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Research priorities for medically not yet explained symptoms expressed by patients, carers, and healthcare professionals in the Netherlands following the James Lind Alliance priority setting partnership approach

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ABSTRACT

Objective: Experiencing physical symptoms that are medically not yet explained (MNYES) is associated with considerable burden in daily life. Research priorities in this area have been primarily investigator-driven. The present study identifies the top 10 research priorities, incorporating the views of patients, carers and healthcare professionals.

Methods: This study used the Priority Setting Partnership approach in collaboration with the James Lind Alliance (JLA). The priority setting approach combines survey-based data from patients with a specific disorder/condition and relevant stakeholders (i.e., caregivers and healthcare professionals) with input from group meetings and a final priority setting consensus meeting. There were three consecutive phases: (1) online survey with an open-ended question to collect topics for future scientific research ($N = 345$ participants); (2) an online survey among stakeholders to prioritise the research questions generated in Phase 1 ($N = 400$); and (3) a final multi-stakeholder consensus meeting, held over two half-days to determine the final top 10 research priorities for the Netherlands (day 1 $N = 25$, day 2 $N = 24$).

Results: Phase 1 resulted in 572 topics, which were reduced to 37 summary research questions. Phase 2 resulted in 18 research priorities, that were ranked and the top 10 priorities were established during the final consensus meeting. The top 10 research priorities included three main themes: optimising efficient diagnosis and treatment, aetiology and prevention, and coping with MNYES.

Conclusion: The top 10 priorities provide insight into what is most important for future research into MNYES from the perspective of patients, carers and healthcare professionals.

1. Introduction

Common symptoms in general practice are chronic pain, fatigue, gastrointestinal complaints, palpitations and dizziness, with an estimated prevalence of up to 40% [1,2]. Based on input from patient representatives, carers and healthcare providers, a recent Priority Setting Partnership project in the United Kingdom coined the term “Medically not yet explained Symptoms” (MNYES) to refer to these conditions [3]. These symptoms are associated with a significant burden on the daily life of the individual and family members [3–6]. Clinical conditions that overlap with MNYES include medically unexplained symptoms, persistent physical symptoms, functional somatic disorders, bodily distress disorders, and somatic symptom and related disorders [7,8]. In addition, comorbid depressive and/or anxiety disorders occur frequently [1,9–11]. Healthcare professionals, for example in primary care and general hospital settings, may face barriers in diagnosing,

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treating and communicating with patients with MNYES and could benefit from targeted support [12–14]. Patients often feel misunderstood and struggle to access the care they need which can complicate the patient-clinician relationship [12–15]. In addition, the scientific evidence for effective treatments is still scarce. Although cognitive behavioural therapy and psychiatric consultation in primary care have shown promising results [16–19], trials have mostly focused on short-term outcomes [20]. Together, these factors might influence the persistence and/or progression of symptoms in primary and secondary care settings.

A considerable amount of scientific research has been conducted to improve the care of patients with MNYES, resulting in the development of several proposals for core outcome measures in this area [21]. However, to date, research has been driven mainly by researchers, with less input from representatives of people with these symptoms and their carers or non-academic clinicians involved in their care (doctors, psychologists, physiotherapists, nurses and other clinicians). A research agenda published by the European Association of Psychosomatic Medicine identified a focus on patient preferences as one of the priorities for scientific research [22]. A recent study in the United Kingdom [3] has identified the priorities for scientific research in the area of MNYES by consulting patient representatives, carers and healthcare professionals, using the Priority Setting Partnership approach developed by the James Lind Alliance (JLA). The JLA approach provides a highly structured method supervised by an independent chair trained by the JLA and following a handbook with guidelines to set up a Priority Setting Partnership and conduct a study to achieve research priorities for conditions and symptoms from the perspective of patients, carers and (non-academic) clinicians dealing with such symptoms and conditions as opposed to researchers alone [23].

The present study was conducted in conjunction with and in parallel to the UK study [3] and documents the research priorities in this area for patients and stakeholders in the Netherlands. The aim of the project was to prioritise a research agenda for MNYES from the perspective of three key stakeholder groups: patient representatives, carers and healthcare professionals. The study focused on people with physical not yet explained symptoms in general and did not pre-select a specific disorder. Participants were informed that MNYES was defined as physical symptoms that are not yet sufficiently explained medically. It was explained that this could include symptoms that are not explained by a medical cause, as well as those that are (partially) explained by a medical cause (see Methods section for details about how participants were informed).

The experiences and expertise of the stakeholder groups were brought together to decide on topics for future research in this area using the JLA Priority Setting Partnership approach. This article describes the process and results of the study in the Netherlands and identifies the themes in which the top 10 priorities can be categorised. The results are discussed in the context of the findings obtained in the UK, with implications for further generalisation of the priority agenda in different national and international settings.

2. Methods

This project consisted of three consecutive phases. In phase 1 (October 2020–September 2021), an online survey was distributed to collect topics for scientific research in the area of MNYES among relevant stakeholders (i.e. patient representatives, carers and healthcare professionals). In Phase 2 (October 2021–January 2022), a second questionnaire was distributed to ask relevant stakeholders to prioritise the research questions identified in Phase 1. In Phase 3 (February 2022), a final consensus meeting with stakeholders was organised to produce a list of the top 10 research priorities for MNYES in the Netherlands. The phases were preceded by Steering Group meetings to prepare the launch of the project.

The methods used in this project followed the JLA approach [23]. The JLA is a not-for-profit initiative established in 2004 to support Priority Setting Partnerships that brings together patients, carers and healthcare professionals to gain insight into research priorities across a wide range of health-related areas. Gaining insight into these priorities from the perspective of these stakeholders helps to create a robust research agenda that also informs health care and research funders about the questions and concerns that are most important to patients, carers, and (healthcare) professionals working in the area of interest. The processes are described in detail in the following sections. The Dutch and the UK Priority Setting Partnership steering groups were supported by an independent JLA advisor.

2.1. *Ethical considerations*

Ethical approval was obtained from the Scientific Review Board of GGz Breburg (number: 2020–15) and the Ethical Review Board of Tilburg University (number: RP269). All participants gave informed consent before completing the questionnaires or attending group sessions. An online survey system was used for the surveys (Webropol 3.0 [24], without automatic storage of e-mail or Internet Protocol (IP) addresses. Participants had the option of providing their contact information if they were interested in being contacted for subsequent phases of this study; contact details were stored separately from the study data. Any potentially identifiable information in participant responses to the open-ended questions was removed prior to analysis.

2.2. *Steering group*

The establishment of a Steering Group consisting of all relevant stakeholders guided by an independent chair is an essential element of the JLA approach. The Steering Group played a key role in the choice of terminology, the development of the questionnaires and the information letter to participants, the fine-tuning of the analyses and the preparation of the final workshop. The Steering Group met five times during the course of the study and its composition is shown in Table 1.

As a consequence of the multiplicity of relevant symptoms and associated terms, the Steering Group had to decide on an appropriate term for the present study. In the UK Priority Setting Partnership, which was slightly ahead of the current Dutch Priority Setting Partnership, the term MNYES was established by a panel of professionals, patients and carers. At the time when this project was started, the term ‘medically insufficiently explained symptoms’ was commonly used in the Netherlands. The Dutch Steering Group agreed to use the term MNYES in order to be consistent with the terminology of the parallel UK project [3]. This was an operational definition not intended to add to or replace existing terms. It was constructed to embrace the views of all stakeholders. The term MNYES was meant to indicate that, although some insights in how the symptoms could be explained might exist, our understanding is still incomplete. This could pertain to biological, psychological and social factors, as well as factors involving the trajectory of patients through various healthcare settings. In that sense, the choice of the term MNYES feeds into the effort to identify research priorities for the condition. The study did not target specific disorders under this

Table 1
Steering Group.

Steering Group members		
Patients / carers	Healthcare professionals	Research team
Patients representatives (3)	Psychiatrist / psychologist (3)	Independent chair (1)
Caregiver (1)	General practitioner (1)	Coordinator (1)
	Gynaecologist (1)	Information specialists / researchers (2)
	Occupational physician (1)	Sr. researcher (1)
	Nurse specialist (1)	
	Internist and psychotherapist (1)	
	Neurologist (1)	

term, instead it focused on the symptom-level and potential participants were informed about which types of symptoms were the target of this project (see below for details).

2.3. Phase 1: initial topic inventory (October 2020–September 2021)

2.3.1. Participants

Patient representatives, carers and healthcare professionals were recruited through the Steering Group network and targeted advertising on relevant stakeholder social media channels. Participants were eligible for participation if they identified themselves as someone with medically not yet explained symptoms, a carer of someone with these complaints, or if they had relevant professional experience. Participation relied on self-assignment by respondents as no specific selection criteria were employed beyond describing MNYES in the questionnaire and allowing individuals to participate if they identified with the symptoms.

To make sure that participants were clear on the focus of this project, the introduction given to introduce MNYES was (in translation from Dutch): *"Many people have physical complaints that are not yet sufficiently explained medically. Such complaints are common and constitute a heavy burden in the daily lives of those affected and people who are close to them. Sometimes, complaints cannot be fully explained by a medical cause. For other people, the complaints may be explained but cause much more difficulties than would be expected based on their medical condition. Examples of such complaints include: pain, fatigue and sleep problems, dizziness or fainting, physical tension, heart palpitations, stomach or intestinal complaints, neurological problems, such as unexpected trembling, paralysis, and non-epileptic seizures."*

2.3.2. Questionnaire

An online survey was distributed in which participants could fill in topics that required (further) research in the area of MNYES. The survey included questions on respondent demographics and experience as a patient representative, carer or healthcare professional, including:

> *"About which problems related to medically not yet sufficiently explained complaints should we gain more knowledge through scientific research? Your answer may address anything related to this issue and you may fill out as many themes as you want."*

2.3.3. Analyses

The first questionnaire provided 'raw' responses and comments, representing the topics identified by participants as important for scientific research. The de-identified responses were first divided into unique topics (most participants provided more than one topic). The topics were categorised collaboratively by two information specialists (IE and WJK) into nine categories: 1) aetiology, 2) diagnosis, 3) treatment, 4) prognosis, 5) prevention and health education, 6) daily life and its quality, 7) healthcare and society, 8) symptom characteristics, or 9) non-specific/out of scope. The topics were translated into a summary research question that covered the content of the responses; these were reviewed by the steering group. Professionals who also experienced MNYES themselves, were coded as 'professionals;' further details are described in the results section. The summary research questions were then checked against the available published evidence to determine whether they had already been answered by prior scientific research in this area; it was found that none of the proposed research questions had been fully answered by previous research.

2.3.4. Steering group meetings and literature review

The responses to Phase 1 questions were discussed at Steering Group meetings 2, 3 and 4; the categorisation made by the information specialists was reviewed by steering group members. Summary research questions were revised in line with the recommendations of the Steering Group.

2.4. Phase 2: interim priority setting

2.4.1. Participants

The target population and recruitment methods for this phase were the same as for Phase 1. In addition, Phase 1 participants who expressed an interest in participating in the follow-up phases were also invited to participate in Phase 2.

2.4.2. Questionnaire

A total of 37 summary research questions were derived from Phase 1. These 37 questions were presented to the participants in Phase 2 in a second online survey. Respondents were asked to select the 10 most important questions for future research to answer from the list of 37 summary questions. To avoid bias, summary questions were presented in random order per participant. Participants could not proceed if fewer or more than 10 summary questions were selected. Participants could also leave their email address if they wished to be invited to the final workshop.

2.4.3. Analyses

Priority setting resulted in a ranking of the list of summary research questions; this ranking was used to select 18 final questions for the final priority setting workshop in Phase 3. The responses from patient representatives and carers were combined and the responses from healthcare professionals were ranked separately by counting the number of times each question was selected. The top 10 questions from each group were then selected as candidate priorities for the final workshop in Phase 3. Where there was overlap, the 11th ranked statement was added for patient representatives and then for healthcare professionals, followed by the 12th, until a total of 18 questions were prioritized. The number of 18 questions was based on the JLA approach, which has a guideline of using 18 questions in the case of an online workshop.

2.5. Phase 3: workshop to set priorities based on responses to phase 2 questions

The online workshop sessions lasted two half days and consisted of four sub-groups per day. The sub-groups were made up of a balanced mix of patient representatives and healthcare professionals. Each subgroup had a facilitator (who focused only on the process and did not intervene with the content) and an observer to ensure: (1) that the process was followed correctly, and (2) that the facilitators were focused on leading the process independently. During each workshop session, emotional and technical support was available to all participants.

2.5.1. Participants

The participants were patient representatives and healthcare professionals. Participants who had indicated in the second phase questionnaire that they wished to participate, were invited to the workshops.

2.5.2. Questions and analysis

In line with the JLA approach, the 18 research questions derived from the second phase were sent to the participants of the final workshop. As a first step, participants were asked to select their own top 3 and bottom 3 priorities. Based on this, the facilitators made an initial ranking of the 18 questions. Participants were then split into four sub-groups to discuss and rearrange the 18 research questions. After the sub-group meeting, the rankings of the sub-groups were combined and an overall ranking was made. This approach resulted in a new ranking of the 18 questions for the whole group. This ranking was presented on the next day of the workshop and used to repeat the whole process in four newly formed sub-groups. The ranking from the second session of all four groups combined was taken as the final rank order of research priorities.

3. Results

3.1. Phase 1: topic inventory results

In Phase 1, 345 participants (210 patient representatives, 7 carers and 128 professionals) completed the questionnaire. Of the 128 professionals, three also had experience of MNYES themselves, and one of these three was also a carer of someone with MNYES. The average age of the patient representatives was 46 years (SD = 11,83), 96% was female and 97% identified with having a Dutch cultural background. Phase 1 participants generated 572 research topics, of which two were non-specific/out of scope (non-specific lifestyle quotes and general comments for more research collaboration). Categorisation by information specialists resulted in 41 summary research questions; which were further reduced to 37 summary research questions after review by the Steering Group. Table 2 provides an overview of these 37 questions.

3.2. Phase 2: interim priority setting

The interim priority setting questionnaire was accessed by 405 participants; three did not provide consent, one did not specify whether they were a patient representative, carer or professional and one did not rate the statements at all. The input of the remaining 400 participants (183 patient representatives, 13 carers and 204 professionals) was included in the analyses. The input from patients and carers was taken together as it represented the patient perspective and the carer group was too small for separate analysis. The scores and rankings of the summary research questions, based on the number of times they were

Table 2
Ranking of summary research questions by stakeholders in phase 2.

	Patient representatives ($N = 196$)		Professionals ($N = 204$)	
Summary research question	Score	Rank	Score	Rank
1. What information/education should be provided to whom in order to prevent MNYES	120	1*	90	6*
2. Which treatment works best for which individual with MNYES?	101	2*	120	2*
3. Some people experience great difficulty with adjusting to their MNYES; others experience less difficulty; why does this differ and what lessons can be learned from these differences?	91	3*	48	20
4. Why does the severity of MNYES fluctuate within people without a clear reason?	89	4*	83	8*
5. What can we learn from the treatment-related experiences of professionals who take care of people with MNYES and how can we use these experiences to improve treatment?	88	5*	125	1*
6. Which issues are relevant in the workplace of people with MNYES and how can these be improved (e.g. adjust working conditions of finding suitable work)?	86	6*	94	5*
7. What can be done to ensure that people with MNYES are correctly diagnosed and appropriately treated more quickly	83	7*	107	4*
8. Which terminology is best for MNYES?	81	8*	108	3*
9. What can be done to reduce the negative feelings (e.g., hopelessness, frustration) that some people – patients as well as healthcare professionals and others involved - have, with regard to MNYES?	78	9*	63	11^{+}
10. Why do multiple conditions with MNYES often occur together within one person?	70	10*	53	18
11. How often is the diagnosis of MNYES missed?	68	11^{+}	22	33
12. Which symptoms are most often reported by people with MNYES and on which symptoms should future research focus?	66	12^{+}	53	19
13. What support do people who are close to someone with MNYES (family, friends) need?	62	13^{+}	54	16
14. Which factors play a role in the development of MNYES?	62	14	63	12^{+}
15. What is the best approach regarding diagnostics for MNYES and which measuring instruments can be used for this?	62	15	32	25
16. How often do people get diagnosed with MNYES?	58	16	82	10*
17. What needs to happen to help people with MNYES understand their symptoms?	55	17	89	7*
18. Are there certain groups of people in society (for instance age groups, cultural or social background) for whom MNYES deserve special attention?	54	18	44	22
19. How can communication between patients with MNYES and care providers be improved?	52	19	29	29
20. How can the cooperation between doctors and other healthcare providers in the treatment of MNYES be improved?	47	21	54	17
21. What is the role of trauma or other adverse childhood life-events in the development of MNYES?	47	22	83	9*
22. What are possible preventative interventions to avoid the development of MNYES?	43	23	62	13^{+}
23. How can doctors and other healthcare providers be efficiently provided with new useful information about MNYES?	48	20	24	32
24. There are sometimes differences between what people experience in terms of complaints and what diagnostic tests show; how often does this occur and how can this be explained?	42	24	60	14
25. How can the understanding of MNYES among doctors and other healthcare providers be improved and what do patients need in order to feel taken seriously?	41	25	30	27
26. In which healthcare setting (e.g., general practice, medical specialist help, mental healthcare) can someone with MNYES best be treated?	39	26	28	30
27. Which factors play a role in the persistence of MNYES?	39	27	27	31
28. What is the influence of MNYES on the daily life of patients, their relatives and their environment?	35	28	22	34
29. What can we learn from individual experiences of patients with MNYES and how can we use these experiences in treatment?	26	29	47	21
30. What can be done when (different) treatments for MNYES do not work and how can perspective be offered in that situation?	24	30	36	24
31. What is the prognosis of MNYES and what influences this?	22	31	30	28
32. How can people with MNYES gain more understanding of their situation and complaints by communicating about this in a good way with relatives?	17	32	56	15
33. What role can general practitioners and medical specialists play in recognizing and treating people with MNYES?	16	33	13	37
34. What is the best approach (for example: through which professional care specialty) to set the diagnosis for MNYES?	15	34	19	36
35. What is the interaction between psychological factors and the development /maintenance of MNYES? Both positive factors (for example: resilience) and negative factors (for example: psychological problems) can play a role here.	12	35	21	35
36. What is known about the cost-effectiveness of different treatments for MNYES?	12	36	38	23
37. How can the compensation of health insurance and government agencies (e.g., UWV) in the context of MNYES, to healthcare institutions as well as individual patients, be improved?	9	37	31	26

Questions were presented in random order to reduce bias related to order effects. * Question is in the top 10 of the patient representatives/carers or in the top 10 of the professionals, $^{+}$ This summary question (rank 11, 12, and 13) is added because the maximum number of 18 statements was not reached yet. It should be noted that in the ranking of the patient representatives statement 13, 14 and 15 had the same score. Statement 14 was chosen, because it was already ranked 12th in the professionals' section, statement 13 and 1 5 were presented to the Steering Group asking them which one to include (question 13 was chosen).

selected by participants in Phase 2, are shown in Table 2 for patient representatives/carers and professionals separately; also indicating the differing priorities.

3.3. *Phase 3:final priority setting consensus meeting*

The final priority setting workshop was conducted online over two consecutive days (day 1: $N = 25$ (13 patient representatives); day 2: $N = 24$ (12 patient representatives)). The final top 10 research questions are presented in Fig. 1. Table 3 provides an overarching overview of the Dutch priority themes versus the priority themes that were derived from the UK Priority Setting Partnership.

4. Discussion

The aim of the present study was to establish a research agenda for MNYES using the Priority Setting Partnership approach that derives research priorities from the preferences of patients, carers and healthcare professionals. The project was conducted in the Netherlands in parallel with the UK-based study; priorities in both countries are compared. The study followed the JLA approach and resulted in a widely supported list of the top 10 research priorities that can be grouped into three main topic themes: ‘Optimising diagnosis and treatment’, ‘Aetiology and prevention’ and ‘Coping with symptoms’.

4.1. *Optimising diagnosis and treatment*

Three priority questions were identified in this theme: (#1) what can be done to ensure that people with these symptoms are correctly diagnosed and appropriately treated more quickly; (#3) which treatment works best for which individual; and (#7) what can be learned from professionals' experience of treatment and how this experience can be used to improve treatment.

Some of these questions have previously been highlighted in the multidisciplinary guideline for MNYES and somatoform disorders, that suggested an approach based on establishing risk profiles with low, moderate and high risk for unfavourable prognosis. The primary care physician has the main coordinating role in case of low risk, consults a psychiatrist in the primary care setting in the moderate risk level, and refers to specialist mental health care in case of high risk [25,26]. Several pharmacological and psychotherapeutic treatments have been developed since [27–33]. The need for more research on diagnosis and personalised treatment is also consistent with the results of a previous Delphi study on the preferences for research among experts in this area [22]. Furthermore, these results - regarding the importance of more research on diagnosis and treatment - are in line with the results of the UK Priority Setting Partnership for MYNES [3]. The importance of more research on this topic is further underlined by the finding that diagnosis and treatment of MNYES are generally difficult because patients present with multiple common symptoms and general practitioners find it difficult to recognize them [34,35]. Research is needed to be able to make more precise recommendations as suggested in the priorities mentioned above.

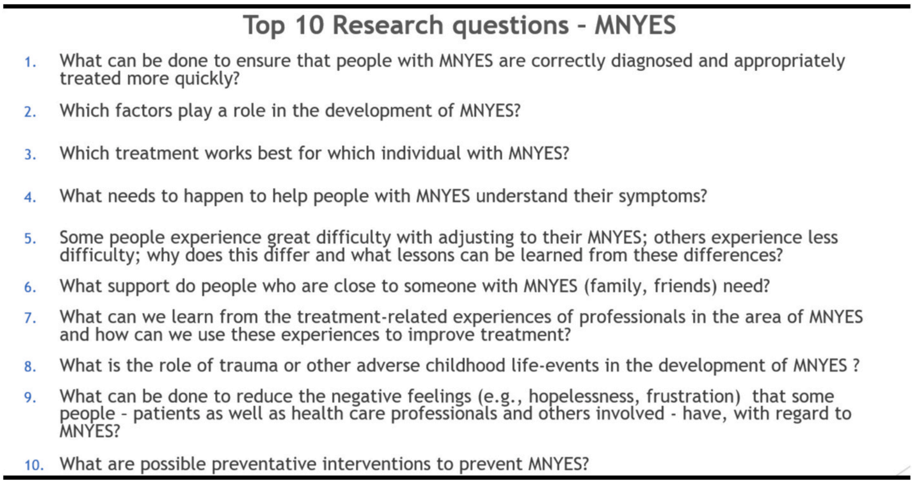
Table 3
Priority themes in the Dutch and UK priority setting partnerships (PSP), a comparison.

Priority theme	Dutch PSP	UK PSP
Effective personalised treatment	+	+
Aetiology	+	+
The role of trauma	+	−
Prevention	+	−
Outcomes relevant to patients	−	+
Support and increasing knowledge by means of helping patients understands their symptoms	+	−
Support and increasing knowledge by focusing on increasing knowledge, awareness, enhancing an empathic approach and collaboration between patient and clinicians	−	+
Support from family and/of significant others	+	+
Coping with negative emotions and effective self-management	+	+

+ = important theme in the PSP, +/− mentioned as theme, but more implicitly, − not important in this PSP.

4.2. *Aetiology and prevention*

With regard to the ‘aetiology and prevention’, three priority questions were considered: (#2) what factors are involved in their development, (#8) what is the role of trauma or other adverse life events in childhood, and (#10) what are the possible preventive interventions to avoid the development of these symptoms. These priorities support the need for more research into the factors involved in the development of MNYES as the underlying causes are in most cases still not well understood. This is inevitably linked to the difficulties and mixed results in research looking into effective treatments. Interestingly this was also one of the research priorities in the UK Priority Setting Partnership and the role of trauma was acknowledged but did not make it to the top 10 there. Some research has been conducted to explore the role of trauma in the development of MNYES, but the findings seem to be contradictory for different aspects of MNYES [36,37]. Trauma is an important factor in conditions that are often comorbid with MNYES, such as anxiety and depression. Addressing trauma in treatment may be an important step to



Top 10 Research questions - MNYES

1. What can be done to ensure that people with MNYES are correctly diagnosed and appropriately treated more quickly?
2. Which factors play a role in the development of MNYES?
3. Which treatment works best for which individual with MNYES?
4. What needs to happen to help people with MNYES understand their symptoms?
5. Some people experience great difficulty with adjusting to their MNYES; others experience less difficulty; why does this differ and what lessons can be learned from these differences?
6. What support do people who are close to someone with MNYES (family, friends) need?
7. What can we learn from the treatment-related experiences of professionals in the area of MNYES and how can we use these experiences to improve treatment?
8. What is the role of trauma or other adverse childhood life-events in the development of MNYES ?
9. What can be done to reduce the negative feelings (e.g., hopelessness, frustration) that some people - patients as well as health care professionals and others involved - have, with regard to MNYES?
10. What are possible preventative interventions to prevent MNYES?

Fig. 1. top 10 research questions for MNYES.

consider in research [38–40].The importance of preventive interventions for MNYES has been pinpointed already in the Dutch multidisciplinary guideline for medically insufficiently explained somatic symptoms [41]. Interestingly, prevention was not one of the priorities in the UK Priority Setting Partnership.

4.3. Coping with symptoms

Four questions fit within this theme: (#5) some people experience great difficulty with adjusting to their MNYES, others experience less difficulty; why does this differ and what lessons can be learned from these differences?, (#4) What needs to happen to help people with MNYES understand their symptoms?, (#6) What support do people who are close to someone with MNYES (family, friends) need?, and (#9) what can be done to reduce the negative feelings (of hopelessness, frustration) experienced by some patients, healthcare professionals and others involved. Prioritising how people cope with these symptoms as a focus for research is in line with the great difficulty that patients experience in terms of social isolation, physical impairment, psychological distress, and the difficulties in coping with these symptoms [42]. In addition, patients with MNYES often report that they are not taken seriously by healthcare professionals and that the time given to discuss their complaints is insufficient which can impact the patient-clinician relationship [13]. Interestingly, exploring ways to support carers and friends of people with MNYES to develop coping strategies was also a priority. The Dutch priorities regarding coping clearly encompassed patients, their carers and the clinicians providing them treatment. The UK Priority Setting Partnership also prioritized coping for patients and their carers as research priorities, as well as training clinicians to increase their awareness. These findings indicate that gaining more insight into how to help patients (and non-patients) with MNYES is important, as people with these types of symptoms have their own concerns and cognitions/explanations for their symptoms [43], and often feel that they are not taken seriously and that healthcare professionals do not spend enough time with them [13]. This support should also be extended to carers who are not yet fully involved in the healthcare of their significant others; the present study involved a small number of carers and the results of the study suggest that it is important for future research to also gain insight into how to support them in caring for their significant others.

The study also highlighted differences between patients' and professionals' preferences regarding research priorities. Patients ranked investigating why some individuals experience significant difficulty adjusting, while others do not, as a top ten priority. This did not appear in the professionals' top ten. Conversely, professionals prioritized research on the prevalence of MNYES diagnoses, helping patients understand their symptoms, and the role of childhood trauma - topics that were not prioritized by patients.

When comparing the results of the top 10 derived from this Dutch priority-setting partnership study with those from the UK [3], the following similarities and differences were noted. In both countries, research into effective, personalised treatment was the highest priority. Research into aetiology and the role of trauma was identified more explicitly in the Dutch study. Prevention was also prioritized in the Dutch Priority Setting Partnership but was not included in the top-10 UK priorities. The UK Priority Setting Partnership identified research that explored outcomes relevant to patients as priorities; this was not highlighted in the Dutch Priority Setting Partnership. In terms of the importance of support and increasing knowledge, the Dutch priorities focused on the importance of helping patients to understand their symptoms, whereas the UK priorities emphasised the need for knowledge, awareness, enhancing an empathic approach and collaboration between patients and clinicians. In addition, both projects highlighted the importance of support from family and/or significant others. Coping with negative emotions and effective self-management were also highlighted as a common important priority for research in this area.

Following the UK priority setting project [3], and based on the input of patients, carers and (non-academic) clinicians in the Priority Setting Partnership, the present study focused on MNYES. After the Dutch study started, the general emphasis among researchers and clinicians in the Netherlands shifted from ‘medically insufficiently explained symptoms’ to ‘persistent physical symptoms’ following the Dutch patient and healthcare professional organisation that aims to promote the care of patients with these symptoms in the Netherlands [44]. The underlying reason for this change is that the emphasis, in approaching these symptoms, should not be on whether they are explained or not, but on the persistence of the symptoms. The current study specifically addresses ‘medically not yet explained symptoms,’ and the findings might therefore primarily be relevant to the management of patients whose symptoms do not occur in the context of a known medical condition. The use of the term MNYES does not imply that symptoms should be explained solely from a biological perspective. Instead, there should be a shared understanding between the patient and clinician of how the symptoms might have developed, considering a wide range of biological, psychological, and social factors. Additionally, the perspective of health care provision is important. Continuous diagnostic procedures and subsequent dismissals by a series of medical specialists may increase the patient's uncertainty. The term MNYES was specifically coined for this study and is not meant to replace existing terms. Nevertheless, it is important to recognize differences in terminology such as ‘persistent physical symptoms,’ ‘medically unexplained symptoms’, ‘functional somatic disorders‘and “‘medically not yet explained symptoms”. And, although it is beyond the scope of the study to discuss all these differences, comprehensive summaries and discussions of the terminology are provided elsewhere in the literature (e.g. [45,46]).

There are several limitations that need to be considered when interpreting the findings of this study. Although patients and healthcare professionals were well represented at all stages of the study, carers were not sufficiently represented in all phases. One of the explanations could be that there are no platforms or organisations that specifically focus on carers of MNYES patients, making it more difficult to recruit them. Another limitation is that participation relied on self-assignment by respondents as no specific selection criteria were employed beyond describing MNYES in the questionnaire and allowing individuals to participate if they identified as experiencing symptoms of this nature. This approach could potentially compromise the generalizability of the findings because participation depended on individuals recognizing themselves within the provided description and no clinical diagnosis was obtained (e.g., [47] see). However, participants were clearly informed about the types of symptoms this project focused on, with a few specific examples. Although the current study specifically addresses ‘medically not yet explained symptoms,’ and the findings might therefore primarily be relevant to this condition, the findings might also be generalisable to people with physical symptoms that meet criteria for other conditions, such as Persistent Physical Symptoms that are not yet completely understood, because the instructions provided to participants would make people with a wide range of persistent symptoms eligible for participation (see Methods for the specific information provided to participants). In addition, because the main aim of this study was to identify priorities for scientific research rather than to apply interventions to a specific group, the resulting heterogeneity might actually increase the generalisability of the findings. In sum, the results are applicable to research on broadly defined, not yet medically explained symptoms.

Due to the online setting of the study, another limitation may be the lack of input from people who do not have easy access to the internet, as the initial questions were based on online surveys. This potential limitation is, however, outweighed by the high proportion (about 97% [48]) of Dutch citizens who have access to the internet at home. The results also show that we did not manage to include the perspective of people who are typically underserved by the healthcare system, such as ethnic minorities, people who do not speak Dutch, and the oldest old.

Moreover, the respondents were mainly female; which might be due to the fact that men are often underrepresented in scientific research in psychology and men also less often report MNYES than women [49,50]. It may therefore be that the results are not completely generalisable to the needs of men experiencing MNYES.

The study also has a number of important strengths. One of the most important strengths of this study is that the research priorities are based on input from patient representatives, carers and healthcare professionals. In the past, research questions and priorities have been driven mainly by researchers in the area, with little input from patient representatives and healthcare professionals (e.g. [22]). Another strength of this study is that more than 700 responses were collected over the two phases, with significant participation from patient representatives. Furthermore, the study followed the JLA approach which is a recognised, transparent approach and ensures that the perspective of patients is considered fully. This study was conducted as part of a larger project carried out in the UK and the Netherlands to explore research priorities, so the results from both countries could be compared.

In summary, the present study identifies the important priorities for future research on MNYES from the perspective of patients, carers and healthcare professionals. The findings are pertinent to research on symptoms that remain unexplained, in a broad sense, and can be used to inform all stakeholders in the design of research and clinical applications. The dissemination and translation of relevant research findings into clinical care can also be improved by making use of these priorities. This study will also be useful to inform funding agencies and other organisations involved in healthcare.

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CRediT authorship contribution statement

Iman Elfeddali: Writing – original draft, Investigation, Formal analysis, Conceptualization. **Willem Johan Kop:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **Margot Metz:** Writing – review & editing, Project administration. **Linh Nguyen:** Writing – review & editing, Project administration. **Jennifer Sweetman:** Writing – review & editing. **Jonathan Gower:** Writing – review & editing, Project administration, Methodology. **Christina M. van der Feltz-Cornelis:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization. **Arjan C. Videler:** Writing – review & editing, Investigation, Conceptualization.

Declaration of competing interest

None.

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