et al, 2013	Determine whether obesity is a risk factor for development of POMS or CIS	↑ BMI = ↑ risk for demyelination
30	Nourbakhsh et al, 2016	Determine if salt intake is associated with time to relapse in POMS	No association between salt intake and relapse rate
31	Gianfrancesco et al, 2017	Determine association between vitamin D, BMI, and POMS using genetic risk scores	Vitamin D associated with increased odds of POMS Significant association between BMI genetic risk score and POMS
32	Brenton et al, 2014	Evaluate prevalence and factors associated with vitamin D insufficiency and deficiency in childhood vs adult-onset demyelinating disease	No difference in vitamin D deficiency between childhood and adult-onset demyelinating disease
33	Mowry et al, 2010	Determine if vitamin D status is associated with relapses in POMS	Vitamin D levels associated with relapse rates
34	Kyrsko et al, 2016	Determine whether BMI at dx of POMS predicts disease activity, including ARR and MRI lesions	>50% POMS were overweight or obese at time of dx No association between BMI at POMS dx and disease activity
35	Azary et al, 2018	Evaluate effect of diet on relapse rate in POMS	↑ fat intake = ↑ hazard to relapse
36	Graves et al, 2016	Determine association between established risk factors for POMS and relapse rate	HLA-DRB1*15 modified association between vitamin D and relapse rate in POMS

**Abbreviations:** ARR, annualized relapse rate; BMI, body mass index; CIS, clinically isolated syndrome; dx, diagnosis; POMS, pediatric-onset multiple sclerosis.

**Table 2** Papers investigating physical activity

Reference number	Author, year	Purpose	Results
19	Yeh, 2012	Provide overview of diagnosis and management of POMS	Exercise may reduce fatigue
37	Grover et al, 2015	Examine PA, fatigue, depression, relapse rate, and MRI metrics in children with POMS and mono-ADS	↓ PA = ↑ fatigue (and vice versa) ↑ PA = ↓ sleep/rest fatigue symptoms POMS had less PA than mono-ADS ↑ strenuous PA = ↓ T2 lesion volumes, sleep/rest fatigue symptoms, and annualized relapse rate
38	Grover et al, 2016	Evaluate PA with objective and self-report measures with children with POMS, healthy controls, and mono-ADS Assessed correlates of PA, including demographic and clinical characteristics, and theory related determinants	Light and total PA associated with sleep/rest and fatigue Exercise goal setting and self-efficacy linked to PA POMS had less min/day vigorous PA than mono-ADS and controls POMS had less total PA than mono-ADS
39	Sawicki et al, 2015	Assess relationship between self-efficacy, functional disability, and PA in POMS	Self-efficacy and functional disability correlate with self-report and objective measures of PA
40	Grover et al, 2015	Investigate and compare PA levels in youth with POMS, healthy controls, and mono-ADS	POMS report ↓ PA self-efficacy and ↑ perceived functional disability than peers POMS had less vigorous PA than peers
41	Yeh et al, 2015	Describe a research agenda on PA and its consequences and promotion in POMS	Effects of PA and PA maintenance track across lifespan, particularly when developed early in life
42	Rocca et al, 2015	Editorial review on PA to control MS from childhood	Physical activity may influence disease outcome
43	Kinnett-Hopkins et al, 2016	Validate the GLTEQ in POMS patients by using accelerometer in combination with a nomological net	↑ Vigorous PA = ↓ depressive and fatigue symptoms POMS had less strenuous and total PA than mono-ADS

**Abbreviations:** GLTEQ, Godin leisure-time exercise questionnaire; mono-ADS, monophasic acquired demyelinating syndrome; PA, physical activity; POMS, pediatric-onset multiple sclerosis.

**Table 3** Papers investigating sleep

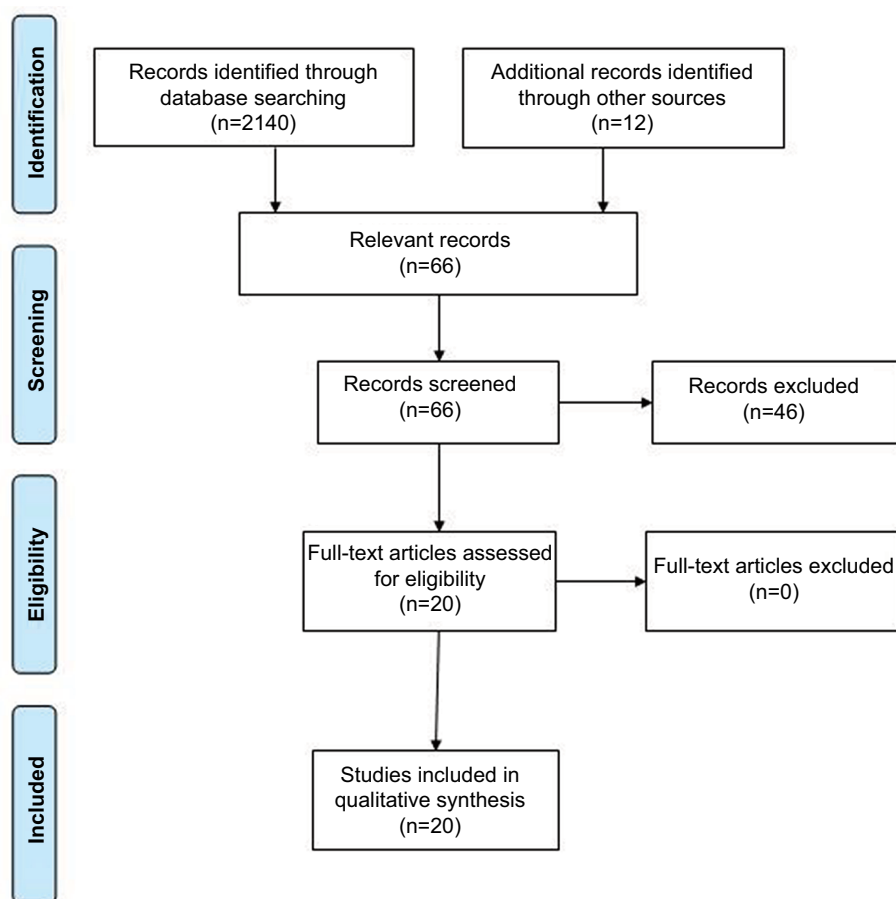
Reference number	Author, year	Purpose	Results
37	Grover et al, 2015	Examine PA, fatigue, depression, relapse rate, and MRI metrics in children with POMS and mono-ADS	Moderate PA associated with fewer sleep/rest fatigue symptoms
38	Grover et al, 2016	Evaluate PA with objective and self-report measures with children with POMS, healthy controls, and mono-ADS Assessed correlates of PA, including demographic and clinical characteristics, and theory related determinants	Moderate PA associated with fewer sleep/rest fatigue symptoms
45	Zafar et al, 2012	Determine whether children with POMS have more sleep disturbances, fatigue, and daytime sleepiness vs healthy controls	POMS more successful in following consistent bedtime routines POMS had comparable fatigue with matched controls

**Abbreviations:** mono-ADS, monophasic acquired demyelinating syndrome; PA, physical activity; POMS, pediatric-onset multiple sclerosis.

MS risk factor (e.g., human leukocyte antigen DRB1\*15:01 or 15:03).<sup>36</sup> Adequate vitamin D<sub>3</sub> status was associated with a 34% decrease in subsequent relapse rates.<sup>33</sup> The fourth paper reported that the vitamin D genetic risk score was associated with a decreased risk of developing MS ( $p=0.02$ ).<sup>31</sup>

Two papers investigated the association between iron and POMS.<sup>27,35</sup> One paper reported no association between iron intake and risk of relapse for children with POMS.<sup>35</sup> The other paper reported that dietary iron was lower in POMS than

controls ( $p=0.04$ ), and POMS was associated with a reduction in the consumption of recommended amounts of iron ( $p<0.01$ ). The paper further reported that iron consumption below the recommended amount was associated with diagnosis of POMS ( $p<0.01$ ).<sup>27</sup> Two papers investigated the role of sodium in POMS.<sup>26,30</sup> One paper reported no association between sodium intake and POMS diagnosis ( $p=0.93$ ), and no significant difference in sodium intake between POMS and healthy controls ( $p=0.99$ ).<sup>26</sup> The second paper reported that



**Figure 1** Flow diagram of paper selection.

sodium was not associated with time to subsequent relapse, and children with POMS who had higher sodium intake did not have less time between relapses compared with those with low sodium intake (medium sodium intake compared with low, hazard ratio [HR]=0.69, high sodium intake compared with low, HR=1.37).<sup>30</sup>

Six of the 11 papers focused on obesity.<sup>28,29,31,32,34,35</sup> Three papers identified high body mass index or obesity as a risk factor for developing POMS.<sup>28,29,31</sup> One of those papers reported that obesity was associated with a higher risk for developing POMS among girls than boys,<sup>29</sup> but the other paper reported that it was a risk factor for both sexes.<sup>28</sup> One case-control study reported that body mass index was higher in children diagnosed with POMS than in controls, and higher body mass index was further associated with younger onset of symptoms.<sup>28</sup> Another study reported that children with POMS were more obese than adults with MS, independent of gender.<sup>32</sup> One final paper reported that over 50% of children were overweight or obese at the time of POMS diagnosis.<sup>34</sup>

## Physical activity

Most papers in this category included a cross-sectional research design (4 of 8).<sup>37-40</sup> Two of the cross-sectional reports were printed as abstract only.<sup>39,40</sup> Two papers were reviewed,<sup>19,41</sup> one was an editorial publication<sup>42</sup> and the other was a validation study.<sup>43</sup>

Four of the 8 studies indicated that children diagnosed with POMS engaged in less physical activity than healthy controls and 2 other types of demyelinating disease (i.e., monophasic acquired demyelinating syndrome or clinically isolated syndrome).<sup>37,38,40,43</sup> The magnitude of difference ranged between  $d=0.02$  and  $d=0.53$ , as measured by accelerometer, and  $d=0.00$  to  $d=0.73$ , as measured by self-report (Godin Leisure-Time Exercise Questionnaire). Of note, the 2 abstracts focusing on physical activity in POMS did not provide enough information to calculate effect sizes. Two papers investigated correlates of physical activity in POMS. One paper reported that exercise goal setting and self-efficacy were associated with physical activity<sup>38</sup> and the other reported self-efficacy and functional disability were correlated with



self-report and objective measures of physical activity.<sup>39</sup> Those with POMS who reported lower exercise goal setting and self-efficacy had lower levels of physical activity, as did those with higher perceived functional limitations. Two papers noted that physical activity and exercise were appropriate methods for managing fatigue,<sup>20,44</sup> and 2 papers suggested that physical activity participation may influence disease burden and outcomes for those with POMS.<sup>37,42</sup> For example, physical activity, particularly participation in strenuous exercise, was associated with smaller T2 lesion volumes in a sample of subjects with POMS. Another study reported that those with POMS who engaged in higher levels of physical activity reported less fatigue, fewer sleep/rest fatigue symptoms, and lower relapse rates.<sup>37,38</sup> On the other hand, no associations were reported between physical activity and total brain volume.<sup>37</sup>

## Sleep in POMS

One paper suggested that children diagnosed with POMS are more successful with managing sleep hygiene (e.g., followed consistent bedtime routines) than age-, sex-, and race-matched healthy controls.<sup>45</sup> This information was based on the Adolescent Sleep Hygiene Scale, which provides a total hygiene score based on physiological, cognitive, emotional, sleep environment, substances, and sleep stability subscales. The children with POMS scored higher than matched controls in the sleep stability subscale, which evaluates the frequency of adherence to regular sleep times on weekends and weekdays. Two other papers reported that those with POMS who participated in higher levels of physical activity reported less sleep/rest fatigue symptoms than those who did not achieve adequate levels of physical activity.<sup>37,38</sup>

## Discussion

We performed a scoping review of research on diet, physical activity, and sleep as health behaviors of importance in POMS. Of those health behaviors, diet and nutritional factors have received the most research attention in POMS. Results from this review indicate that 1) dietary factors and obesity are related to risk of developing POMS, 2) vitamin D intake is related to relapse rate, and 3) children with POMS are more obese than both healthy controls and adults with MS. Vitamin D supplements are frequently recommended for children with POMS, but there are no interventions targeting diet or nutrition for this group to date. Vitamin D represents an interesting and exciting avenue for intervention as relapse rates are twice as high in POMS as in adults with MS. Obesity is thought to be a consequence of health-

compromising behaviors (i.e., physical inactivity, nutritional insufficiency, over consumption of energy). Obesity further is a commonly identified concern for youth with POMS, but there are no studies to date that have investigated strategies to influence diet, nutrition, or physical activity participation as causes of obesity. Campaigns to prevent obesity are prevalent in the USA, and many have been deemed effective in terms of preventing and reducing obesity.<sup>46</sup> This information has not yet been translated to youth with POMS, but this group would benefit from these types of interventions in the future.

The second most common focus of research on health behaviors in POMS involved physical activity. Collectively, the 3 observations from this body of research include 1) there is reduced physical activity participation in POMS; 2) goal-setting, self-efficacy, and perceived limitations represented Social Cognitive Theory correlates of physical activity in POMS; and 3) physical activity might be associated with markers of disease burden and symptomology. Such observations are important as physical activity represents a modifiable factor for symptom management in POMS. There are currently no interventions designed to target physical activity participation for this group. Future research is required to identify appropriate study designs and intervention strategies, as well as measure outcomes of such interventions on primary and secondary symptoms of POMS.

With regard to the measurement of physical activity for future interventions, accelerometry provides 1 method that is objective and non-biased. Unfortunately, accelerometers are unable to capture all types of physical activities (i.e., swimming and cycling) due to required placement on the body and/or water resistance issues with the devices. There has been a single self-reported measure of physical activity (Godin Leisure-Time Exercise Questionnaire) validated for use in research and clinical practice with children diagnosed with POMS,<sup>43</sup> and it is a useful tool for capturing those types of physical activity behaviors that are not captured by accelerometry. The Godin Leisure-Time Exercise Questionnaire is a simple, effective, and useful tool that may be utilized in clinical environments and research to measure physical activity and intervention outcomes. Thus, future interventions designed to promote physical activity behaviors may utilize this validated measure.

With regard to sleep, only 1 paper focused on this health behavior as a primary variable of interest, and 2 papers included it as a secondary endpoint. Youth with POMS demonstrated more appropriate methods for sleep hygiene than healthy peers. This is an interesting factor to consider. Perhaps, children with POMS unconsciously regulate sleep

patterns to adjust for daytime fatigue or sleepiness. Another factor for this improved sleep self-management may be familial involvement or scheduling. As children and adolescents frequently follow schedules set by family or caregivers, these consistent bedtime routines may be a result of habits learned at earlier ages. The aforementioned paper did not measure the average amount of sleep this population obtains, but previous data with regard to all children in the USA report inadequate amounts of sleep. A poll by the National Sleep Foundation in 2014 reported that children between the ages of 13 and 17 years old average 7 hours sleep per night, based on parental report, but between 8 and 10 hours per night is recommended for this age range by the American Academy of Sleep Medicine.<sup>47</sup> Previous research further indicates children with other chronic illnesses exhibit higher rates of sleep problems, including frequent nighttime waking and problems falling asleep.<sup>48</sup> Future research is required to determine average amount of sleep obtained by youth with POMS, and the impact of this amount and quality of sleep.

### Limitations of the research

As in all reviews, there is the potential for missing literature published after the search was conducted, but we repeated the search immediately before finishing this paper. Only 1 author conducted the search and reviewed papers, reducing the option for a second opinion with regard to inclusion and data extraction; all authors discussed the characterization of results and description of all the studies. The relatively small number of papers located, combined with the generally small sample sizes, limit the generalizability of results and, perhaps, the precision of the findings per paper and overall.

Unfortunately, there is very little research on health behaviors, particularly outside of diet/nutrition and physical activity, in youth with POMS, and published papers primarily investigate the etiologic role of health behavior in disease development and progression. There is substantially less known about the effect of health behaviors on secondary manifestations of POMS such as symptoms, function, quality of life, academic performance, and participation.

### Future directions

The possible benefits of health behavior engagement have not been thoroughly vetted in POMS. We believe there is an abundant opportunity for descriptive research on healthy behaviors in POMS (e.g., what are common health behaviors in POMS?); validation research on appropriate methods for measuring health behaviors (e.g., diary vs questionnaire)

and the reliability of such measures; qualitative and cross-sectional research on predictors (e.g., self-efficacy and goal setting) and consequences (e.g., reduced relapse rates and increased quality of life) of health behaviors in POMS; longitudinal research on changes in health behaviors over time (e.g., youth with POMS participate in higher amounts of physical activity in the summer compared with the winter) and associated predictors and consequences; and experimental research testing the feasibility and efficacy on interventions for changing health behaviors and examining the effects on disease and symptomatic outcomes in POMS. One particularly important focus might involve the effect of health behavior interventions on psychological distress in POMS, but there is currently limited research in this area in the literature. If researchers systematically address these opportunities, clinicians will have a greatly expanded body of research for supporting the promotion of health behavior change in the management of POMS.

### Conclusion

Overall, the secondary and residual symptoms associated with POMS may be managed effectively by health behavior participation and self-management, as has been described in adults with MS.<sup>49</sup> Beyond the potential for beneficial effects of health behavior on disease and symptom outcomes for those with POMS, health behavior participation in adolescence likely tracks into adulthood.<sup>50</sup> For example, youth who engage in health-promoting behaviors like regular physical activity, appropriate nutrition, and good sleep patterns often continue this behavior into adulthood. To that end, the potential benefits of health behavior promotion may directly address the needs of POMS and provide a clinical opportunity toward establishing and supporting health behavior habits that track throughout the lifespan among those with MS. We collectively and anxiously await research that systematically addresses health behavior in POMS – this represents an exciting opportunity for empowering self-managing through health behavior change among children and adolescents living with MS.

### Disclosure

The authors report no conflicts of interest in this work.

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