

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Identifying the top research priorities in medically not yet explained symptoms (MNYES): a James Lind Alliance priority setting partnership

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061263
Article Type:	Original research
Date Submitted by the Author:	21-Jan-2022
Complete List of Authors:	van der Feltz-Cornelis, Christina; University of York, Dept. of Health Sciences, HYMS; Tees Esk and Wear Valleys NHS Foundation Trust Sweetman, Jennifer; University of York Edwards, Mark; St George's University of London; St George's University Hospitals NHS Foundation Trust Gall, Nicholas; University of London Kings College Hospital, Department of Cardiology Gilligan, Jennifer; Tees Esk and Wear Valleys NHS Foundation Trust Hayle, Steph; Patient representative Kaul, Arvind; St George's University Hospitals NHS Foundation Trust Moriarty, Andrew; University of York Department of Health Sciences; Hull York Medical School, Perros, Petros; Royal Victoria Infirmary, Department of Endocrinology Sampford, James; Tees Esk and Wear Valleys NHS Foundation Trust Smith, Natalie; University of York Elfeddali, Iman; Tilburg University, Tranzo Dept.; GGz Breburg, Tilburg, the Netherlands, Centre for Body Mind and Health Varley, Danielle; University of York Department of Health Sciences Gower, Jonathan; JLA
Keywords:	Adult psychiatry < PSYCHIATRY, Adult cardiology < CARDIOLOGY, Functional bowel disorders < GASTROENTEROLOGY, Rheumatology < INTERNAL MEDICINE, Adult neurology < NEUROLOGY, PRIMARY CARE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Identifying the top research priorities in medically not yet explained symptoms (MNYES): a**
4 **James Lind Alliance priority setting partnership**
5
6
7

8 Christina M van der Feltz-Cornelis,^{1,2,3} Jennifer F Sweetman,¹ Mark Edwards,^{4,5} Nicholas Gall,⁶
9 Jennifer Gilligan,³ Steph Hayle,⁷ Arvind Kaul,⁵ Andrew S Moriarty,^{1,2} Petros Perros,⁸ James
10 Sampford,³ Natalie Smith,¹ Iman Elfeddali,^{9,10} Danielle Varley,¹ Jonathan Gower¹¹
11
12
13
14

15 Corresponding author: Christina van der Feltz-Cornelis, Dept. of Health Sciences, HYMS,
16 University of York, ARRC Building, T204, Heslington, York, United Kingdom. Phone
17 +441904321313 Email christina.vanderfeltz-cornelis@york.ac.uk
18
19
20
21

22 ¹ Dept of Health Sciences, University of York, York, United Kingdom
23
24

25 ² Hull York Medical School, (HYMS), University of York, York, United Kingdom
26
27

28 ³ Tees Esk and Wear Valley NHS Foundation Trust, Darlington, United Kingdom
29
30

31 ⁴ Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St George's
32 University of London, London, United Kingdom.
33
34

35 ⁵ St. George's University Hospitals NHS Foundation Trust, London, United Kingdom
36
37

38 ⁶ Department of Cardiology, King's College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom
39
40

41 ⁷ Patient representative, North Yorkshire, United Kingdom
42
43

44 ⁸ Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, United
45 Kingdom
46
47

48 ⁹ Tranzo Dept., Tilburg University, Tilburg, the Netherlands
49
50

51 ¹⁰ Centre for Body Mind and Health, GGz Breburg, Tilburg, the Netherlands
52
53

54 ¹¹ James Lind Alliance, Southampton, United Kingdom
55
56
57
58
59
60

Abstract

Objectives Research into medical symptoms that cannot be explained by known medical conditions, termed Medically Not Yet Explained Symptoms (MNYES), in general has been poorly funded over the years. However, such symptoms lead to distress and high disability, both individually and societally. Patients often cannot work and depend on family for care. Research so far has been primarily researcher-led with minimal input from patients, caregivers and clinicians; and sometimes has been controversial. Hence we brought together patients, caregivers and clinicians in a priority setting partnership (PSP) to identify the most important unanswered research questions in MNYES from their perspectives, following the James Lind Alliance (JLA) approach.

Design Delphi study according to the JLA priority setting method.

Methods The study involved five key stages: defining the appropriate term for the conditions under study by the PSP Steering Group; gathering questions on MNYES from patients, caregivers and clinicians in a publicly accessible survey; checking these research questions against existing evidence; interim prioritisation in a second survey; and a final multi-stakeholder consensus meeting to determine the top 10 unanswered research questions using the modified nominal group methodology.

Results Over 700 responses from UK patients, caregivers and clinicians were identified in the two surveys and charities contributed from a broad range of medical specialties and primary care. The final top 10 unanswered research questions cover, amongst others: treatment strategies, collaborative care pathways, training for clinicians, outcomes that matter to patients, and personalisation of treatment.

Interpretation The top 10 unanswered research questions are expected to generate much needed, relevant and impactful research into MNYES.

Word count: 4375

Key words: James Lind Alliance; Priority Setting; Medically Not Yet Explained Symptoms (MNYES); Medically Unexplained Symptoms (MUS); Delphi study

Article summary

- This study establishes research priorities for medically not yet explained symptoms (MNYES) from the perspective of patients, caregivers and clinicians.
- The term MNYES was chosen by the PSP Steering Group as an operational definition not intended to add to or replace other definitions already in use, but was constructed to embrace the views of all stakeholders for the duration of the study.

Strengths and limitations of this study

- Use of established and transparent James Lind Alliance methodology.
- Over 700 responses were gathered from patients, caregivers and clinicians from the whole array of medical specialties including primary care, indicating that the priorities were widely supported.
- The contributions of people from ethnic and gender minority groups within the PSP steering group, surveys and final workshop supports the inclusive nature of this work and indicates these priorities are important to a diverse range of people.

Review only

Introduction

Medically Not Yet Explained Symptoms (MNYES), represent up to 30% of presentations in primary care and internal medicine settings (1-3). They can include fatigue, pain, dizziness, irritable bowel syndrome, and functional neurological symptoms (FND)(3). They are often deemed to be stress-related, or of psychological origin, and comorbid depressive or anxiety disorder occur in approximately 30% of cases (2). Patients diagnosed with these symptoms often feel that they are not taken seriously, although care may have been taken to explain their condition properly. It takes too long to reach the conclusion that they have MNYES, whereas they typically experience high disability and visit many clinics for diagnostic procedures to hear no cause can be found for their symptoms, from clinicians who often have a dualistic view of health and disease. This inevitably leads to disappointment and frustration (4). Many clinicians lack confidence in the assessment and management of MNYES, or may exhibit behaviours perceived as dismissive. Patients often perceive a stigmatising attitude from clinicians and a sense that they are being judged as neurotic or mentally unwell (5-7). Moreover, management plans may not be sufficiently holistic to address all patient concerns, and effective treatments are scarce. All the above impact negatively on long-term prognosis.

The focus of research on MNYES is often on particular subsets of symptoms, such as chronic pain, chronic fatigue, irritable bowel syndrome, and dizziness, but lacks a comprehensive view. This has ramifications for patients who visit different clinics for their various symptoms, without sustained improvement, and as such experience unmet needs (8, 9). To address this, the University of York through the lead author (CFC) established a Priority Setting Partnership (PSP) for research needed to address MNYES. We engaged with members of the public, patients with MNYES and their carers, clinicians of all medical specialties known to have patients with MNYES (10), and other key stakeholders such as charities and the Royal College of Psychiatry Liaison Faculty. Close collaboration with the James Lind Alliance (JLA) enabled this PSP to follow their established, rigorous approach to identify the treatment and management priorities of stakeholders (patients, caregivers, clinicians and support organisations) and to incorporate these into a research agenda (11).

The European Association of Psychosomatic Medicine has published a research agenda in this domain with one of the research priorities being patient preferences for research in this field

1
2
3 (12). Until now, however, there has been relatively little support available for people with
4 MNYES and those who care for them, to enable them in setting up the research agenda.
5 Engaging patients in the research process incorporates their perspective as ‘experts’ from
6 their unique experience of living with symptoms, as well as their personal knowledge
7 regarding diagnostic trajectories and treatments in the healthcare setting if such symptoms
8 remain (partially) unexplained (13). This study aims to address this knowledge gap.
9
10
11
12
13
14

15 The aim of this PSP was therefore to develop a research agenda with the joint perspectives
16 of patients, caregivers, clinicians and support organisations across the United Kingdom as the
17 frame of reference, to identify the most important unanswered research questions in MNYES.
18
19
20

21 **Methods**

22 *Acquiring funding, international aspect, and establishing support by the James Lind Alliance*

23
24 Funding for the study was acquired by the PSP lead (CFC) in November 2019. Part of the
25 collaboration was envisioned to support setting up a parallel PSP Steering Group to explore
26 the same question in the Netherlands, in order to have an international perspective. This
27 article focuses on the description of the process in the UK. Support by the James Lind Alliance
28 Priority Setting Partnership was secured in December 2019 and a JLA Advisor (JG) appointed
29 to the project.
30
31
32
33
34
35
36

37 *Establishing the Steering Group*

38 In March 2020 the MNYES PSP Steering Group met for the first time. The Steering Group was
39 tasked with overseeing the Priority Setting Partnership by having meetings every six weeks,
40 chaired by the JLA advisor, and making critical decisions at key points of the project (14). The
41 composition of the Steering Group is shown in Box 1 below.
42
43
44
45
46
47

48 **Box 1: Steering group composition**

49
50
51 Clinicians: One general practitioner(GP); consultants in cardiology (1), neurology (1),
52 endocrinology (1), clinical liaison psychiatry (3) and rheumatology (1) one stroke physician, a
53 clinical psychologist and one physiotherapist.

54
55 Patients and caregivers: Four patients with a variety of pain, fatigue and functional
56 neurological symptoms; one caregiver;

57
58 Other: Two information specialists and two project coordinators.
59
60

Terminology

Many terms are used for these symptoms, as shown in a non-exhaustive list in Box 2, below. Therefore, the study's PSP Steering Group took time to decide what terminology to use in the study. A common concern appeared to be the distress caused to patients, caregivers and clinicians alike by the lack of adequate explanations, diagnostic methods and treatments for these symptoms – which are often poorly understood across these groups too. This was felt to have a negative impact on clinical work and research pertaining to these conditions and to stigmatise them at a societal level.

Box 2: Terminology

Persistent Somatic Symptoms (PSS)
Somatic Symptom and Related Disorders (SSRD) (15)
Bodily Distress Disorders (BDD) (16)
Medically Unexplained Symptoms (MUS)
Functional symptoms
Chronic pain
Conversion disorder (CD)
Dissociative neurological symptoms
Functional Neurological Disorder (FND)
Irritable Bowel Syndrome (IBS)
Dissociative syncope

After deliberation, the PSP Steering Group agreed to use the term *Medically Not Yet Explained Symptoms (MNYES)* to describe the subject matter for the duration of the study. This was an operational definition not intended to add to or replace other definitions already in use, that was constructed to embrace the views of all stakeholders. MNYES was meant to indicate that although some insights 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 conveys a message of hope, which feeds into the effort to identify research priorities for the condition. There is an ongoing debate amongst researchers and clinicians about how to refer

1
2
3 to these conditions. This may seem semantic, however it underpins the conceptual confusion
4 that exists regarding these symptoms (17). Unfortunately, in some cases such uncertainty can
5 give rise to deeply rooted controversy that ultimately can be traced back to lack of knowledge
6 regarding the underlying conditions, and to related stigma. This knowledge gap could either
7 be a factual lack of evidence, or a lack of availability of existing knowledge to clinicians,
8 patients and the general public alike.
9
10
11
12
13

14 *Inclusion and exclusion criteria*

15
16
17 The PSP's Steering Group agreed that the remit should include the aetiology, diagnosis and
18 treatment or medical care of patients with MNYES in the UK, as well as the organisation of
19 services, social consequences and long term outcomes including cost implications for patients.
20 Confirmed topics included (but were not limited to): pain, fatigue, dizziness, functional
21 neurological disorder, bowel symptoms, palpitations and syncope. Ages 16 and older were
22 included. Although fatigue as a symptom was considered for inclusion, Chronic Fatigue
23 Syndrome was considered out of scope since there was another PSP addressing this.
24
25
26
27
28
29

30 *The consultative process*

31
32 The study followed several steps in order to establish research priorities, using a mix of online
33 surveys and a priority setting workshop. We created a website to host the surveys (18) and
34 sent out the website link for our partner organisations to distribute within their networks.
35
36
37
38

39 *Gathering uncertainties*

40
41 The initial survey was launched between June 2020 and January 2021 and asked patients,
42 caregivers and healthcare professionals to indicate their priorities for future research related
43 to MNYES (18). We promoted the survey through partner organisations' websites, and their
44 social media platforms. In addition, the clinics of clinicians involved in the PSP Steering Group
45 distributed the QR code to their patients. We sent out email reminders to members of
46 professional associations, sent Twitter invitations and placed the survey on the University of
47 York and JLA websites. Distribution of the survey was supported by the members of the PSP,
48 several associations, networks, networking groups and charities. An overview of supporting
49 organisations is shown in Table 1, below.
50
51
52
53
54
55
56
57
58
59
60

Table 1: Supporting organisations who have promoted this work

Charities	Professional networks	Other networks and Social media groups
British Thyroid Association	Allied Health Professional FND Networking groups	INCLUDE (University of York Disability Network)
Fibromyalgia Association UK	Clinical special interest groups	James Lind Alliance
FND Hope	Liaison psychiatry networks	People who have shared information with their friends and family
Graham Hughes International	Royal College of Psychiatrists	Individuals and organisations active on twitter
Guts UK		Special interest and support groups on facebook
Health Unlocked		
Pain UK		
POTS-UK		

We targeted patients with MNYES such as pain, bowel problems, functional neurological symptoms, or with diagnoses which comprise a set of symptoms which are medically unexplained such as postural orthostatic tachycardia syndrome (PoTS); their caregivers; and the clinicians who treat them, to participate. Survey respondents were asked whether they had experienced MYNES, in which case they were to select their symptoms from a list, or were healthcare professionals, in which case they were asked to state their profession. Anonymity was preserved in all cases accordance with General Data Protection regulations.

Data analysis and verifying uncertainties

We downloaded the online survey (11) results through Qualtrics and exported them into Microsoft Excel. The responses to this survey were organised into summary questions and these were then checked to make sure that they had not already been answered by research. Our health information specialists (DV and JS) and PSP lead (CFC) grouped the responses into themes and each was analysed in small groups by 3 or 4 members of the Steering Group; one member of each small group was a patient or caregiver and the other members were healthcare professionals. Summary questions were developed, which encapsulated groupings of similar responses to the survey. Responses were removed if they were outside the scope of the survey or general statements which would be unanswerable by research. The outputs from the small group discussions were reviewed at a subsequent meeting of the full PSP Steering Group.

1
2
3 One health information specialist (JS) checked each in-scope question with existing clinical
4 guidelines published by multi-disciplinary guideline committees and systematic reviews, to
5 ensure that the question had not been already fully answered with high-level evidence.
6
7 44 articles were shortlisted from searches conducted in the Cochrane Library, Medline and
8
9 Google Scholar; key words for the search used are included in the appendix. Reference lists of
10
11 these studies were also reviewed to identify further relevant references. Articles published
12
13 between 2011 and 2021 were considered relevant by the Steering Group. Each question was
14
15 coded to indicate whether it was 'answered'; 'partially answered' or 'unanswered' through
16
17 the research literature. All of the questions fell within the latter two categories and were
18
19 carried forward to the interim priority setting stage.
20

21 22 *Interim priority setting*

23
24 Between May and July 2021, the second online survey asked participants to select their top
25
26 10 priorities from the list of uncertainties presented (14). Questions were presented in a
27
28 random order to each survey participant to reduce bias. The priorities of patients and
29
30 caregivers and the priorities from healthcare professionals were ranked separately. The top
31
32 10 priorities identified by patients and caregivers were then combined with the top 10
33
34 priorities from healthcare professionals to create a shortlist of 17 priorities as there were 3
35
36 overlapping priorities.

37 38 *Final workshop*

39
40 The 17 top ranked questions were taken forward to the final priority setting consensus
41
42 meeting that took place virtually on 16th and 17th September 2021. We invited volunteers
43
44 from supporting organisations, two of whom joined the meeting. We also invited individuals
45
46 who took part in the online survey to participate in the meeting. 25 participants took part in
47
48 the workshop comprising 10 patients with a variety of MNYES symptoms, 1 caregiver, and 14
49
50 health care professionals. The workshop participants were divided into four groups, each with
51
52 a balanced mix of patients/caregivers and clinicians. Each group also had observers who did
53
54 not participate in the process, to fulfill the requirement of transparency of the JLA process.
55
56 Each group was asked to rank the uncertainties through group discussions using the modified
57
58 nominal group technique facilitated by an independent JLA Advisor. Each participant was
59
60 provided with a printed and electronic copy of the different 'unanswered' questions, and the
JLA Advisor leading each group shared an image containing the unanswered questions to aid

1
2
3 the group in ranking the 17 uncertainties. The rankings from the four groups were combined
4 and all the workshop participants then came together to discuss these rankings. Similarities
5 and differences between the group rankings were highlighted by the JLA facilitator leading the
6 workshop (JG) and participants were invited to comment on the initial combined ranking.
7 Following this, participants were reallocated into four new groups, maintaining the
8 representation of patients/caregivers and clinicians within each group, to consider the
9 combined group ranking from the previous session. During this session, there was a specific
10 focus placed on the ordering of uncertainties across the top 17 unanswered questions. The
11 rankings from each of the four groups were once again combined and were presented to the
12 whole group for discussion. By the end of the priority setting meeting, we reached consensus
13 on the top 10 UK research priorities for MNYES.
14
15
16
17
18
19
20
21
22
23

24 *Patient and public involvement*

25
26 A core principle of JLA priority setting partnerships is collaboration between all stakeholders
27 (patients, caregivers, and clinicians) to ensure their views are represented at each stage of the
28 process. Patients, caregivers and clinicians were members of the MNYES Steering Group,
29 represented at every meeting, involved in the development of PSP surveys. They participated
30 in the initial and interim surveys, and were involved in the organisation of uncertainties, the
31 wording of summary questions, and the verification of evidence checking. The final workshop
32 also included patients, caregivers and clinicians in the final prioritisation process to establish
33 the top 10 research priorities for MNYES. Furthermore, there were observers representing
34 supporting organisations and relevant charitable organisations during the final workshop. All
35 Steering Group members were invited to contribute to the dissemination of the surveys; the
36 information shared by this PSP was developed with members from all stakeholder groups. All
37 PSP steering group members were invited to contribute to the article describing the findings
38 and one of them indeed contributed as a co-author.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53

54 **Results**

55
56
57
58 The process is shown in the project flowdiagram presented in Figure 1 below.
59
60

1
2
3 - Insert **Figure 1. Flow diagram of MNYES question prioritisation processes –**
4
5

6
7 *First survey*
8

9 There were 705 respondents across the UK who accessed the initial survey. 443 of those
10 people provided at least one question or statement within this survey. 68% of the participants
11 were patients or caregivers as reported in Table 2 below, which also shows the demographic
12 characteristics of the participants.
13
14
15

16
17
18 The respondents were 77% female, 86% white; data from the 2011 census show that 51% of
19 the England and Wales population were female (19) and 86% of the same population were
20 White (20).
21
22
23

24 Of the 884 statements, 852 were in scope and 32 out-of-scope.
25

26 The out-of-scope submissions included general statements (N = 11), children/paediatric
27 services (N = 9), information seeking statements (N = 6), or pertaining to COVID-19 (N = 5) and
28 chronic fatigue syndrome (N = 1).
29
30
31

32 The information specialists (DV and JS) and PSP lead (CFC), grouped similar or duplicate
33 questions into 5 domains, generating 96 draft summary questions on aetiology, diagnosis,
34 health care services, treatment, outcomes, prognosis, and other. Those 96 draft questions
35 were reviewed by small groups of PSP Steering Group members that comprised clinicians,
36 patients and caregivers. Further consolidations were made resulting in 46 summary questions
37 which were reviewed again and signed off at a meeting of the whole PSP Steering Group. Of
38 these 46 questions, 22% related to aetiology, 24% to health and clinical services, 15% to
39 diagnosis, 24% to the treatment of MNYES, and 15% to outcomes.
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 2: Participant demographic information

	Initial Survey (n=443)	Interim Survey (n=270)	Final Workshop (n=25)***
Gender (%)			
Male	89 (20)	33 (12)	6 (24)
Female	339 (77)	227 (84)	18 (72)
Other	14*(3)	2** (1)	1 (4)
Ethnicity (%)			
Asian/ Asian British	12 (3)	5 (2)	-
Arab	1 (<1)	-	-
Black/ Black British	3 (1)	2 (1)	-
Mixed/ Multiple	7 (2)	7 (2)	-
White	381 (86)	242 (90)	25 (100)
Other	17 (4)	4 (1)	-
Age, mean (SD)	47.65 (12.15)	42.55 (13.26)	39.29 (13.74)
Experience (%)			
Patient	288 (65)	183 (68)	10 (40)
Carer	13 (3)	17 (6)	1 (4)
Clinician	121 (27)	65 (24)	14 (56)
Other	21 (5)	5 (2)	-
MNYES symptoms (%)			
Pain	219 (49)	147 (54)	6 (24)
Fatigue	236 (53)	146 (54)	8 (32)
Dizziness	156 (35)	91 (34)	5 (20)
Heart palpitations/fainting	134 (30)	83 (31)	5 (20)
Stomach/bowel problems	197 (44)	119 (44)	5 (20)
Problems with movement (tremors, shakes, weakness)	133 (30)	114 (42)	6 (24)
Unexplained blackouts, seizures, sudden loss of awareness	54 (12)	60 (22)	3 (12)
Other (e.g. brain fog, eye and skin problems)	126 (28)	44 (16)	4 (16)
Age when first developed MNYES, mean (SD)	31.77 (15.08)	29.89 (15.13)	-
Clinical role as self-described			
Cardiologist	-	1 (<1)	-
Consultant in emergency medicine	-	1 (<1)	-
Doctor	10 (2)	2 (1)	-
Gastroenterologist	-	-	1 (4)
GP	4 (1)	5 (2)	3 (12)
Occupational therapist	9 (2)	6 (2)	1 (4)
Neurologist	9 (2)	3 (1)	1 (4)
Neuropsychiatrist	1 (<1)	1 (<1)	-
Neuropsychologist	-	1 (<1)	-
Nurse	3 (1)	2 (1)	-
Physiotherapist	16 (4)	8 (3)	2 (8)
Psychiatrist	44 (10)	18 (7)	4 (16)
Psychologist	9 (2)	5 (2)	1 (4)
Psychotherapist	3 (1)	2 (1)	-
Other	9 (2)	2 (1)	-
Speech and language therapist	1 (<1)	4 (1)	-
Stroke specialist	-	-	1 (4)
Assistant psychologist/Support worker	3 (1)	2 (1)	-

*14 prefer not to say **1 non-binary, and 1 self describing as agender

1
2
3
4 Figure 2 shows the proportion of original questions from each topic, which were posed by
5 patients, caregivers, clinicians and others, who were generally individuals who met the criteria
6 for more than one role. As can be seen, patients preferred aetiology and diagnostic questions,
7 while clinicians emphasized treatment and outcomes. Health care services and prognosis were
8 divided equally between patients or caregivers and clinicians.
9
10
11
12
13
14

15 - Insert **Figure 2 proportion of questions posed by patients, caregivers, clinicians and others**
16

17 18 19 *Evidence check*

20 As an evidence check, the 46 summary questions were checked against published systematic
21 reviews and clinical guidelines. We found that none of the 46 summary questions had been
22 fully answered by previous research; some questions had been answered for specific
23 symptoms, but not comprehensively across all MNYES symptoms. At a subsequent meeting,
24 the Steering Group reviewed the 46 summary questions in relation to the original questions
25 and statements from which they derived. This process resulted in minor changes to the
26 wording of these 46 questions which were then included in the interim prioritisation survey.
27
28
29
30
31
32

33 34 35 *Interim survey*

36 This online survey was completed by 270 participants from across the UK. Patients and
37 caregivers made up 74% of the participants. Demographic information on the participants is
38 shown in Table 2, however it was not mandatory for this survey and therefore not all
39 respondents provided this information. 227 of the 264 (86%) people who reported gender
40 were female and 242 of the 260 (93.1%) people who reported ethnicity, were white. The 17
41 resulting priorities were shortlisted for consideration at the final priority setting consensus
42 workshop.
43
44
45
46
47
48

49 50 51 *Final priority setting workshop*

52 The final priority setting workshop was conducted remotely over two days. In total, 25 people
53 participated in the workshop sessions; four JLA Advisors facilitated the subgroups, eight
54 people observed and one person provided technical support. Participants included 11 people
55 with MNYES or caregivers, and 14 healthcare professionals representing psychiatry, general
56 practice, stroke, neurology, physiotherapy, psychology, occupational therapy and
57
58
59
60

1
2
3 gastroenterology. The final top 10 research priorities were agreed by consensus between all
4 the participants as listed in Figure 3. They were placed on the James Lind Alliance Website
5 (21). They are listed below:
6
7

8
9
10 - Insert **Figure 3. Top 10 research priorities** -
11

12 The research priorities which were ranked 11 – 17 are also listed on the JLA website and
13 shown in Box 3:
14

15
16
17 **Box 3: research priority 11 through 17.**
18
19

- | |
|--|
| 20
21 11. What is the relationship between mental health problems and MNYES?
22
23 12. What is the relationship over time between MNYES and known medical conditions
24 and does that suggest some shared pathological process?
25
26 13. What is the best practice to offer optimal care for patients with MNYES?
27
28 14. What are current clinical attitudes and levels of knowledge about MNYES?
29
30 15. What are the most effective physical treatments for different symptoms of MNYES?
31
32 16. What are the most effective psychological treatments for different symptoms of
33 MNYES?
34
35 17. Why do symptoms of MNYES fluctuate?
36
37
38
39
40 |
|--|

41
42
43
44
45 **Discussion**
46
47
48

49 In this study, we used the JLA Priority Setting Partnership processes to identify the top 10
50 unanswered research questions for MNYES. We utilised the collective perspectives of patients,
51 caregivers, and clinicians, and focused on areas where up-to-date, reliable research evidence
52 is lacking. This process was supported by charitable and professional organisations across the
53 United Kingdom. The study highlighted the paucity of evidence-driven practice in MNYES care
54 since none of the 46 research questions gathered from our survey have been previously
55 answered by level I evidence. Based on the extensive discussions that took place during the
56
57
58
59
60

1
2
3 meetings, the following major themes emerged from the top 10 unanswered research
4 questions.
5

6 7 THEME 1: TREATMENT 8

9
10 The first and sixth research priorities concern treatment. The first, *What are the most effective*
11 *treatment strategies for different symptoms of MNYES?* pertains to all potential treatment
12 strategies (for example: pharmacological, psychological, physical, or collaboration models) to
13 help manage or alleviate any MNYES or combination of symptoms, such as pain, fatigue,
14 dizziness, functional neurological disorder, bowel symptoms, palpitations and syncope. The
15 sixth research priority, *How can the most appropriate treatment be selected, dependent on*
16 *different MNYES symptoms, that a person with MNYES is most likely to benefit from?* is about
17 identifying the best ways to match people who experience specific MNYES with the
18 treatments that are most likely to benefit them. This relates to personalisation of treatment
19 based on diagnostic factors, such as a history of trauma, biomarkers or treatment needs. Given
20 the high unmet clinical need and the heterogeneity of MNYES, it is no surprise that this is
21 considered to be an important research priority. Interestingly, this was also a research priority
22 identified by the Delphi study conducted amongst experts in the field on behalf of the
23 European Association of Psychosomatic Medicine (12); treatment and personalised treatment
24 are therefore considered to be research priorities which are widely supported in this field.
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 THEME 2: THE ROLE OF CLINICIANS 40

41
42 Several research priorities involve the role of the clinicians in the diagnostic and treatment
43 process. The second research priority, *How can clinicians collaborate effectively to form the*
44 *most appropriate care pathway and service model to offer assessment and treatment for*
45 *patients with MNYES?* pertains to the role that clinicians play towards each other. It includes
46 the professionals and services which may be involved for the purpose of assessment, diagnosis
47 and the provision or coordination of treatment. It relates to the fact that there are often many
48 clinicians providing diagnostic assessments to people with MNYES, or are sought to provide
49 treatment to them. This priority is focused on finding the best ways for clinicians to collaborate
50 with each other to form an appropriate care pathway to support people with MNYES. This
51 could be psychiatric consultation models, multi-disciplinary team models, collaborative care
52
53
54
55
56
57
58
59
60

1
2
3 models or other integrated care pathways. The third research priority, *What are the most*
4 *effective methods for training clinicians to diagnose and treat their patients with MNYES with*
5 *compassion, empathy and respect?* refers to medical practitioners who are already qualified
6 and employed in positions that involve the diagnosis and treatment of people with MNYES.
7
8 The focus of attention here is on the communication of information which acknowledges the
9 perspective and concerns of the person experiencing MNYES. Priority five, *What are the most*
10 *effective ways to support patients with MNYES and their carers to live with their symptoms?*
11 focuses on identifying the range of different options for supporting people with MNYES and
12 their caregivers. These may include but are not limited to: finding the most appropriate and
13 acceptable ways to discuss MNYES with people who experience them and their caregivers;
14 guidance about how to discuss MNYES with family members and friends; shared decision
15 making when discussing treatment options; peer support organisations; reasonable
16 adjustments in employment settings; adaptations to accommodation; psychological support
17 to cope while living with symptoms; recovery and rehabilitation approaches. Another research
18 priority fitting with this theme is priority nine: *What strategies are effective at promoting*
19 *awareness and up to date clinical knowledge about MNYES amongst healthcare professionals?*
20 This priority emphasises strategies to consistently and effectively ensure that clinicians are
21 aware of and have the most up to date information about MNYES which will enable the care
22 people receive to reflect current evidence. Given the existing knowledge gaps this is
23 considered an important priority.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 THEME 3: SYMPTOMS AND OUTCOMES

42
43 Patients were involved in all discussions regarding research priorities. However, some
44 research priorities mention the patient perspective explicitly, such as, for example, priority
45 four, *What outcomes matter most to patients with MNYES?* Based upon the survey answers,
46 these may include, but are not limited to: symptom reduction; changes in biomarkers;
47 improvements in abilities to undertake daily tasks; improvements in quality of life; individual
48 goal achievements; or improvements in functioning. Priority seven, *What symptoms are*
49 *commonly reported by people with MNYES and what links them?* relates to the fact that the
50 list of MNYES is extensive and people who experience these symptoms often report living with
51 multiple MNYES. The aim of this priority is to identify the symptoms which most commonly
52 co-occur and the underlying factors and mechanisms between them. For priority eight, *What*
53
54
55
56
57
58
59
60

1
2
3 *factors affect outcomes for MNYES?* it was agreed the diversity of factors affecting outcomes
4 should include biomarkers, psychological factors and trauma, health services-related issues
5 such as feedback from recovered patients about what helped them, the availability and quality
6 of information clinicians have access to, the way information is shared between clinicians and
7 people experiencing MNYES, and social factors such as poverty, education, family dysfunction
8 or domestic abuse, and work environment. Given the number of questions that pertained to
9 aetiological factors, and the fact that the related uncertainty plays a role in the choice of
10 MNYES as a term, this can be considered an important research theme.
11
12
13
14
15
16
17
18

19 THEME 4: RECOVERY

20
21 Research priority number ten relates to recovery: *Which self-management techniques are*
22 *effective in MNYES?* this priority concerns the strategies that people experiencing MNYES can
23 use separately from visits to clinics. The focus is to identify the most effective self-
24 administered therapies for managing or alleviating MNYES, used separately, or in combination
25 with formal treatment. Examples of self-management approaches include education,
26 exercise, and dietary changes. It should be noted that this research priority, in contrast to ones
27 covered by the other themes, considers that recovery in MNYES can occur, either by recovery
28 of symptoms, or by personal recovery with ongoing symptomatology. Recovery of
29 symptomatology is referred to as clinical recovery and is covered by the other themes.
30 Recovery whilst symptoms are ongoing is called personal recovery (22), meaning that despite
31 symptoms being present, function has to some extent been restored through treatment, self-
32 management or disability management.
33
34
35
36
37
38
39
40
41
42
43
44

45 In mental health research and clinical practice, especially in relation to psychotic conditions,
46 personal recovery is a construct that has increasingly gained attention over the past thirty
47 years; however, so far the term has not been used in the context of MNYES. Generally, the
48 emphasis, both in clinical practice and in research, seems to have been to either attempt to
49 attain clinical recovery, or to send the patient home with the message that MNYES cannot be
50 cured and that one would have to live with the condition. This dichotomy has fed into the
51 ongoing controversy about how to approach MNYES. This polarising stance is unhelpful.
52 Developing this research priority would require embracing the concept that personal recovery
53 refers to an individual process of adaptation and development where one does not simply
54
55
56
57
58
59
60

1
2
3 return to, but rather grows beyond the premorbid self (23), with an emphasis on the patient
4 perspective. It could provide an important contribution to the further development of
5 research in this domain, alongside the research priorities summarised in the other themes.
6
7
8
9

10 *Strengths of the study*

11
12 This is the first study establishing research priorities for MNYES, according to the JLA Priority
13 Setting Partnership method which incorporates the views of patients, caregivers and
14 clinicians. This is a highly contentious area; however, the study outcomes were widely
15 supported by over 400 participants including clinicians from a variety of disciplines, patients
16 with a range of symptoms, caregivers, charitable organisations, and the Royal College of
17 Psychiatry Liaison Faculty. The themes identified in this PSP cover a broad range of ideas,
18 issues and uncertainties; these are outlined in the top 10 research priorities and also reflected
19 in the seven research priorities that did not make the top 10. Research priorities 11, 12 and
20 17 would link well with theme 3 in the exploration of associations of MNYES with mental
21 health and somatic comorbidity, as well as the development of symptoms over time. Priorities
22 13 and 14 would fit in theme two, the role of clinicians; 15 and 16 link with theme one,
23 treatment. This suggests that the themes covered by the top 10 priorities are consistent with
24 the rest of the research priorities which were proposed during this priority setting process.
25
26
27
28
29
30
31
32
33
34
35
36

37 *Limitations of the study*

38
39
40 The study provides a good overview of research priorities for MYNES in the UK, however given
41 the specific cultural aspects and health care organisation in the UK, the findings may not be
42 generalisable to other countries. As indicated earlier, a similar PSP is currently being
43 conducted in the Netherlands and may shed light on research priorities in a non-NHS
44 healthcare setting. This will give us an opportunity to compare and evaluate the
45 generalisability of these findings and the influence of different cultural and healthcare
46 settings. Future research highlighting the situation in Low and Middle Income Countries would
47 be beneficial.
48
49
50
51
52
53
54
55
56
57
58
59
60

Conclusion

MYNES are common and reflect a high level of unmet clinical need. Incorporating patient-driven research in MNYES research can allow researchers to better address the complex care needs of people with MNYES. The most important aspect of this priority setting exercise was strengthening the relationship between patients, caregivers, clinicians and support organisations and generating a list of priorities valued by these stakeholders, which we hope will guide future research.

We have identified the top 10 research priorities in MNYES using the rigorous JLA priority setting method that may open the door to further research addressing the knowledge gaps and controversies in this area, and hopefully alleviate some of the stigma related to these conditions. Identification of these top 10 research priorities is an important first step to generating relevant and impactful research that will ultimately improve the lives of people with MNYES.

Acknowledgements: The steering group would like to thank to all the patients, carers, families, friends, healthcare professionals and supporting organisations who contributed to this work. In addition to the co-authors, Philippa Bolton, Sally Brabyn, Tracey Cunningham, Rosie Evans, Miriam Lomas, Margot Metz, Chris Price, Annie Shaw, Scott Spain, Lesley Spain were members of the PSP steering group. The following people who attended the final workshop for priority setting agreed to be named: Anna Burneika, Kit Byatt, Phoebe Cole, Tracey Cunningham, Mark Edwards, Rosie Evans, Eve Fazakerley, Jennifer Gilligan, Stephanie Johnston, Claire Jones, Hilary Lewis, Joseph Littlewood, Miriam Lomas, Andrew Moriarty, Elizabeth Paul, Emma Reinhold, Keziah Reiss, James Sampford, Annie Shaw, Gemma Smith, Martin Veysey, Juliet Wilson, Jennifer Wilson.

Ethics statement: Ethical approval was not required as confirmed by the research governance board of the Department of Health Sciences of the University of York.

Data availability statement

Data relevant to the study are included in the article or on the James Lind Alliance website (<https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/>) and linked University of York website (<https://www.york.ac.uk/healthsciences/research/mental-health/projects/mnyes/>).

Conflicts of interest statement

The authors have no conflicts of interest to declare.

Author statement

CFC was the project lead, instigating the application to the JLA. CFC, NS, JFS and JG organised the steering group meetings. JFS and DV designed and built the surveys, analysed the data, and conducted the evidence check under supervision of JG and CFC. CFC, JFS, and NS wrote the majority of the final manuscript. JG (JLA Chair) chaired all the meetings, led the consensus workshop and ensured compliance with methodology throughout. NS and JFS took minutes for steering group meetings, built and distributed surveys, and organised the consensus workshop. JFS conducted the searches for the evidence check and screened the results with CFC. Members of the steering committee CFC, JFS, ME, NG, JG, SH, AK, ASM, PP, JS, NS, IE, DV, PB, SB, TC, RE, ML, MM, CP, AS, SS, LS all attended a majority of the meetings, agreed the initial protocol and the evidence check protocol, piloted and signed off the surveys and disseminated them, checked the raw questions against the indicative ones, reviewed the evidence check results and agreed the final longlist. TC, ME, JG, ML, ASM, JFS, and AS were present at the final consensus workshop. All authors reviewed and contributed to the final manuscript and approved it prior to submission.

Funding

This work was part-funded by the Wellcome Trust [ref: 204829] from the overall Wellcome Trust ISSF award through the Centre for Future Health (CFH) at the University of York.

References

1. Hoedeman R, Blankenstein AH, van der Feltz-Cornelis CM, Krol B, Stewart R, Groothoff JW. Consultation letters for medically unexplained physical symptoms in primary care. *Cochrane Database of Systematic Reviews*. 2010(12).
2. Van Hemert AM, Hengeveld MW, Bolk JH, Rooijmans HG, Vandenbroucke JP. Psychiatric disorders in relation to medical illness among patients of a general medical out-patient clinic. *Psychological medicine*. 1993;23(1):167-73.
3. Kirmayer LJ, Groleau D, Looper KJ, Dao MD. Explaining medically unexplained symptoms. *The Canadian journal of psychiatry*. 2004;49(10):663-72.
4. Salmon P, Peters S, Stanley I. Patients' perceptions of medical explanations for somatisation disorders: qualitative analysis. *Bmj*. 1999;318(7180):372-6.
5. Tolchin B, Tolchin DW, Stein MA. How Should Clinicians Minimize Harms and Maximize Benefits When Diagnosing and Treating Disorders Without Biomarkers? *AMA journal of ethics*. 2021;23(7):530-6.
6. Hatcher S, Arroll B. Assessment and management of medically unexplained symptoms. *Bmj*. 2008;336(7653):1124-8.
7. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". *Bmj*. 2002;325(7378):1449-50.
8. Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. *Journal of Neurology, Neurosurgery & Psychiatry*. 2000;68(2):207-10.
9. Reid S, Wessely S, Crayford T, Hotopf M. Frequent attenders with medically unexplained symptoms: service use and costs in secondary care. *The British Journal of Psychiatry*. 2002;180(3):248-53.
10. Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. *Journal of psychosomatic research*. 2001;51(1):361-7.
11. James Lind Alliance. The James Lind Alliance Guidebook Version 7. 2018.
12. van der Feltz-Cornelis CM, Elfeddali I, Werneke U, Malt UF, Van den Bergh O, Schaefer R, et al. A European research agenda for somatic symptom disorders, bodily distress disorders, and functional disorders: results of an estimate-talk-estimate Delphi expert study. *Frontiers in psychiatry*. 2018;9:151.
13. Gill PJ, Cartwright E. Partnering with patients in the production of evidence. *Royal Society of Medicine*; 2021.
14. James Lind Alliance. Priority Setting Partnership: Medically Not Yet Explained Symptoms 2021 [Available from: <https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/>].
15. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. Arlington, VA. 2013.
16. World Health Organization. International Classification of Diseases-11 (ICD-11)2019.
17. Van der Feltz-Cornelis C, Van Dyck R. The notion of somatization: an artefact of the conceptualization of body and mind. *Psychotherapy and psychosomatics*. 1997;66(3):117-27.
18. University of York. Research priority setting for Medically Not Yet Explained Symptoms (MNYES) in an Anglo-Dutch partnership with the James Lind Alliance 2021 [Available from: <https://www.york.ac.uk/healthsciences/research/mental-health/projects/mnyes/>].
19. GOV.UK. Male and female populations 2018 [Available from: <https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest>].
20. GOV.UK. Population of England and Wales 2018 [Available from: <https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest>].

- 1
2
3 21. James Lind Alliance. Medically Not Yet Explained Symptoms Top 10 priorities 2021 [Available
4 from: [https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-
6 symptoms/top-10-priorities.htm](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-
5 symptoms/top-10-priorities.htm).
7 22. Slade M, Amering M, Oades L. Recovery: an international perspective. *Epidemiology and
8 Psychiatric Sciences*. 2008;17(2):128-37.
9 23. Slade M. *Personal recovery and mental illness: A guide for mental health professionals*:
10 Cambridge University Press; 2009.
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Figure 1: Flow diagram of MNYES question prioritisation processes

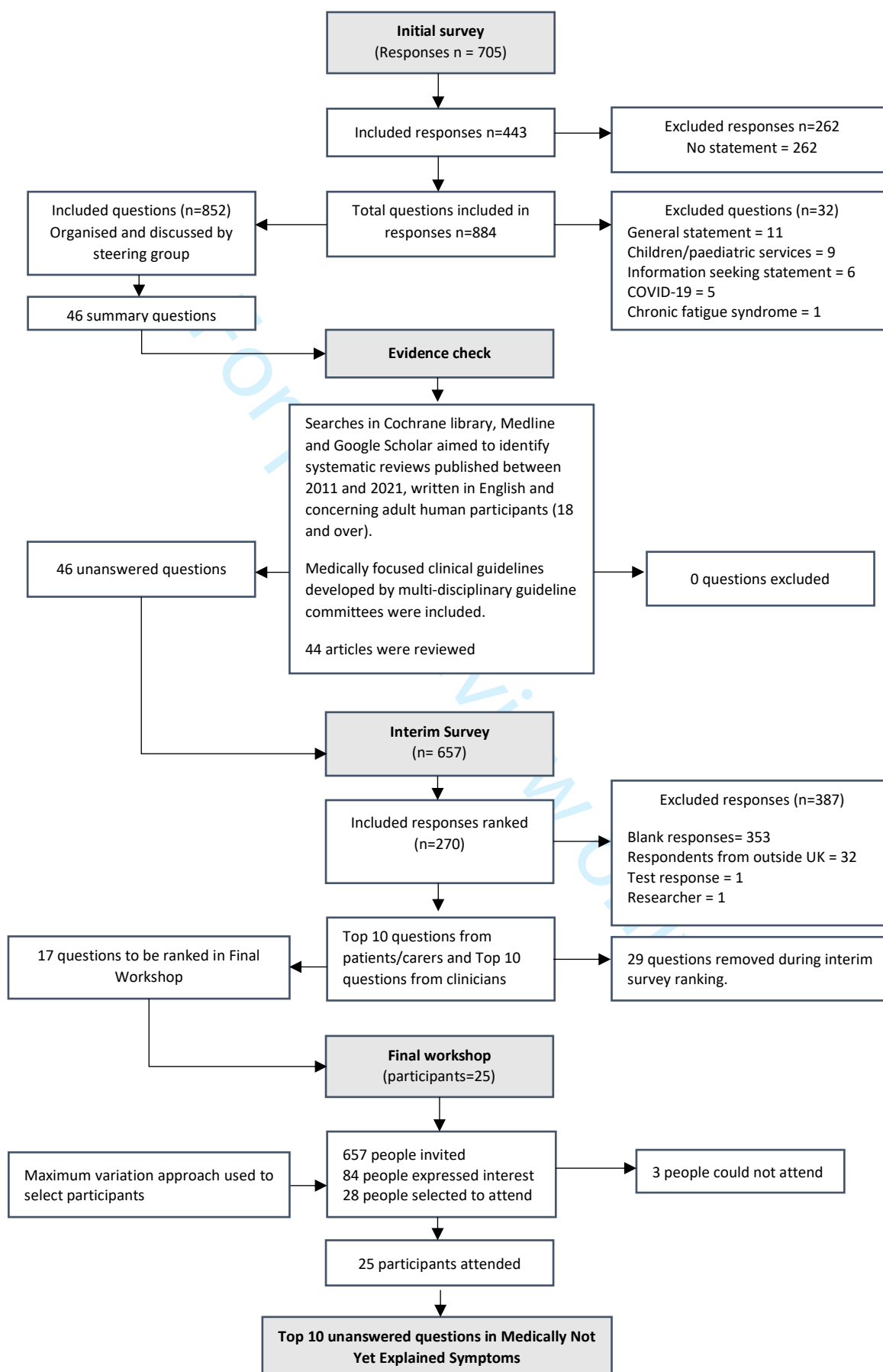
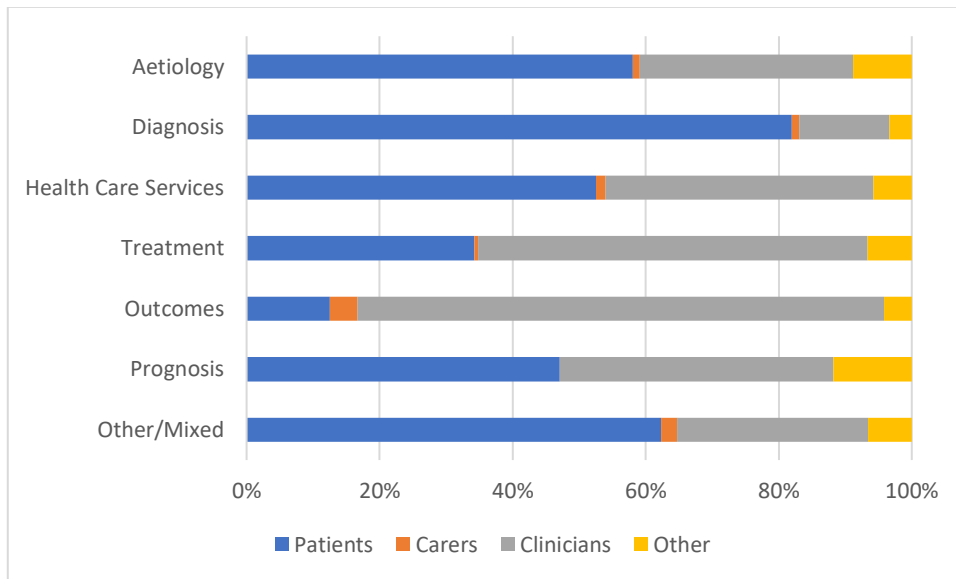


Figure 2: The proportion of questions per domain suggested by patients, caregivers, clinicians and other



Top-10 Research Priorities Medically Not Yet Explained Symptoms (MNYES)

1. What are the most effective treatment strategies for different symptoms of MNYES?
2. How can clinicians collaborate effectively to form the most appropriate care pathway and service model to offer assessment and treatment for patients with MNYES?
3. What are the most effective methods for training clinicians to diagnose and treat their patients with MNYES with compassion, empathy and respect?
4. What outcomes matter most to patients with MNYES?
5. What are the most effective ways to support patients with MNYES and their carers to live with their symptoms?
6. How can the most appropriate treatment be selected, dependent on different MNYES symptoms, that a person with MNYES is most likely to benefit from?
7. What symptoms are commonly reported by people with MNYES and what links them?
8. What factors affect outcomes for MNYES?
9. What strategies are effective at promoting awareness and up to date clinical knowledge about MNYES amongst healthcare professionals?
10. Which self-management techniques are effective in MNYES?



UNIVERSITY
of York



James
Lind
Alliance
Priority Setting Partnerships



Figure 3: Top 10 Research Priorities for Medically Not Yet Explained Symptoms

Appendix

Key words included in evidence check searches

Symptom terms	Publication focus
Medically not yet explained symptoms	Guideline
Medically unexplained symptoms (MUS)	Mechanism
Persistent Somatic Symptoms	Pathology
Somatic Symptom and Related Disorders (SSRD)	Development
Chronic pain	Assessment
Unexplained pain	Diagnosis
Fatigue	Investigation
Unexplained fatigue	Treatment
Conversion disorder	Management
Neurological conversion symptoms	Healthcare service
Functional neurological disorder	Patient care
Functional symptoms	Care pathway
Functional neurological symptom	Outcome
Functional cognitive symptom	Prognosis
Functional weakness	
Dissociative disorders	
Dissociative neurological disorder	
Dissociative syncope	
Unexplained dizziness	
Fibromyalgia	
Irritable bowel syndrome (IBS)	
Nonepileptic seizures	

BMJ Open

Identifying the top research priorities in medically not yet explained symptoms (MNYES): a James Lind Alliance priority setting partnership

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061263.R1
Article Type:	Original research
Date Submitted by the Author:	18-May-2022
Complete List of Authors:	van der Feltz-Cornelis, Christina; University of York, Dept. of Health Sciences, HYMS; Tees Esk and Wear Valleys NHS Foundation Trust Sweetman, Jennifer; University of York Edwards, Mark; St George's University of London; St George's University Hospitals NHS Foundation Trust Gall, Nicholas; University of London Kings College Hospital, Department of Cardiology Gilligan, Jennifer; Tees Esk and Wear Valleys NHS Foundation Trust Hayle, Steph; Patient representative Kaul, Arvind; St George's University Hospitals NHS Foundation Trust Moriarty, Andrew; University of York Department of Health Sciences; Hull York Medical School, Perros, Petros; Royal Victoria Infirmary, Department of Endocrinology Sampford, James; Tees Esk and Wear Valleys NHS Foundation Trust Smith, Natalie; University of York Elfeddali, Iman; Tilburg University, Tranzo Dept.; GGz Breburg, Tilburg, the Netherlands, Centre for Body Mind and Health Varley, Danielle; University of York Department of Health Sciences Gower, Jonathan; JLA
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Mental health
Keywords:	Adult psychiatry < PSYCHIATRY, Adult cardiology < CARDIOLOGY, Functional bowel disorders < GASTROENTEROLOGY, Rheumatology < INTERNAL MEDICINE, Adult neurology < NEUROLOGY, PRIMARY CARE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Identifying the top research priorities in medically not yet explained symptoms (MNYES): a**
4 **James Lind Alliance priority setting partnership**
5
6
7

8 Christina M van der Feltz-Cornelis,^{1,2,3} Jennifer F Sweetman,¹ Mark Edwards,^{4,5} Nicholas Gall,⁶
9 Jennifer Gilligan,³ Steph Hayle,⁷ Arvind Kaul,⁵ Andrew S Moriarty,^{1,2} Petros Perros,⁸ James
10 Sampford,³ Natalie Smith,¹ Iman Elfeddali,^{9,10} Danielle Varley,¹ Jonathan Gower¹¹
11
12
13
14

15 Corresponding author: Christina van der Feltz-Cornelis, Dept. of Health Sciences, HYMS,
16 University of York, ARRC Building, T204, Heslington, York, United Kingdom. Phone
17 +441904321313 Email christina.vanderfeltz-cornelis@york.ac.uk
18
19
20
21

22 ¹ Dept of Health Sciences, University of York, York, United Kingdom
23
24

25 ² Hull York Medical School, (HYMS), University of York, York, United Kingdom
26
27

28 ³ Tees Esk and Wear Valley NHS Foundation Trust, Darlington, United Kingdom
29
30

31 ⁴ Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St George's
32 University of London, London, United Kingdom.
33
34

35 ⁵ St. George's University Hospitals NHS Foundation Trust, London, United Kingdom
36
37
38

39 ⁶ Department of Cardiology, King's College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom
40
41

42 ⁷ Patient representative, North Yorkshire, United Kingdom
43
44

45 ⁸ Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, United
46 Kingdom
47
48

49 ⁹ Tranzo Dept., Tilburg University, Tilburg, the Netherlands
50
51

52 ¹⁰ Centre for Body Mind and Health, GGz Breburg, Tilburg, the Netherlands
53
54

55 ¹¹ James Lind Alliance, Southampton, United Kingdom
56
57
58
59
60

Abstract

Objectives This study establishes research priorities for Medically Not Yet Explained Symptoms, also known as Persistent Physical Symptoms (PPS) or Medically Unexplained Symptoms (MUS), from the perspective of patients, caregivers and clinicians, in a priority setting partnership (PSP) following the James Lind Alliance (JLA) approach. Research into such symptoms in general has been poorly funded over the years and so far has been primarily researcher-led with minimal input from patients, caregivers and clinicians; and sometimes has been controversial.

Design JLA priority setting partnership method. The PSP termed these symptoms Medically Not Yet Explained Symptoms (MNYES).

Methods The study was conducted according to the JLA's detailed methodology for conducting priority setting exercises. It involved five key stages: defining the appropriate term for the conditions under study by the PSP Steering Group; gathering questions on MNYES from patients, caregivers and clinicians in a publicly accessible survey; checking these research questions against existing evidence; interim prioritisation in a second survey; and a final multi-stakeholder consensus meeting to determine the top 10 unanswered research questions using the modified nominal group methodology.

Results Over 700 responses from UK patients, caregivers and clinicians were identified in the two surveys and charities contributed from a broad range of medical specialties and primary care. The final top 10 unanswered research questions cover, amongst others: treatment strategies, collaborative care pathways, training for clinicians, outcomes that matter to patients, and personalisation of treatment.

Interpretation The top 10 unanswered research questions are expected to generate much needed, relevant and impactful research into MNYES.

Word count: 4000

Key words: James Lind Alliance; Priority Setting; Medically Not Yet Explained Symptoms (MNYES); Medically Unexplained Symptoms (MUS); Persistent Physical Symptoms (PPS)

Introduction

Medically Not Yet Explained Symptoms (MNYES), also known as Medically Unexplained Symptoms (MUS) or Persistent Physical Symptoms (PPS)(1), represent up to 30% of presentations in primary care and internal medicine settings (2-4). They can include fatigue, pain, dizziness, irritable bowel syndrome, and functional neurological symptoms (FND)(4). They are often deemed to be stress-related, or of psychological origin, and comorbid depressive or anxiety disorder occur in approximately 30% of cases (3). Patients diagnosed with these symptoms often feel that they are not taken seriously, although care may have been taken to explain their condition properly. It can take a long time to reach the conclusion that patients have MNYES; during this time they typically experience high levels of disability and face repeating appointments and diagnostic procedures. They hear that no cause can be found for their symptoms and this is often delivered by clinicians who have a dualistic view of health and disease. Disability and absenteeism occurs frequently even in patients who present only within primary care with a low number of symptoms and where the effect of demographic factors, anxiety and depressive disorder are taken into account(5-8). This inevitably leads to disappointment and frustration (9). Many clinicians lack confidence in the assessment and management of MNYES, or may exhibit behaviours perceived as dismissive. Patients often perceive a stigmatising attitude from clinicians and a sense that they are being judged as neurotic or mentally unwell (10-12). Moreover, management plans may not be sufficiently holistic to address all patient concerns, and effective treatments are scarce. All the above impact negatively on long-term prognosis.

The focus of research on MNYES is often on particular subsets of symptoms, such as chronic pain, chronic fatigue, irritable bowel syndrome, and dizziness, but lacks a comprehensive view. This has ramifications for patients who visit different clinics for their various symptoms, without sustained improvement, and as such experience unmet needs (13, 14). To address this, the University of York through the lead author (CFC) established a Priority Setting Partnership (PSP) for research needed to address MNYES. We engaged with members of the public, patients with MNYES and their caregivers, clinicians of all medical specialties known to have patients with MNYES (15), and other key stakeholders such as charities and the Royal College of Psychiatry Liaison Faculty. Close collaboration with the James Lind Alliance (JLA) enabled this PSP to follow their established, rigorous approach to identify the treatment and

1
2
3 management priorities of stakeholders (patients, caregivers, clinicians and support
4 organisations) and to incorporate these into a research agenda (16).

5
6
7
8 The European Association of Psychosomatic Medicine has published a research agenda in this
9 domain with one of the research priorities being patient preferences for research in this field
10 (17). Until now, however, there has been relatively little support available for people with
11 MNYES and those who care for them, to enable them in setting up the research agenda.
12 Engaging patients in the research process incorporates their perspective as 'experts' from
13 their unique experience of living with symptoms, as well as their personal knowledge
14 regarding diagnostic trajectories and treatments in the healthcare setting if such symptoms
15 remain (partially) unexplained (18). This study aims to address this knowledge gap.
16
17
18
19
20
21
22

23 The aim of this PSP was therefore to develop a research agenda with the joint perspectives
24 of patients, caregivers, clinicians and support organisations across the United Kingdom as the
25 frame of reference, to identify the most important unanswered research questions in MNYES.
26
27
28
29

30 **Methods**

31
32 This study was undertaken according to the JLA's method for undertaking PSPs as delineated
33 in the JLAs Guidebook (16). An independent JLA Adviser (JG) guided the study team through
34 the project and ensured that every step followed the JLA's methodology and adhered to the
35 JLA's principles of transparency and balanced inclusion of patients, caregivers and clinicians.
36 All materials related to this PSP can be found on the JLA website (19).
37
38
39
40
41
42

43 *Establishing the Steering Group*

44
45 In March 2020 the MNYES PSP Steering Group met for the first time. Members of the Steering
46 Group were selected by a snowballing method, asking clinics and clinicians providing diagnosis
47 and treatment of the different conditions potentially covered by MNYES to signpost
48 colleagues with an interest in MNYES. Also, charities, patient networks and PPI networks were
49 approached to identify patients and caregivers. They were invited and selected based upon
50 the capability, motivation and consent to contribute to the JLA PSP working group standards
51 of reference as described in the JLA website. Efforts were made to have a representation of
52 patients with pain, fatigue, FND, IBS and dizziness, as they are the most common MNYES
53 conditions as shown in the literature (20). Efforts were made to include people from areas
54
55
56
57
58
59
60

1
2
3 outside of London, including rural areas and underserved areas as delineated by clinics and
4 GPs in the North of England in the Steering Group. The Steering Group was tasked with
5 overseeing the Priority Setting Partnership by having meetings every six weeks, chaired by the
6 JLA advisor, and making critical decisions at key points of the project (19). The composition of
7 the Steering Group is shown in Box 1 (Supplement).
8
9
10
11
12

13 *Terminology*

14
15 Many terms are used for these symptoms, including, but not limited to, Persistent Somatic
16 Symptoms (PPS) (1), Somatic Symptom and Related Disorders (SSRD)(21), Bodily Distress
17 Disorders (BDD) (22), Medically Unexplained Symptoms (MUS), Functional symptoms, and
18 Functional Neurological Disorder (FND). There is an ongoing debate amongst researchers and
19 clinicians about how to refer to these conditions. Many of such terms have been deemed
20 unsatisfactory by patients, caregivers and clinicians as well as researchers for a variety of
21 reasons, leading to ongoing efforts from researchers to find a better term; (23-25) however,
22 so far the patient, carer and clinician perspective regarding the choice of preferred term has
23 been lacking. This may seem semantic, however it underpins the conceptual confusion that
24 exists regarding these symptoms (26). Unfortunately, in some cases such uncertainty can give
25 rise to deeply rooted controversy that ultimately can be traced back to lack of knowledge
26 regarding the underlying conditions, and to related stigma. This knowledge gap could either
27 be a factual lack of evidence, or a lack of availability of existing knowledge to clinicians,
28 patients and the general public alike. Therefore, the study's PSP Steering Group took time to
29 decide what terminology to use in the study.
30
31
32
33
34
35
36
37
38
39
40
41
42

43 A common concern appeared to be the distress caused to patients, caregivers and clinicians
44 alike by the lack of adequate explanations, diagnostic methods and treatments for these
45 symptoms – which are often poorly understood across these groups too. This was felt to have
46 a negative impact on clinical work and research pertaining to these conditions and to
47 stigmatise them at a societal level. After deliberation, the PSP Steering Group agreed to use
48 the term *Medically Not Yet Explained Symptoms (MNYES)* to describe the subject matter for
49 the duration of the study. This was an operational definition not intended to add to or replace
50 other definitions already in use, that was constructed to embrace the views of all
51 stakeholders. MNYES was meant to indicate that although some insights might exist, our
52 understanding is still incomplete. This could pertain to biological, psychological and social
53
54
55
56
57
58
59
60

1
2
3 factors, as well as factors involving the trajectory of patients through various healthcare
4 settings. In that sense, the choice of the term MNYES conveys a message of hope, which feeds
5 into the effort to identify research priorities for the condition.
6
7

8 9 *Inclusion and exclusion criteria*

10
11
12 The PSP's Steering Group agreed that the remit should include the aetiology, diagnosis and
13 treatment or medical care of patients with MNYES in the UK, as well as the organisation of
14 services, social consequences and long term outcomes including cost implications for patients.
15 Confirmed topics included (but were not limited to): pain, fatigue, dizziness, functional
16 neurological disorder, bowel symptoms, palpitations and syncope. Ages 16 and older were
17 included. Although fatigue as a symptom was considered for inclusion, Chronic Fatigue
18 Syndrome was considered out of scope since there was another PSP addressing this.
19
20
21
22
23
24

25 *Patient and public involvement*

26
27
28 A core principle of JLA priority setting partnerships is collaboration between all stakeholders
29 (patients, caregivers, and clinicians) to ensure their views are represented at each stage of the
30 process. At the level of the steering group, patients, caregivers and clinicians were members
31 of the MNYES Steering Group, represented at every meeting, and involved in the development
32 of PSP surveys. They participated in the initial and interim surveys, and were involved in the
33 organisation of uncertainties, the wording of summary questions, and the verification of
34 evidence checking. At the level of the surveys, patients, public and supporting organisations
35 participated in the surveys as shown in Table 1 (Supplement). The final workshop also included
36 patients, caregivers and clinicians in the final prioritisation process to establish the top 10
37 research priorities for MNYES. Furthermore, there were observers representing supporting
38 organisations and relevant charitable organisations during the final workshop. All Steering
39 Group members were invited to contribute to the dissemination of the surveys; the
40 information shared by this PSP was developed with members from all stakeholder groups. All
41 PSP steering group members were invited to contribute to the article describing the findings
42 and one of them indeed contributed as a co-author.
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Results

The process is shown in the project flowdiagram presented in Figure 1 below.

- Insert **Figure 1. Flow diagram of MNYES question prioritisation processes** –

First survey

The initial survey (June 2020 - January 2021) asked patients, caregivers and healthcare professionals to indicate their priorities for future research related to MNYES (27). There were 705 respondents who accessed the initial survey; 443 provided at least one question or statement. Respondents were 77% female, 86% white. Data from the 2011 census show that 51% of the England and Wales population were female (28) and 86% of the same population were White (29). 68% of the participants were patients or caregivers as reported in Table 2 (Supplement).

The information specialists (DV and JS) and PSP lead (CFC), grouped similar or duplicate questions into 5 domains, generating 96 draft summary questions on aetiology, diagnosis, health care services, treatment, outcomes, prognosis, and other. Those 96 draft questions were reviewed by small groups of PSP Steering Group members that comprised clinicians, patients and caregivers. Further consolidations were made resulting in 46 summary questions which were reviewed again and signed off at a meeting of the whole PSP Steering Group. A document illustrating this is available on the JLA website (30). Of these 46 questions, 22% related to aetiology, 24% to health and clinical services, 15% to diagnosis, 24% to the treatment of MNYES, and 15% to outcomes. The proportion of questions posed by stakeholder groups, organised by topic, is shown in Figure S1 (Supplement).

Evidence check

The 46 summary questions were checked against published systematic reviews and clinical guidelines. We found that none of the 46 summary questions had been fully answered by previous research; some questions had been answered for specific symptoms, but not comprehensively across all MNYES symptoms. At a subsequent meeting, the Steering Group reviewed the 46 summary questions in relation to the original questions and statements from

1
2
3 which they derived. This resulted in minor changes to the wording of these 46 questions which
4 were then included in the interim prioritisation survey.
5
6

7 *Interim survey*

8
9 This online survey was completed by 270 participants from across the UK. Patients and
10 caregivers made up 74% of the participants. Demographic information is shown in Table 2
11 (Supplement).
12
13

14 *Final priority setting workshop*

15
16 The final priority setting workshop was conducted remotely over two days. In total, 25 people
17 participated in the workshop sessions; four JLA advisors facilitated the subgroups, eight
18 people observed and one person provided technical support. Participants included 11 people
19 with MNYES or caregivers, and 14 healthcare professionals representing psychiatry, general
20 practice, stroke, neurology, physiotherapy, psychology, occupational therapy and
21 gastroenterology. The final top 10 research priorities were agreed by consensus between all
22 the participants as listed in Figure 2. They were placed on the James Lind Alliance Website
23 (31).
24
25
26
27
28
29
30
31

32
33 - Insert **Figure 2. Top 10 research priorities** -
34

35
36 The research priorities which were ranked 11 – 17 are also listed on the JLA website (31)
37 and in Box 2 (Supplement).
38
39
40
41
42
43

44 **Discussion**

45
46
47
48 In this study, we used the JLA Priority Setting Partnership processes to identify the top 10
49 unanswered research questions for MNYES. We utilised the collective perspectives of patients,
50 caregivers, and clinicians, and focused on areas where up-to-date, reliable research evidence
51 is lacking. This process was supported by charitable and professional organisations across the
52 United Kingdom. The study highlighted the paucity of evidence-driven practice in MNYES care
53 since none of the 46 research questions gathered from our survey have been previously
54 answered by level I evidence. Based on the extensive discussions that took place during the
55
56
57
58
59
60

1
2
3 meetings, the following major themes emerged from the top 10 unanswered research
4 questions.
5

6 7 THEME 1: TREATMENT 8

9
10 The first and sixth research priorities concern treatment. The first, *What are the most effective*
11 *treatment strategies for different symptoms of MNYES?* pertains to all potential treatment
12 strategies (for example: pharmacological, psychological, physical, or collaboration models) to
13 help manage or alleviate any MNYES or combination of symptoms, such as pain, fatigue,
14 dizziness, functional neurological disorder, bowel symptoms, palpitations and syncope. The
15 sixth research priority, *How can the most appropriate treatment be selected, dependent on*
16 *different MNYES symptoms, that a person with MNYES is most likely to benefit from?* focuses
17 on the best ways to match people who experience specific MNYES with the treatments that
18 are most likely to benefit them. This relates to personalisation of treatment based on
19 diagnostic factors, such as a history of trauma, biomarkers or treatment needs. Given the high
20 unmet clinical need and the heterogeneity of MNYES, it is no surprise that this is considered to
21 be an important research priority. Interestingly, this was also a research priority identified by
22 the Delphi study conducted amongst experts in the field on behalf of the European Association
23 of Psychosomatic Medicine (17); treatment and personalised treatment are therefore
24 considered to be research priorities which are widely supported in this field.
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 THEME 2: THE ROLE OF CLINICIANS 40

41
42 Several research priorities involve the role of the clinicians in the diagnostic and treatment
43 process. The second research priority, *How can clinicians collaborate effectively to form the*
44 *most appropriate care pathway and service model to offer assessment and treatment for*
45 *patients with MNYES?* pertains to the role that clinicians play towards each other. It includes
46 the professionals and services which may be involved for the purpose of assessment, diagnosis
47 and the provision or coordination of treatment. It relates to the fact that often many different
48 clinicians provide diagnostic assessments to people with MNYES, or are sought to provide
49 treatment to them. This priority is focused on finding the best ways for clinicians to collaborate
50 with each other to form an appropriate care pathway to support people with MNYES. This
51 could be psychiatric consultation models, multi-disciplinary team models, collaborative care
52
53
54
55
56
57
58
59
60

1
2
3 models or other integrated care pathways. The third research priority, *What are the most*
4 *effective methods for training clinicians to diagnose and treat their patients with MNYES with*
5 *compassion, empathy and respect?* refers to medical practitioners who are already qualified
6 and employed in positions that involve the diagnosis and treatment of people with MNYES.
7
8 The focus of attention here is on the communication of information which acknowledges the
9 perspective and concerns of the person experiencing MNYES. Priority five, *What are the most*
10 *effective ways to support patients with MNYES and their carers to live with their symptoms?*
11 focuses on identifying the range of different options for supporting people with MNYES and
12 their caregivers. These may include but are not limited to: finding the most appropriate and
13 acceptable ways to discuss MNYES with people who experience them and their caregivers;
14 guidance about how to discuss MNYES with family members and friends; shared decision
15 making when discussing treatment options; peer support organisations; reasonable
16 adjustments in employment settings; adaptations to accommodation; psychological support
17 to cope while living with symptoms; recovery and rehabilitation approaches. Another research
18 priority fitting with this theme is priority nine: *What strategies are effective at promoting*
19 *awareness and up to date clinical knowledge about MNYES amongst healthcare professionals?*
20 This priority emphasises strategies to consistently and effectively ensure that clinicians are
21 aware of and have the most up to date information about MNYES which will enable the care
22 people receive to reflect current evidence. Given the existing knowledge gaps this is
23 considered an important priority.
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

41 THEME 3: SYMPTOMS AND OUTCOMES

42
43 Patients were involved in all discussions regarding research priorities. However, some
44 research priorities mention the patient perspective explicitly, such as, for example, priority
45 four, *What outcomes matter most to patients with MNYES?* Based upon the survey answers,
46 these may include, but are not limited to: symptom reduction; changes in biomarkers;
47 improvements in abilities to undertake daily tasks; improvements in quality of life; individual
48 goal achievements; or improvements in functioning. Priority seven, *What symptoms are*
49 *commonly reported by people with MNYES and what links them?* relates to the fact that the
50 list of MNYES is extensive and people who experience these symptoms often report living with
51 multiple MNYES. The aim of this priority is to identify the symptoms which most commonly
52 co-occur and the underlying factors and mechanisms between them. For priority eight, *What*
53
54
55
56
57
58
59
60

1
2
3 *factors affect outcomes for MNYES?* it was agreed the diversity of factors affecting outcomes
4 should include biomarkers, psychological factors and trauma, health services-related issues
5 such as feedback from recovered patients about what helped them, the availability and quality
6 of information clinicians have access to, the way information is shared between clinicians and
7 people experiencing MNYES, and social factors such as poverty, education, family dysfunction
8 or domestic abuse, and work environment. Given the number of questions that pertained to
9 aetiological factors, and the fact that the related uncertainty plays a role in the choice of
10 MNYES as a term, this can be considered an important research theme.
11
12
13
14
15
16
17
18

19 THEME 4: RECOVERY

20
21 Research priority number ten relates to recovery: *Which self-management techniques are*
22 *effective in MNYES?* this priority concerns the strategies that people experiencing MNYES can
23 use separately from visits to clinics. The focus is to identify the most effective self-
24 administered therapies for managing or alleviating MNYES, used separately, or in combination
25 with formal treatment. Examples of self-management approaches include education,
26 exercise, and dietary changes. It should be noted that this research priority, in contrast to ones
27 covered by the other themes, considers that recovery in MNYES can occur, either by recovery
28 of symptoms, or by personal recovery with ongoing symptomatology. Recovery of
29 symptomatology is referred to as clinical recovery and is covered by the other themes.
30 Recovery whilst symptoms are ongoing is called personal recovery (32), meaning that despite
31 symptoms being present, function has to some extent been restored through treatment, self-
32 management or disability management.
33
34
35
36
37
38
39
40
41
42
43

44 In mental health research and clinical practice, especially in relation to psychotic conditions,
45 personal recovery is a construct that has increasingly gained attention over the past thirty
46 years; however, so far the term has not been used in the context of MNYES. Generally, the
47 emphasis, both in clinical practice and in research, seems to have been to either attempt to
48 attain clinical recovery, or to send the patient home with the message that MNYES cannot be
49 cured and that one would have to live with the condition. This dichotomy has fed into the
50 ongoing controversy about how to approach MNYES. This polarising stance is unhelpful.
51 Developing this research priority would require embracing the concept that personal recovery
52 refers to an individual process of adaptation and development where one does not simply
53
54
55
56
57
58
59
60

1
2
3 return to, but rather grows beyond the premorbid self (33), with an emphasis on the patient
4 perspective. It could provide an important contribution to the further development of
5 research in this domain, alongside the research priorities summarised in the other themes.
6
7
8
9

10 *Strengths of the study*

11
12 This is the first study establishing research priorities for MNYES, according to the JLA Priority
13 Setting Partnership method which incorporates the views of patients, caregivers and
14 clinicians. The use of established and transparent James Lind Alliance methodology is a
15 strength of this study.
16
17
18
19

20 This is a highly contentious area; however, the research priorities were widely supported by
21 over 400 participants including clinicians from a variety of disciplines, patients with a range of
22 symptoms, caregivers, charitable organisations, and other supporting organisations. Over 700
23 responses were gathered from patients, caregivers and clinicians from an array of medical
24 specialties including primary care, indicating that the priorities were widely supported.
25 Contributions of people from ethnic and gender minority groups and from underserved areas
26 within the PSP Steering Group, surveys and final workshop supports the inclusive nature of
27 this work and indicates these priorities are important to a diverse range of people.
28
29
30
31
32
33
34
35

36 The themes identified in this PSP cover a broad range of ideas, issues and uncertainties; these
37 are outlined in the top 10 research priorities and also reflected in the seven research priorities
38 that did not make the top 10. Research priorities 11, 12 and 17 would link well with theme 3
39 in exploring associations of MNYES with mental health and somatic comorbidity, as well as the
40 development of symptoms over time. Priorities 13 and 14 would fit in theme two, the role of
41 clinicians; 15 and 16 link with theme one, treatment. This suggests that the themes covered
42 by the top 10 priorities are consistent with the other research priorities which were proposed
43 during this priority setting process.
44
45
46
47
48
49
50
51
52
53
54

55 *Limitations of the study*

56
57 When comparing the participants of survey 1 with survey 2, there were 443 participants in
58 survey 1, and 270 in survey 2. The final workshop was attended by 25 people. These are high
59
60

1
2
3 numbers and certainly adequate for priority setting according to the JLA method. However, as
4 the description of the roles is self-described, the variety of investigative participants remains
5 unclear in some respects. For example, it should be pointed out that in Table 2, 10 people self
6 described as “doctor,” and 8 as “other” clinician and they may well have been doctors working
7 in primary care as GPs, or rheumatologists; however, we do not know for sure. Regarding the
8 patients, they would state their self-described main symptom as “pain” in approximately half
9 of the cases; from their answers to the open questions, it emerged that this often would refer
10 to musculo-skeletal or rheumatological pain. So, while the exact variety is uncertain, however,
11 it is unlikely that this contributed to priorities in the final list of issues related to MNYES.
12
13
14
15
16
17
18
19
20

21 The study provides a good overview of research priorities for MYNES in the UK, however given
22 the specific cultural aspects and health care organisation in the UK, the findings may not be
23 generalisable to other countries. A similar PSP is currently being conducted in the Netherlands
24 and may shed light on research priorities in a non-NHS healthcare setting. This will provide an
25 opportunity to compare and evaluate the generalisability of these findings and the influence
26 of different cultural and healthcare settings. Future research highlighting the situation in Low
27 and Middle Income Countries would be beneficial. The results of this PSP will enable funders
28 to prioritise research in MNYES as outlined here and hopefully will provide new, much needed
29 knowledge in this domain.
30
31
32
33
34
35
36
37

38 **Conclusion**

39
40 MYNES are common and reflect a high level of unmet clinical need. Incorporating patient-
41 driven research in MNYES research can allow researchers to better address the complex care
42 needs of people with MNYES. The most important aspect of this priority setting exercise was
43 strengthening the relationship between patients, caregivers, clinicians and support
44 organisations and generating a list of priorities valued by these stakeholders, which we hope
45 will guide future research.
46
47
48
49
50
51

52 We have identified the top 10 research priorities in MNYES using the rigorous JLA priority
53 setting method that may open the door to further research addressing the knowledge gaps
54 and controversies in this area, and hopefully alleviate some of the stigma related to these
55 conditions and the people suffering from MNYES. Identification of these top 10 research
56
57
58
59
60

1
2
3 priorities is an important first step to generating relevant, impactful research that will
4 ultimately improve the lives of people with MNYES.
5
6
7

8 **Acknowledgements:** The Steering Group would like to thank to all the patients, caregivers,
9 families, friends, healthcare professionals and supporting organisations who contributed to
10 this work. In addition to the co-authors, Philippa Bolton, Sally Brabyn, Tracey Cunningham,
11 Rosie Evans, Miriam Lomas, Margot Metz, Chris Price, Annie Shaw, Scott Spain, Lesley Spain
12 were members of the PSP Steering Group. The following people who attended the final
13 workshop for priority setting agreed to be named: Anna Burneika, Kit Byatt, Phoebe Cole,
14 Tracey Cunningham, Mark Edwards, Rosie Evans, Eve Fazakerley, Jennifer Gilligan, Stephanie
15 Johnston, Claire Jones, Hilary Lewis, Joseph Littlewood, Miriam Lomas, Andrew Moriarty,
16 Elizabeth Paul, Emma Reinhold, Keziah Reiss, James Sampford, Annie Shaw, Gemma Smith,
17 Martin Veysey, Juliet Wilson, Jennifer Wilson.
18
19
20
21
22
23
24
25
26
27

28 **Ethics statement:** Ethical approval was not required as confirmed by the research
29 governance board of the Department of Health Sciences of the University of York.
30
31
32

33 **Data availability statement**

34 Data relevant to the study are included in the article or on the James Lind Alliance website
35 ([https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/)
36 [symptoms/](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/)) and linked University of York website
37 (<https://www.york.ac.uk/healthsciences/research/mental-health/projects/mnyes/>).
38
39
40
41
42

43 **Conflicts of interest statement**

44 The authors have no conflicts of interest to declare.
45
46
47

48 **Author statement**

49 CFC was the project lead, instigating the application to the JLA. CFC, NS, JFS and JG organised
50 the Steering Group meetings. JFS and DV designed and built the surveys, analysed the data,
51 and conducted the evidence check under supervision of JG and CFC. CFC, JFS, and NS wrote
52 the majority of the final manuscript. JG (JLA Chair) chaired all the meetings, led the consensus
53 workshop and ensured compliance with methodology throughout. NS and JFS took minutes
54 for Steering Group meetings, built and distributed surveys, and organised the consensus
55
56
57
58
59
60

1
2
3 workshop. JFS conducted the searches for the evidence check and screened the results with
4 CFC. Members of the Steering Group CFC, JFS, ME, NG, JG, SH, AK, ASM, PP, JS, NS, IE, DV, PB,
5 SB, TC, RE, ML, MM, CP, AS, SS, LS all attended a majority of the meetings, agreed the initial
6 protocol and the evidence check protocol, piloted and signed off the surveys and disseminated
7 them, checked the raw questions against the indicative ones, reviewed the evidence check
8 results and agreed the final longlist. TC, ME, JG, ML, ASM, JFS, and AS were present at the final
9 consensus workshop. All authors reviewed and contributed to the final manuscript and
10 approved it prior to submission.
11
12
13
14
15
16
17

18 **Funding**

19 This work was part-funded by the Wellcome Trust [ref: 204829] from the
20 overall Wellcome Trust ISSF award through the Centre for Future Health (CFH) at the University
21 of York.
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

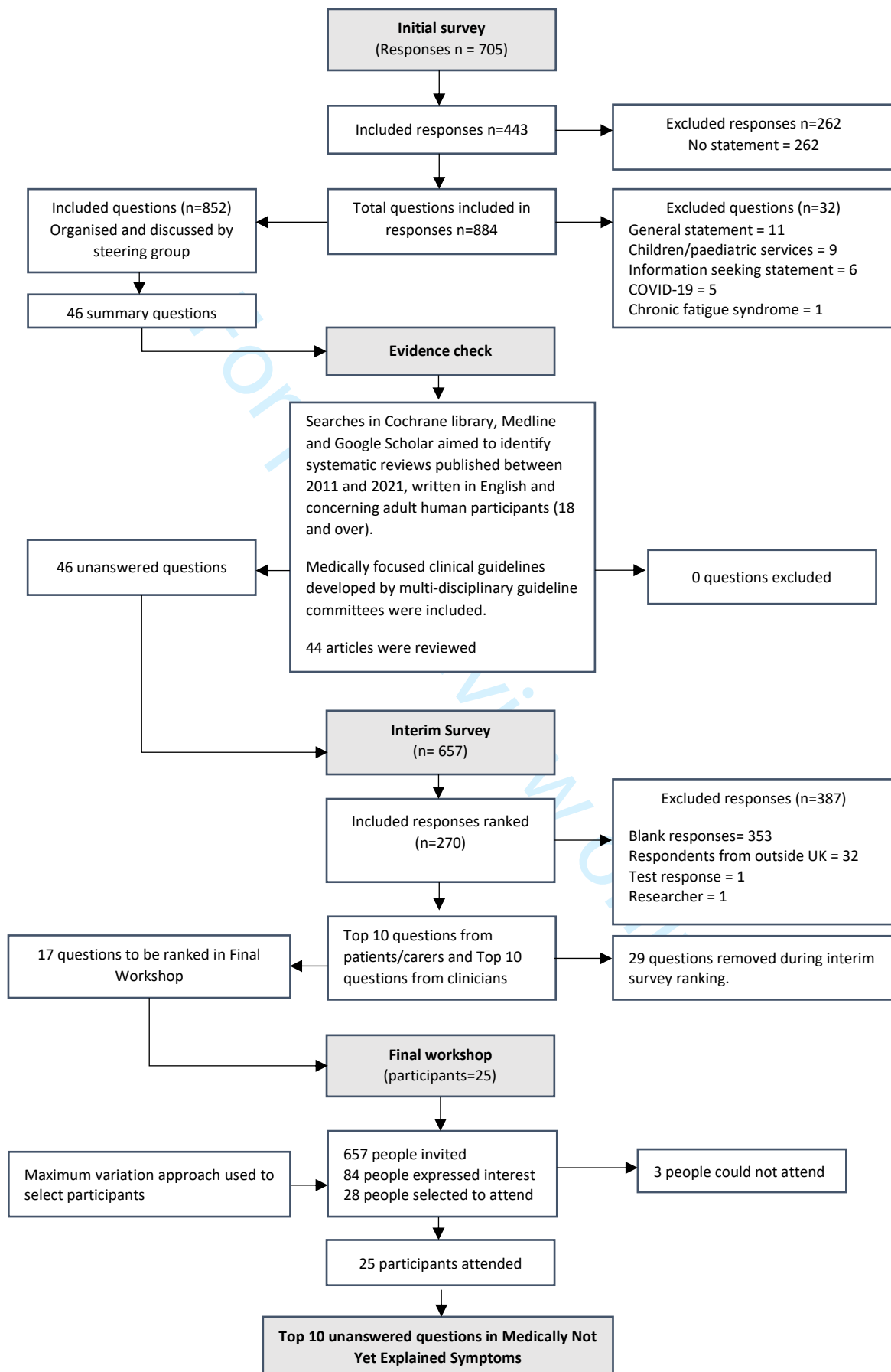
er review only

References

1. Patel M, James K, Moss-Morris R, Husain M, Ashworth M, Frank P, Ferreira N, Mosweu I, McCrone P, Hotopf M, David A, Landau S, Chalder T. Persistent physical symptoms reduction intervention: a system change and evaluation (PRINCE)-integrated GP care for persistent physical symptoms: protocol for a feasibility and cluster randomised waiting list, controlled trial. *BMJ Open*. 2019 Jul 23;9(7):e025513. doi: 10.1136/bmjopen-2018-025513.
2. Hoedeman R, Blankenstein AH, van der Feltz-Cornelis CM, Krol B, Stewart R, Groothoff JW. Consultation letters for medically unexplained physical symptoms in primary care. *Cochrane Database of Systematic Reviews*. 2010(12).
3. Van Hemert AM, Hengeveld MW, Bolk JH, Rooijmans HG, Vandenbroucke JP. Psychiatric disorders in relation to medical illness among patients of a general medical out-patient clinic. *Psychological medicine*. 1993;23(1):167-73.
4. Kirmayer LJ, Groleau D, Looper KJ, Dao MD. Explaining medically unexplained symptoms. *The Canadian journal of psychiatry*. 2004;49(10):663-72.
5. van der Leeuw G, Gerrits MJ, Terluin B, Numans ME, van der Feltz-Cornelis CM, van der Horst HE, Penninx BW, van Marwijk HW. The association between somatization and disability in primary care patients. *J Psychosom Res*. 2015 Aug;79(2):117-22. doi: 10.1016/j.jpsychores.2015.03.001. Epub 2015 Mar 11. PMID: 25824596.
6. den Boeft M, Twisk JW, Hoekstra T, Terluin B, Penninx BW, van der Wouden JC, Numans ME, van der Horst HE. Medically unexplained physical symptoms and work functioning over 2 years: their association and the influence of depressive and anxiety disorders and job characteristics. *BMC Fam Pract*. 2016 Apr 14;17:46. doi: 10.1186/s12875-016-0443-x. PMID: 27079909; PMCID: PMC4831095.
7. Hoedeman R, Krol B, Blankenstein N, Koopmans PC, Groothoff JW. Severe MUPS in a sick-listed population: a cross-sectional study on prevalence, recognition, psychiatric co-morbidity and impairment. *BMC Public Health*. 2009 Dec 1;9:440. doi: 10.1186/1471-2458-9-440. PMID: 19951415; PMCID: PMC2793259.
8. Escobar JI, Waitzkin H, Silver RC, Gara M, Holman A. Abridged somatization: a study in primary care. *Psychosom Med*. 1998 Jul-Aug;60(4):466-72. doi: 10.1097/00006842-199807000-00012. PMID: 9710292.
9. Salmon P, Peters S, Stanley I. Patients' perceptions of medical explanations for somatisation disorders: qualitative analysis. *Bmj*. 1999;318(7180):372-6.
10. Tolchin B, Tolchin DW, Stein MA. How Should Clinicians Minimize Harms and Maximize Benefits When Diagnosing and Treating Disorders Without Biomarkers? *AMA journal of ethics*. 2021;23(7):530-6.
11. Hatcher S, Arroll B. Assessment and management of medically unexplained symptoms. *Bmj*. 2008;336(7653):1124-8.
12. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". *Bmj*. 2002;325(7378):1449-50.
13. Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. *Journal of Neurology, Neurosurgery & Psychiatry*. 2000;68(2):207-10.
14. Reid S, Wessely S, Crayford T, Hotopf M. Frequent attenders with medically unexplained symptoms: service use and costs in secondary care. *The British Journal of Psychiatry*. 2002;180(3):248-53.
15. Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. *Journal of psychosomatic research*. 2001;51(1):361-7.
16. James Lind Alliance. *The James Lind Alliance Guidebook Version 7*. 2018.
17. van der Feltz-Cornelis CM, Elfeddali I, Werneke U, Malt UF, Van den Bergh O, Schaefer R, et al. A European research agenda for somatic symptom disorders, bodily distress disorders, and

- 1
2
3 functional disorders: results of an estimate-talk-estimate Delphi expert study. *Frontiers in psychiatry*.
4 2018;9:151.
- 5 18. Gill PJ, Cartwright E. Partnering with patients in the production of evidence. Royal Society of
6 Medicine; 2021.
- 7 19. James Lind Alliance. Priority Setting Partnership: Medically Not Yet Explained Symptoms 2021
8 [Available from: [https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/)
9 [explained-symptoms/](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/)].
- 10 20. Kellner R & Sheffield BF. The one-week prevalence of symptoms in neurotic patients and
11 normals. *Am J Psychiatry* 1973;50:734-41
- 12 21. American Psychiatric Association. Diagnostic and statistical manual of mental disorders:
13 DSM-5. Arlington, VA. 2013.
- 14 22. World Health Organization. International Classification of Diseases-11 (ICD-11)2019.
- 15 23. van der Feltz-Cornelis CM, Elfeddali I, Werneke U, Malt UF, Omer Van den Bergh O, Schaefer
16 R, Kop WJ, Lobo A, Sharpe M, Söllner W, Löwe B. A European Research Agenda for Somatic Symptom
17 Disorders, Bodily Distress Disorders, and Functional Disorders: Results of an Estimate-Talk-
18 Estimate Delphi Expert Study. *Front Psychiatry* 2018 May 14;9:151. DOI: [10.3389/fpsy.2018.00151](https://doi.org/10.3389/fpsy.2018.00151)
- 19 24. Ding JM, Kanaan RA. What should we say to patients with unexplained neurological
20 symptoms? How explanation affects offence. *J Psychosom Res*. 2016 Dec;91:55-60. doi:
21 [10.1016/j.jpsychores.2016.10.012](https://doi.org/10.1016/j.jpsychores.2016.10.012).
- 22 25. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, Warlow CP, Sharpe M. What
23 should we say to patients with symptoms unexplained by disease? The "number needed to offend".
24 *BMJ*. 2002 Dec 21;325(7378):1449-50.
- 25 26. Van der Feltz-Cornelis C, Van Dyck R. The notion of somatization: an artefact of the
26 conceptualization of body and mind. *Psychotherapy and psychosomatics*. 1997;66(3):117-27.
- 27 27. University of York. Research priority setting for Medically Not Yet Explained Symptoms
28 (MNYES) in an Anglo-Dutch partnership with the James Lind Alliance 2021 [Available from:
29 <https://www.york.ac.uk/healthsciences/research/mental-health/projects/mnyes/>].
- 30 28. GOV.UK. Male and female populations 2018 [Available from: [https://www.ethnicity-facts-](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest)
31 [figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest)
32 [populations/latest](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest)].
- 33 29. GOV.UK. Population of England and Wales 2018 [Available from: [https://www.ethnicity-](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest)
34 [facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest)
35 [populations/population-of-england-and-wales/latest](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest)].
- 36 30. [https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/downloads/medically-not-yet-explained-symptoms-psp-all-questions-data.doc)
37 [symptoms/downloads/medically-not-yet-explained-symptoms-psp-all-questions-data.doc](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/downloads/medically-not-yet-explained-symptoms-psp-all-questions-data.doc)
- 38 31. James Lind Alliance. Medically Not Yet Explained Symptoms Top 10 priorities 2021 [Available
39 from: [https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/top-10-priorities.htm)
40 [symptoms/top-10-priorities.htm](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/top-10-priorities.htm)].
- 41 32. Slade M, Amering M, Oades L. Recovery: an international perspective. *Epidemiology and*
42 *Psychiatric Sciences*. 2008;17(2):128-37.
- 43 33. Slade M. Personal recovery and mental illness: A guide for mental health professionals:
44 Cambridge University Press; 2009.
- 45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1: Flow diagram of MNYES question prioritisation processes



Top-10 Research Priorities Medically Not Yet Explained Symptoms (MNYES)

1. What are the most effective treatment strategies for different symptoms of MNYES?
2. How can clinicians collaborate effectively to form the most appropriate care pathway and service model to offer assessment and treatment for patients with MNYES?
3. What are the most effective methods for training clinicians to diagnose and treat their patients with MNYES with compassion, empathy and respect?
4. What outcomes matter most to patients with MNYES?
5. What are the most effective ways to support patients with MNYES and their carers to live with their symptoms?
6. How can the most appropriate treatment be selected, dependent on different MNYES symptoms, that a person with MNYES is most likely to benefit from?
7. What symptoms are commonly reported by people with MNYES and what links them?
8. What factors affect outcomes for MNYES?
9. What strategies are effective at promoting awareness and up to date clinical knowledge about MNYES amongst healthcare professionals?
10. Which self-management techniques are effective in MNYES?



UNIVERSITY
of York



James
Lind
Alliance
Priority Setting Partnerships



Figure 2: Top 10 Research Priorities for Medically Not Yet Explained Symptoms

Appendix

Key words included in evidence check searches

Symptom terms	Publication focus
Medically not yet explained symptoms	Guideline
Medically unexplained symptoms (MUS)	Mechanism
Persistent Somatic Symptoms	Pathology
Somatic Symptom and Related Disorders (SSRD)	Development
Chronic pain	Assessment
Unexplained pain	Diagnosis
Fatigue	Investigation
Unexplained fatigue	Treatment
Conversion disorder	Management
Neurological conversion symptoms	Healthcare service
Functional neurological disorder	Patient care
Functional symptoms	Care pathway
Functional neurological symptom	Outcome
Functional cognitive symptom	Prognosis
Functional weakness	
Dissociative disorders	
Dissociative neurological disorder	
Dissociative syncope	
Unexplained dizziness	
Fibromyalgia	
Irritable bowel syndrome (IBS)	
Nonepileptic seizures	

Acquiring funding, international aspect, and establishing support by the James Lind Alliance

Funding for the study was acquired by the PSP lead (CFC) in November 2019. Part of the collaboration was envisioned to support setting up a parallel PSP Steering Group to explore the same question in the Netherlands, in order to have an international perspective. This article focuses on the description of the process in the UK. Support by the James Lind Alliance Priority Setting Partnership was secured in December 2019 and a JLA Advisor (JG) appointed to the project.

Box 1: Steering group composition

Clinicians: One general practitioner(GP); consultants in cardiology (1), neurology (1), endocrinology (1), clinical liaison psychiatry (3) and rheumatology (1) one stroke physician, a clinical psychologist and one physiotherapist.

Patients and caregivers: Four patients with a variety of pain, fatigue and functional neurological symptoms; one caregiver;

Other: Two information specialists and two project coordinators to facilitate the PSP working group. They prepared meeting documents, surveys, supported recruitment, completed evidence checking and analysis but did not engage in the priority setting.

The consultative process

The study followed several steps in order to establish research priorities, using a mix of online surveys and a priority setting workshop. We created a website to host the surveys (27) and sent out the website link for our partner organisations to distribute within their networks.

Gathering uncertainties

The initial survey was launched between June 2020 and January 2021 and asked patients, caregivers and healthcare professionals to indicate their priorities for future research related to MNYES (27). We promoted the survey through partner organisations' websites, and their social media platforms. In addition, the clinics of clinicians involved in the PSP Steering Group distributed the QR code to their patients. We sent out email reminders to members of professional associations, sent Twitter invitations and placed the survey on the University of York and JLA websites. Distribution of the survey was supported by the members of the PSP, several associations, networks, networking groups and charities. An overview of supporting

organisations is shown in Table 1, below. Some of them collaborated because they found that patients with unexplained symptoms often visit their websites and related specialists to assess their symptoms.

Table 1: Supporting organisations who have promoted this work

Charities	Professional networks	Other networks and Social media groups
British Thyroid Foundation	Allied Health Professional FND Networking groups	INCLUDE (University of York Disability Network)
Fibromyalgia Association UK	Clinical special interest groups	James Lind Alliance
FND Hope	Liaison psychiatry networks	People who have shared information with their friends and family
Graham Hughes International	Royal College of Psychiatrists	Individuals and organisations active on twitter
Guts UK		Special interest and support groups on facebook
Health Unlocked		
Pain UK		
POTS-UK		

We targeted patients with MNYES such as pain, bowel problems, functional neurological symptoms, or with diagnoses which comprise a set of symptoms which are medically unexplained such as postural orthostatic tachycardia syndrome (PoTS); their caregivers; and the clinicians who treat them, to participate. Survey respondents were asked whether they had experienced MYNES, in which case they were to select their symptoms from a list, or were healthcare professionals, in which case they were asked to state their profession. Anonymity was preserved in all cases accordance with General Data Protection regulations.

Data analysis and verifying uncertainties

We downloaded the online survey results through Qualtrics and exported them into Microsoft Excel. The responses to this survey were organised into summary questions and these were then checked to make sure that they had not already been answered by research.⁽¹⁶⁾ Our health information specialists (DV and JS) and PSP lead (CFC) grouped the responses into themes and each was analysed in small groups by 3 or 4 members of the Steering Group; one member of each small group was a patient or caregiver and the other members were healthcare professionals. Summary questions were developed, which encapsulated groupings of similar responses to the survey. Responses were removed if they were outside the scope

1
2
3 of the survey or general statements which would be unanswerable by research. The outputs
4 from the small group discussions were reviewed at a subsequent meeting of the full PSP
5 Steering Group.
6
7

8
9 One health information specialist (JS) checked each in-scope question with existing clinical
10 guidelines published by multi-disciplinary guideline committees and systematic reviews, to
11 ensure that the question had not been already fully answered with high-level evidence.
12 44 articles were shortlisted from searches conducted in the Cochrane Library, Medline and
13 Google Scholar; key words for the search used are included in the appendix. Reference lists
14 of these studies were also reviewed to identify further relevant references. Articles published
15 between 2011 and 2021 were considered relevant by the Steering Group. Each question was
16 coded to indicate whether it was 'answered'; 'partially answered' or 'unanswered' through
17 the research literature.
18
19

20 21 22 23 24 25 26 *Interim priority setting*

27
28 Between May and July 2021, the second online survey asked participants to select their top
29 10 priorities from the list of uncertainties presented (19). The second survey was launched
30 independently from the first survey. Questions were presented in a random order to each
31 survey participant to reduce bias. The priorities of patients and caregivers and the priorities
32 from healthcare professionals were ranked separately. The top 10 priorities identified by
33 patients and caregivers were then combined with the top 10 priorities from healthcare
34 professionals to create a shortlist of 17 priorities as there were 3 overlapping priorities.
35
36
37
38
39

40 41 42 43 *Final workshop*

44 The 17 top ranked questions were taken forward to the final priority setting consensus
45 meeting that took place virtually on 16th and 17th September 2021. We invited volunteers
46 from supporting organisations, two of whom joined the meeting. We also invited individuals
47 who took part in the online survey to participate in the meeting. 25 participants took part in
48 the workshop comprising 10 patients with a variety of MNYES symptoms, 1 caregiver, and 14
49 health care professionals. The workshop participants were divided into four groups, each with
50 a balanced mix of patients/caregivers and clinicians. Each group also had observers who did
51 not participate in the process, to fulfill the requirement of transparency of the JLA process.
52 Each group was asked to rank the uncertainties through group discussions using the modified
53
54
55
56
57
58
59
60

nominal group technique facilitated by an independent JLA Advisor. Each participant was provided with a printed and electronic copy of the different 'unanswered' questions, and the JLA Advisor leading each group shared an image containing the unanswered questions to aid the group in ranking the 17 uncertainties. The rankings from the four groups were combined and all the workshop participants then came together to discuss these rankings. Similarities and differences between the group rankings were highlighted by the JLA facilitator leading the workshop (JG) and participants were invited to comment on the initial combined ranking. Following this, participants were reallocated into four new groups, maintaining the representation of patients/caregivers and clinicians within each group, to consider the combined group ranking from the previous session. During this session, there was a specific focus placed on the ordering of uncertainties across the top 17 unanswered questions. The rankings from each of the four groups were once again combined and were presented to the whole group for discussion. By the end of the priority setting meeting, we reached consensus on the top 10 UK research priorities for MNYES.

The respondents were 77% female, 86% white; data from the 2011 census show that 51% of the England and Wales population were female (28) and 86% of the same population were White (29). Of the 884 statements, 852 were in scope and 32 out-of-scope. The out-of-scope submissions included general statements (N = 11), children/paediatric services (N = 9), information seeking statements (N = 6), or pertaining to COVID-19 (N = 5) and chronic fatigue syndrome (N = 1).

Table 2: Participant demographic information

	Initial Survey (n=443)	Interim Survey (n=270)	Final Workshop (n=25)***
Gender (%)			
Male	89 (20)	33 (12)	6 (24)
Female	339 (77)	227 (84)	18 (72)
Other	14*(3)	2** (1)	1 (4)
Ethnicity (%)			
Asian/ Asian British	12 (3)	5 (2)	-
Arab	1 (<1)	-	-
Black/ Black British	3 (1)	2 (1)	-
Mixed/ Multiple	7 (2)	7 (2)	-
White	381 (86)	242 (90)	25 (100)
Other	17 (4)	4 (1)	-
Age, mean (SD)	47.65 (12.15)	42.55 (13.26)	39.29 (13.74)
Experience (%)			
Patient	288 (65)	183 (68)	10 (40)

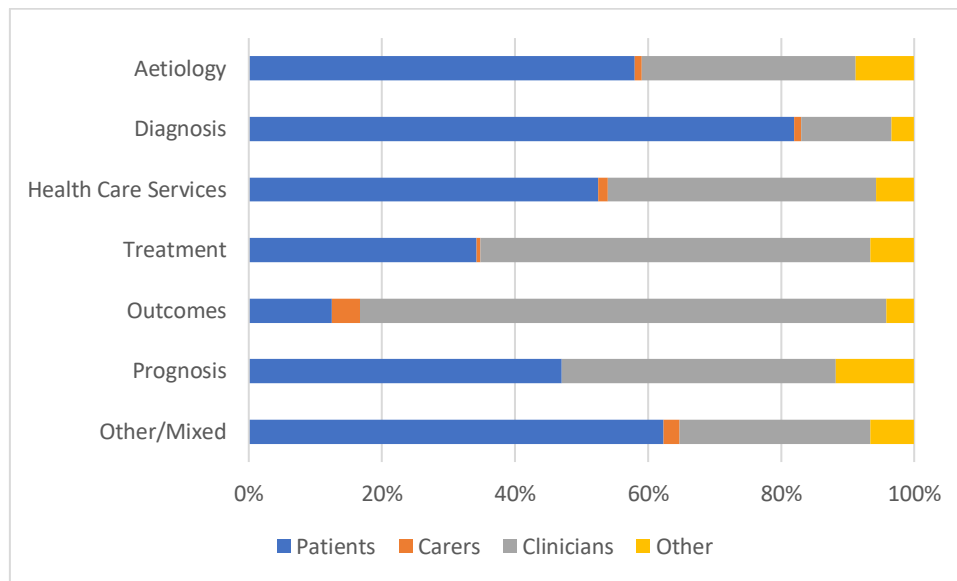
Caregiver	13 (3)	17 (6)	1 (4)
Clinician	121 (27)	65 (24)	14 (56)
Other	21 (5)	5 (2)	-
MNYES symptoms as self-described(%)			
Pain	219 (49)	147 (54)	6 (24)
Fatigue	236 (53)	146 (54)	8 (32)
Dizziness	156 (35)	91 (34)	5 (20)
Heart palpitations/fainting	134 (30)	83 (31)	5 (20)
Stomach/bowel problems	197 (44)	119 (44)	5 (20)
Problems with movement (tremors, shakes, weakness)	133 (30)	114 (42)	6 (24)
Unexplained blackouts, seizures, sudden loss of awareness	54 (12)	60 (22)	3 (12)
Other (e.g. brain fog, eye and skin problems)	126 (28)	44 (16)	4 (16)
Age when first developed MNYES, mean (SD)			
	31.77 (15.08)	29.89 (15.13)	-
Clinical role as self-described			
Cardiologist	-	1 (<1)	-
Consultant in emergency medicine	-	1 (<1)	-
Doctor	10 (2)	2 (1)	-
Gastroenterologist	-	-	1 (4)
GP	4 (1)	5 (2)	3 (12)
Occupational therapist	9 (2)	6 (2)	1 (4)
Neurologist	9 (2)	3 (1)	1 (4)
Neuropsychiatrist	1 (<1)	1 (<1)	-
Neuropsychologist	-	1 (<1)	-
Nurse	3 (1)	2 (1)	-
Physiotherapist	16 (4)	8 (3)	2 (8)
Psychiatrist	44 (10)	18 (7)	4 (16)
Psychologist	9 (2)	5 (2)	1 (4)
Psychotherapist	3 (1)	2 (1)	-
Other	8 (2)	1 (1)	-
Rheumatologist	1 (<1)	1 (<1)	-
Speech and language therapist	1 (<1)	4 (1)	-
Stroke specialist	-	-	1 (4)
Assistant psychologist/Support worker	3 (1)	2 (1)	-

*14 prefer not to say **1 non-binary,

Not mandatory and therefore not always provided

Figure S1 shows the proportion of original questions from each topic, which were posed by patients, caregivers, clinicians and others, who were generally individuals who met the criteria for more than one role. As can be seen, patients preferred aetiology and diagnostic questions, while clinicians emphasized treatment and outcomes. Health care services and prognosis were divided equally between patients or caregivers and clinicians.

Figure S1: The proportion of questions per domain suggested by patients, caregivers, clinicians and other



227 of the 264 (86%) people who reported gender were female and 242 of the 260 (93.1%) people who reported ethnicity, were white. The 17 resulting priorities were shortlisted for consideration at the final priority setting consensus workshop.

Box 2: research priority 11 through 17.

11. What is the relationship between mental health problems and MNYES?
12. What is the relationship over time between MNYES and known medical conditions and does that suggest some shared pathological process?
13. What is the best practice to offer optimal care for patients with MNYES?
14. What are current clinical attitudes and levels of knowledge about MNYES?
15. What are the most effective physical treatments for different symptoms of MNYES?
16. What are the most effective psychological treatments for different symptoms of MNYES?
17. Why do symptoms of MNYES fluctuate?

BMJ Open

Identifying the top research priorities in medically not yet explained symptoms (MNYES): a James Lind Alliance priority setting partnership

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-061263.R2
Article Type:	Original research
Date Submitted by the Author:	13-Jun-2022
Complete List of Authors:	van der Feltz-Cornelis, Christina; University of York, Dept. of Health Sciences, HYMS; Tees Esk and Wear Valleys NHS Foundation Trust Sweetman, Jennifer; University of York Edwards, Mark; St George's University of London; St George's University Hospitals NHS Foundation Trust Gall, Nicholas; University of London Kings College Hospital, Department of Cardiology Gilligan, Jennifer; Tees Esk and Wear Valleys NHS Foundation Trust Hayle, Steph; Patient representative Kaul, Arvind; St George's University Hospitals NHS Foundation Trust Moriarty, Andrew; University of York Department of Health Sciences; Hull York Medical School, Perros, Petros; Royal Victoria Infirmary, Department of Endocrinology Sampford, James; Tees Esk and Wear Valleys NHS Foundation Trust Smith, Natalie; University of York Elfeddali, Iman; Tilburg University, Tranzo Dept.; GGz Breburg, Tilburg, the Netherlands, Centre for Body Mind and Health Varley, Danielle; University of York Department of Health Sciences Gower, Jonathan; JLA
Primary Subject Heading:	Evidence based practice
Secondary Subject Heading:	Mental health
Keywords:	Adult psychiatry < PSYCHIATRY, Adult cardiology < CARDIOLOGY, Functional bowel disorders < GASTROENTEROLOGY, Rheumatology < INTERNAL MEDICINE, Adult neurology < NEUROLOGY, PRIMARY CARE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Identifying the top research priorities in medically not yet explained symptoms (MNYES): a**
4 **James Lind Alliance priority setting partnership**
5
6
7

8 Christina M van der Feltz-Cornelis,^{1,2,3} Jennifer F Sweetman,¹ Mark Edwards,^{4,5} Nicholas Gall,⁶
9 Jennifer Gilligan,³ Steph Hayle,⁷ Arvind Kaul,⁵ Andrew S Moriarty,^{1,2} Petros Perros,⁸ James
10 Sampford,³ Natalie Smith,¹ Iman Elfeddali,^{9,10} Danielle Varley,¹ Jonathan Gower¹¹
11
12
13
14

15 Corresponding author: Christina van der Feltz-Cornelis, Dept. of Health Sciences, HYMS,
16 University of York, ARRC Building, T204, Heslington, York, United Kingdom. Phone
17 +441904321313 Email christina.vanderfeltz-cornelis@york.ac.uk
18
19
20
21

22 ¹ Dept of Health Sciences, University of York, York, United Kingdom
23
24

25 ² Hull York Medical School, (HYMS), University of York, York, United Kingdom
26
27

28 ³ Tees Esk and Wear Valley NHS Foundation Trust, Darlington, United Kingdom
29
30

31 ⁴ Neuroscience Research Centre, Institute of Molecular and Clinical Sciences, St George's
32 University of London, London, United Kingdom.
33
34

35 ⁵ St. George's University Hospitals NHS Foundation Trust, London, United Kingdom
36
37

38 ⁶ Department of Cardiology, King's College Hospital, Denmark Hill, London, SE5 9RS, United Kingdom
39
40

41 ⁷ Patient representative, North Yorkshire, United Kingdom
42
43

44 ⁸ Department of Endocrinology, Royal Victoria Infirmary, Newcastle upon Tyne, United
45 Kingdom
46
47

48 ⁹ Tranzo Dept., Tilburg University, Tilburg, the Netherlands
49
50

51 ¹⁰ Centre for Body Mind and Health, GGz Breburg, Tilburg, the Netherlands
52
53

54 ¹¹ James Lind Alliance, Southampton, United Kingdom
55
56
57
58
59
60

Abstract

Objectives This study establishes research priorities for Medically Not Yet Explained Symptoms, also known as Persistent Physical Symptoms (PPS) or Medically Unexplained Symptoms (MUS), from the perspective of patients, caregivers and clinicians, in a priority setting partnership (PSP) following the James Lind Alliance (JLA) approach. Research into such symptoms in general has been poorly funded over the years and so far has been primarily researcher-led with minimal input from patients, caregivers and clinicians; and sometimes has been controversial.

Design JLA priority setting partnership method. The PSP termed these symptoms Medically Not Yet Explained Symptoms (MNYES).

Methods The study was conducted according to the JLA's detailed methodology for conducting priority setting exercises. It involved five key stages: defining the appropriate term for the conditions under study by the PSP Steering Group; gathering questions on MNYES from patients, caregivers and clinicians in a publicly accessible survey; checking these research questions against existing evidence; interim prioritisation in a second survey; and a final multi-stakeholder consensus meeting to determine the top 10 unanswered research questions using the modified nominal group methodology.

Results Over 700 responses from UK patients, caregivers and clinicians were identified in the two surveys and charities contributed from a broad range of medical specialties and primary care. The final top 10 unanswered research questions cover, amongst others: treatment strategies, collaborative care pathways, training for clinicians, outcomes that matter to patients, and personalisation of treatment.

Interpretation The top 10 unanswered research questions are expected to generate much needed, relevant and impactful research into MNYES.

Word count: 3916

Key words: James Lind Alliance; Priority Setting; Medically Not Yet Explained Symptoms (MNYES); Medically Unexplained Symptoms (MUS); Persistent Physical Symptoms (PPS)

Strengths and limitations of this study

- Establishing research priorities for medically not yet explained symptoms (MNYES) from the perspective of patients, caregivers and clinicians for the first time is a strength of the study.
- The use of the established and transparent James Lind Alliance methodology is a strength of the study.
- Over 700 responses were gathered from patients, caregivers and clinicians from a wide range of medical specialties including primary care, indicating that the priorities were widely supported.
- Contributions of people from ethnic and gender minority groups and from underserved areas within the PSP Steering Group, surveys and final workshop supports the inclusive nature of this work and indicates these priorities are important to a diverse range of people.
- Self-descriptions of participant roles and symptoms did not always provide sufficient detail to clearly describe the variety of the participants in the sample.

Introduction

Medically Not Yet Explained Symptoms (MNYES), also known as Medically Unexplained Symptoms (MUS) or Persistent Physical Symptoms (PPS)(1), represent up to 30% of presentations in primary care and internal medicine settings (2-4). They can include fatigue, pain, dizziness, irritable bowel syndrome, and functional neurological symptoms (FND)(4). They are often deemed to be stress-related, or of psychological origin, and comorbid depressive or anxiety disorder occur in approximately 30% of cases (3). Patients diagnosed with these symptoms often feel that they are not taken seriously, although care may have been taken to explain their condition properly. It can take a long time to reach the conclusion that patients have MNYES; during this time they typically experience high levels of disability and face repeating appointments and diagnostic procedures. They hear that no cause can be found for their symptoms and this is often delivered by clinicians who have a dualistic view of health and disease. Disability and absenteeism occurs frequently even in patients who present only within primary care with a low number of symptoms and where the effect of demographic factors, anxiety and depressive disorder are taken into account(5-8). This inevitably leads to disappointment and frustration (9). Many clinicians lack confidence in the assessment and management of MNYES, or may exhibit behaviours perceived as dismissive. Patients often perceive a stigmatising attitude from clinicians and a sense that they are being judged as neurotic or mentally unwell (10-12). Moreover, management plans may not be sufficiently holistic to address all patient concerns, and effective treatments are scarce. All the above impact negatively on long-term prognosis.

The focus of research on MNYES is often on particular subsets of symptoms, such as chronic pain, chronic fatigue, irritable bowel syndrome, and dizziness, but lacks a comprehensive view. This has ramifications for patients who visit different clinics for their various symptoms, without sustained improvement, and as such experience unmet needs (13, 14). To address this, the University of York through the lead author (CFC) established a Priority Setting Partnership (PSP) for research needed to address MNYES. We engaged with members of the public, patients with MNYES and their caregivers, clinicians of all medical specialties known to have patients with MNYES (15), and other key stakeholders such as charities and the Royal

1
2
3 College of Psychiatry Liaison Faculty. Close collaboration with the James Lind Alliance (JLA)
4 enabled this PSP to follow their established, rigorous approach to identify the treatment and
5 management priorities of stakeholders (patients, caregivers, clinicians and support
6 organisations) and to incorporate these into a research agenda (16).
7
8
9

10
11 The European Association of Psychosomatic Medicine has published a research agenda in this
12 domain with one of the research priorities being patient preferences for research in this field
13 (17). Until now, however, there has been relatively little support available for people with
14 MNYES and those who care for them, to enable them in setting up the research agenda.
15 Engaging patients in the research process incorporates their perspective as 'experts' from
16 their unique experience of living with symptoms, as well as their personal knowledge
17 regarding diagnostic trajectories and treatments in the healthcare setting if such symptoms
18 remain (partially) unexplained (18). This study aims to address this knowledge gap.
19
20
21
22
23
24
25

26
27 The aim of this PSP was therefore to develop a research agenda with the joint perspectives
28 of patients, caregivers, clinicians and support organisations across the United Kingdom as the
29 frame of reference, to identify the most important unanswered research questions in MNYES.
30
31
32

33 **Methods**

34
35
36
37
38

39 This study was undertaken according to the JLA's method for undertaking PSPs as delineated
40 in the JLA's Guidebook (16). An independent JLA Adviser (JG) guided the study team through
41 the project and ensured that every step followed the JLA's methodology and adhered to the
42 JLA's principles of transparency and balanced inclusion of patients, caregivers and clinicians.
43 All materials related to this PSP can be found on the JLA website (19).
44
45
46
47

48 *Establishing the Steering Group*

49 In March 2020 the MNYES PSP Steering Group met for the first time. The remit of the Steering
50 Group was to oversee, project manage and publicise the PSP, networking with charitable,
51 patient and professional organisations to maximise the response to the surveys. The Steering
52 Group ensured that the JLA's methodology and principles were adhered to and had no
53 influence on the choice and ranking of the research priorities which were solely determined
54 by the survey responses and final priority setting workshop.
55
56
57
58
59
60

1
2
3 Members of the Steering Group were selected by a snowballing method via clinics and
4 supporting organisations, inviting clinicians providing diagnosis and treatment of the different
5 conditions potentially covered by MNYES. Also, charities, patient networks and PPI networks
6 were approached to recruit patients and caregivers. They were invited and selected based
7 upon the capability, motivation and consent to contribute to the JLA PSP working group
8 standards of reference as described in the JLA website. Efforts were made to have a
9 representation of patients with pain, fatigue, FND, IBS and dizziness, as they are the most
10 common MNYES conditions as shown in the literature (20). Efforts were made to include
11 people from areas outside of London, including rural areas and underserved areas as
12 delineated by clinics and GPs in the North of England in the Steering Group. The Steering
13 Group was tasked with overseeing the Priority Setting Partnership by having meetings every
14 six weeks, chaired by the JLA advisor, and making critical decisions at key points of the project
15 (19). The composition of the Steering Group is shown in Box 1 (Supplementary File 1).

26 27 *Terminology*

28
29
30 Many terms are used for these symptoms, including, but not limited to, Persistent Somatic
31 Symptoms (PPS) (1), Somatic Symptom and Related Disorders (SSRD)(21), Bodily Distress
32 Disorders (BDD) (22), Medically Unexplained Symptoms (MUS), Functional symptoms, and
33 Functional Neurological Disorder (FND). There is an ongoing debate amongst researchers and
34 clinicians about how to refer to these conditions. Many of such terms have been deemed
35 unsatisfactory by patients, caregivers and clinicians as well as researchers for a variety of
36 reasons, leading to ongoing efforts from researchers to find a better term; (23-25) however,
37 so far the patient, carer and clinician perspective regarding the choice of preferred term has
38 been lacking. This may seem semantic, however it underpins the conceptual confusion that
39 exists regarding these symptoms (26). Unfortunately, in some cases such uncertainty can give
40 rise to deeply rooted controversy that ultimately can be traced back to lack of knowledge
41 regarding the underlying conditions, and to related stigma. This knowledge gap could either
42 be a factual lack of evidence, or a lack of availability of existing knowledge to clinicians,
43 patients and the general public alike. Therefore, the study's PSP Steering Group took time to
44 decide what terminology to use in the study.

45
46
47 A common concern appeared to be the distress caused to patients, caregivers and clinicians
48 alike by the lack of adequate explanations, diagnostic methods and treatments for these
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 symptoms – which are often poorly understood across these groups too. This was felt to have
4 a negative impact on clinical work and research pertaining to these conditions and to
5 stigmatise them at a societal level. After deliberation, the PSP Steering Group agreed to use
6 the term *Medically Not Yet Explained Symptoms (MNYES)* to describe the subject matter for
7 the duration of the study. This was an operational definition not intended to add to or replace
8 other definitions already in use, that was constructed to embrace the views of all
9 stakeholders. MNYES was meant to indicate that although some insights might exist, our
10 understanding is still incomplete. This could pertain to biological, psychological and social
11 factors, as well as factors involving the trajectory of patients through various healthcare
12 settings. In that sense, the choice of the term MNYES conveys a message of hope, which feeds
13 into the effort to identify research priorities for the condition.
14
15
16
17
18
19
20
21
22

23 24 *Inclusion and exclusion criteria*

25
26 The PSP's Steering Group agreed that the remit should include the aetiology, diagnosis and
27 treatment or medical care of patients with MNYES in the UK, as well as the organisation of
28 services, social consequences and long term outcomes including cost implications for patients.
29 Confirmed topics included (but were not limited to): pain, fatigue, dizziness, functional
30 neurological disorder, bowel symptoms, palpitations and syncope. Ages 16 and older were
31 included. Although fatigue as a symptom was considered for inclusion, Chronic Fatigue
32 Syndrome was considered out of scope since there was another PSP addressing this.
33
34
35
36
37
38
39

40 *Patient and public involvement*

41
42
43 A core principle of JLA priority setting partnerships is collaboration between all stakeholders
44 (patients, caregivers, and clinicians) to ensure their views are represented at each stage of the
45 process. At the level of the steering group, patients, caregivers and clinicians were members
46 of the MNYES Steering Group, represented at every meeting, and involved in the development
47 of PSP surveys. They were involved in the organisation of uncertainties, the wording of
48 summary questions, and the verification of evidence checking. At the level of the surveys,
49 patients, public and supporting organisations participated in the surveys as shown in Table 1
50 (Supplementary File 1). The final workshop also included patients, caregivers and clinicians in
51 the final prioritisation process to establish the top 10 research priorities for MNYES.
52
53
54
55
56
57
58
59
60 Furthermore, there were observers representing supporting organisations and relevant

1
2
3 charitable organisations during the final workshop. All Steering Group members were invited
4 to contribute to the dissemination of the surveys; the information shared by this PSP was
5 developed with members from all stakeholder groups. All PSP steering group members were
6 invited to contribute to the article describing the findings and one of them indeed contributed
7 as a co-author.
8
9
10
11
12
13
14
15
16

17 Results

18
19
20 The process is shown in the project flowdiagram presented in Figure 1 below.

21
22
23 - Insert **Figure 1. Flow diagram of MNYES question prioritisation processes** –
24
25
26

27 *First survey*

28
29 The initial survey (June 2020 - January 2021) asked patients, caregivers and healthcare
30 professionals to indicate their priorities for future research related to MNYES (27). There were
31 705 respondents who accessed the initial survey; 443 provided at least one question or
32 statement. Respondents were 77% female, 86% white. Data from the 2011 census show that
33 51% of the England and Wales population were female (28) and 86% of the same population
34 were White (29). 68% of the participants were patients or caregivers as reported in Table 2
35 (Supplementary File 1).
36
37
38
39
40
41
42

43 The information specialists (DV and JS) and PSP lead (CFC), grouped similar or duplicate
44 questions into 5 domains, generating 96 draft summary questions on aetiology, diagnosis,
45 health care services, treatment, outcomes, prognosis, and other. Those 96 draft questions
46 were reviewed by small groups of PSP Steering Group members that comprised clinicians,
47 patients and caregivers. Further consolidations were made resulting in 46 summary questions
48 which were reviewed again and signed off at a meeting of the whole PSP Steering Group. A
49 document illustrating this is available on the JLA website (30). Of these 46 questions, 22%
50 related to aetiology, 24% to health and clinical services, 15% to diagnosis, 24% to the
51 treatment of MNYES, and 15% to outcomes. The proportion of questions posed by stakeholder
52 groups, organised by topic, is shown in Figure S1 (Supplementary File 1).
53
54
55
56
57
58
59
60

Evidence check

The 46 summary questions were checked against published systematic reviews and clinical guidelines. We found that none of the 46 summary questions had been fully answered by previous research; some questions had been answered for specific symptoms, but not comprehensively across all MNYES symptoms. At a subsequent meeting, the Steering Group reviewed the 46 summary questions in relation to the original questions and statements from which they derived. This resulted in minor changes to the wording of these 46 questions which were then included in the interim prioritisation survey.

Interim survey

This online survey was completed by 270 participants from across the UK. Patients and caregivers made up 74% of the participants. Demographic information is shown in Table 2 (Supplementary File 1).

Final priority setting workshop

The final priority setting workshop was conducted remotely over two days. In total, 25 people participated in the workshop sessions; four JLA advisors facilitated the subgroups, eight people observed and one person provided technical support. Participants included 11 people with MNYES or caregivers, and 14 healthcare professionals representing psychiatry, general practice, stroke, neurology, physiotherapy, psychology, occupational therapy and gastroenterology. The final top 10 research priorities were agreed by consensus between all the participants as listed in Figure 2. They were placed on the James Lind Alliance Website (31).

- Insert **Figure 2. Top 10 research priorities** -

The research priorities which were ranked 11 – 17 are also listed on the JLA website (31) and in Box 2 (Supplementary File 1).

Discussion

Summary of the results

In this study, we used the JLA Priority Setting Partnership processes to identify the top 10 unanswered research questions for MNYES. We utilised the collective perspectives of patients,

1
2
3 caregivers, and clinicians and focused on areas where up-to-date, reliable research evidence
4 is lacking. This process was supported by charitable and professional organisations across the
5 United Kingdom. The study highlighted the paucity of evidence-driven practice in MNYES care
6 since none of the 46 research questions gathered from our survey have been previously
7 answered by level I evidence. Based on the extensive discussions during the meetings, the
8 following major themes emerged from the top 10 unanswered research questions.
9
10
11
12
13

14 THEME 1: TREATMENT

15
16 *What are the most effective treatment strategies for different symptoms of MNYES?*

17
18 *How can the most appropriate treatment be selected, dependent on different MNYES*
19 *symptoms, that a person with MNYES is most likely to benefit from?*

20
21 This pertains to all potential treatment strategies (for example: pharmacological,
22 psychological, physical, or collaboration models) to help manage or alleviate any MNYES or
23 combination of symptoms, such as pain, fatigue, dizziness, functional neurological disorder,
24 bowel symptoms, palpitations and syncope. It also focuses on the best ways to match people
25 who experience specific MNYES with the treatments that are most likely to benefit them,
26 personalising treatment based on diagnostic factors such as a history of trauma, biomarkers
27 or treatment needs.
28

29 Given the high unmet clinical need and the heterogeneity of MNYES, it is no surprise that this
30 is considered an important research priority. Interestingly, treatment and personalised
31 treatment were also research priority identified by the Delphi study conducted amongst
32 experts in the field on behalf of the European Association of Psychosomatic Medicine (17);
33 they can therefore be considered widely supported research priorities in this field.
34
35
36
37
38
39
40
41
42

43 THEME 2: THE ROLE OF CLINICIANS

44
45 *How can clinicians collaborate effectively to form the most appropriate care pathway and*
46 *service model to offer assessment and treatment for patients with MNYES?*

47
48 *What are the most effective methods for training clinicians to diagnose and treat their patients*
49 *with MNYES with compassion, empathy and respect?*

50
51 *What are the most effective ways to support patients with MNYES and their carers to live with*
52 *their symptoms?*

53
54 *What strategies are effective at promoting awareness and up to date clinical knowledge about*
55 *MNYES amongst healthcare professionals?*
56
57
58
59
60

1
2
3 Four of the ten research priorities involve the role of the clinicians in the diagnostic and
4 treatment process, an indicator of the high relevance of this theme. Many different clinicians
5 provide diagnostic assessments to people with MNYES, or are sought to provide treatment to
6 them. The focus here is on finding the best ways for clinicians to collaborate, forming an
7 appropriate care pathway to support people with MNYES. These could be psychiatric
8 consultation models, multi-disciplinary team models, collaborative care models or other
9 integrated care pathways. There is a focus on communication which acknowledges the
10 perspective and concerns of the person experiencing MNYES. Another priority focuses on
11 identifying options for supporting people with MNYES and their caregivers, such as for
12 example shared decision making regarding treatment options; coping with symptoms; and
13 rehabilitation approaches. Another priority emphasises strategies to consistently and
14 effectively ensure that clinicians know the most up-to-date information about MNYES and let
15 care reflect current evidence. Given the existing knowledge gaps, this is considered an
16 important priority.

THEME 3: SYMPTOMS AND OUTCOMES

30 *What outcomes matter most to patients with MNYES?*

31 *What symptoms are commonly reported by people with MNYES and what links them?*

32 *What factors affect outcomes for MNYES?*

33 Some research priorities mention the patient perspective explicitly. Based upon the survey
34 answers, outcomes relevant for patients may include but are not limited to: symptom
35 reduction, changes in biomarkers; improvements in abilities to undertake daily tasks;
36 improvements in quality of life; individual goal achievements; or improvements in functioning.
37 The list of MNYES is extensive, and people who experience these symptoms often report living
38 with multiple MNYES. One priority aims to identify the most commonly co-occurring
39 symptoms and their underlying factors and mechanisms. Given the number of questions that
40 pertained to aetiological factors and the fact that the related uncertainty plays a role in the
41 choice of MNYES as a term, this can be considered an important research theme. Factors
42 affecting outcome should include biomarkers, psychological factors, health services, how
43 information is shared between clinicians and people experiencing MNYES, and social factors
44 such as poverty, education, family dysfunction or domestic abuse, trauma and work
45 environment.

THEME 4: RECOVERY

Which self-management techniques are effective in MNYES?

This priority concerns the strategies that people experiencing MNYES can use separately from clinic visits. The focus is to identify the most effective self-administered therapies for managing or alleviating MNYES, used separately or in combination with formal treatment. Examples of self-management approaches include education, exercise, and dietary changes. It should be noted that this research priority, in contrast to ones covered by the other themes, considers that recovery in MNYES can occur, either by recovery of symptoms or by personal recovery with ongoing symptomatology. Recovery of symptomatology is referred to as clinical recovery and is covered by the other themes. Recovery whilst symptoms are ongoing is called personal recovery (32), meaning that despite symptoms being present, the function has to some extent been restored through treatment, self-management or disability management. In mental health research and clinical practice, especially concerning psychotic conditions, personal recovery is a construct that has increasingly gained attention over the past thirty years; however, the term has not been used in MNYES. Generally, both in clinical practice and in research, the emphasis seems to have been to either attempt to attain clinical recovery or send the patient home with the message that MNYES cannot be cured and that one would have to live with the condition. This dichotomy has fed into the ongoing controversy about how to approach MNYES. This polarising stance is unhelpful. It could provide an essential contribution to further research development in this domain, alongside the research priorities summarised in the other themes. Developing this research priority would require embracing the concept that personal recovery refers to an individual process of adaptation and development where one does not simply return to but instead grows beyond the premorbid self (33), emphasising the patient perspective.

Strengths of the study

This is the first study establishing research priorities for MNYES from the perspective of patients, caregivers and clinicians. The study follows the JLA method which offers a unique, and internationally highly regarded, approach to setting research priorities through an equal partnership between patients, carers and healthcare professionals. The priorities represent a "snapshot in time" of the areas which matter the most to patient, caregivers and clinicians. It is reproducible (the Handbook and all relevant materials are available on the JLA website for

1
2
3 this purpose) and the method can be used to "refresh" priorities at a future date to reflect
4 changes in the management of the condition and patient/carer experiences. The use of this
5 established and transparent James Lind Alliance methodology supports the generalisability of the
6 results and is a strength of this study.
7
8
9

10
11 This is a highly contentious area; however, the research priorities were widely supported by
12 over 400 participants including clinicians from a variety of disciplines, patients with a range of
13 symptoms, caregivers, charitable organisations, and other supporting organisations. Over 700
14 responses were gathered from patients, caregivers and clinicians from an array of medical
15 specialties including primary care, indicating that the priorities were widely supported.
16 Contributions of people from ethnic and gender minority groups and from underserved areas
17 within the PSP Steering Group, surveys and final workshop supports the inclusive nature of
18 this work and indicates these priorities are important to a diverse range of people.
19
20
21
22
23
24
25

26
27 The themes identified in this PSP cover a broad range of ideas, issues and uncertainties; these
28 are outlined in the top 10 research priorities and also reflected in the seven research priorities
29 that did not make the top 10. Research priorities 11, 12 and 17 would link well with theme 3
30 in exploring associations of MNYES with mental health and somatic comorbidity, as well as the
31 development of symptoms over time. Priorities 13 and 14 would fit in theme two, the role of
32 clinicians; 15 and 16 link with theme one, treatment. This suggests that the themes covered
33 by the top 10 priorities are consistent with the other research priorities which were proposed
34 during this priority setting process.
35
36
37
38
39
40
41

42 *Limitations of the study*

43
44
45 When comparing the participants of survey 1 with survey 2, there were 443 participants in
46 survey 1, and 270 in survey 2. The final workshop was attended by 25 people. These are high
47 numbers and certainly adequate for priority setting according to the JLA method. However, as
48 the description of the roles is self-described, the variety of investigative participants remains
49 unclear in some respects. For example, it should be pointed out that in Table 2, 10 people self
50 described as "doctor," and 8 as "other" clinician and they may well have been doctors working
51 in primary care as GPs, or rheumatologists; however, we do not know for sure. Regarding the
52 patients, they would state their self-described main symptom as "pain" in approximately half
53 of the cases; from their answers to the open questions, it emerged that this often would refer
54
55
56
57
58
59
60

1
2
3 to musculo-skeletal or rheumatological pain. So, while the exact variety is uncertain, however,
4 it is unlikely that this contributed to priorities in the final list of issues related to MNYES.
5
6
7

8 The study provides a good overview of research priorities for MYNES in the UK, however given
9 the specific cultural aspects and health care organisation in the UK, the findings may not be
10 generalisable to other countries. A similar PSP is currently being conducted in the Netherlands
11 and may shed light on research priorities in a non-NHS healthcare setting. This will provide an
12 opportunity to compare and evaluate the generalisability of these findings and the influence
13 of different cultural and healthcare settings. Future research highlighting the situation in Low
14 and Middle Income Countries would be beneficial. The results of this PSP will enable funders
15 to prioritise research in MNYES as outlined here and hopefully will provide new, much needed
16 knowledge in this domain.
17
18
19
20
21
22
23
24

25 **Conclusion**

26
27
28
29
30

31 MYNES are common and reflect a high level of unmet clinical need. Incorporating patient-
32 driven research in MNYES research can allow researchers to better address the complex care
33 needs of people with MNYES. The most important aspect of this priority setting exercise was
34 strengthening the relationship between patients, caregivers, clinicians and support
35 organisations and generating a list of priorities valued by these stakeholders, which we hope
36 will guide future research.
37
38
39
40
41
42

43 We have identified the top 10 research priorities in MNYES using the rigorous JLA priority
44 setting method that may open the door to further research addressing the knowledge gaps
45 and controversies in this area, and hopefully alleviate some of the stigma related to these
46 conditions and the people suffering from MNYES. Identification of these top 10 research
47 priorities is an important first step to generating relevant, impactful research that will
48 ultimately improve the lives of people with MNYES.
49
50
51
52
53
54
55
56

57 **Acknowledgements:** The Steering Group would like to thank to all the patients, caregivers,
58 families, friends, healthcare professionals and supporting organisations who contributed to
59
60

1
2
3
4 this work. In addition to the co-authors, Philippa Bolton, Sally Brabyn, Tracey Cunningham,
5
6 Rosie Evans, Miriam Lomas, Margot Metz, Chris Price, Annie Shaw, Scott Spain, Lesley Spain
7
8 were members of the PSP Steering Group. The following people who attended the final
9
10 workshop for priority setting agreed to be named: Anna Burneika, Kit Byatt, Phoebe Cole,
11
12 Tracey Cunningham, Mark Edwards, Rosie Evans, Eve Fazakerley, Jennifer Gilligan, Stephanie
13
14 Johnston, Claire Jones, Hilary Lewis, Joseph Littlewood, Miriam Lomas, Andrew Moriarty,
15
16 Elizabeth Paul, Emma Reinhold, Keziah Reiss, James Sampford, Annie Shaw, Gemma Smith,
17
18 Martin Veysey, Juliet Wilson, Jennifer Wilson.

19
20 **Ethics statement:** Ethical approval was not required as confirmed by the research governance
21
22 board of the Department of Health Sciences of the University of York.

23 24 25 **Data availability statement**

26
27 Data relevant to the study are included in the article or on the James Lind Alliance website
28
29 ([https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/)
30
31 [symptoms/](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/)) and linked University of York website
32
33 (<https://www.york.ac.uk/healthsciences/research/mental-health/projects/mnyes/>).

34 35 **Conflicts of interest statement**

36
37 The authors have no conflicts of interest to declare.

38 39 **Author statement**

40
41
42 CFC was the project lead, instigating the application to the JLA. CFC, NS, JFS and JG organised
43
44 the Steering Group meetings. JFS and DV designed and built the surveys, analysed the data,
45
46 and conducted the evidence check under supervision of JG and CFC. CFC, JFS, and NS wrote
47
48 the majority of the final manuscript. JG (JLA Chair) chaired all the meetings, led the consensus
49
50 workshop and ensured compliance with methodology throughout. NS and JFS took minutes
51
52 for Steering Group meetings, built and distributed surveys, and organised the consensus
53
54 workshop. JFS conducted the searches for the evidence check and screened the results with
55
56 CFC. Members of the Steering Group CFC, JFS, ME, NG, JG, SH, AK, ASM, PP, JS, NS, IE, DV, PB,
57
58 SB, TC, RE, ML, MM, CP, AS, SS, LS all attended a majority of the meetings, agreed the initial
59
60 protocol and the evidence check protocol, piloted and signed off the surveys and disseminated

1
2
3 them, checked the raw questions against the indicative ones, reviewed the evidence check
4 results and agreed the final longlist. TC, ME, JG, ML, ASM, JFS, and AS were present at the final
5 consensus workshop. All authors reviewed and contributed to the final manuscript and
6 approved it prior to submission.
7
8
9

10 **Funding**

11 This work was part-funded by the Wellcome Trust [ref: 204829] from the
12 overall Wellcome Trust ISSF award through the Centre for Future Health (CFH) at the University
13 of York.
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Or peer review only

References

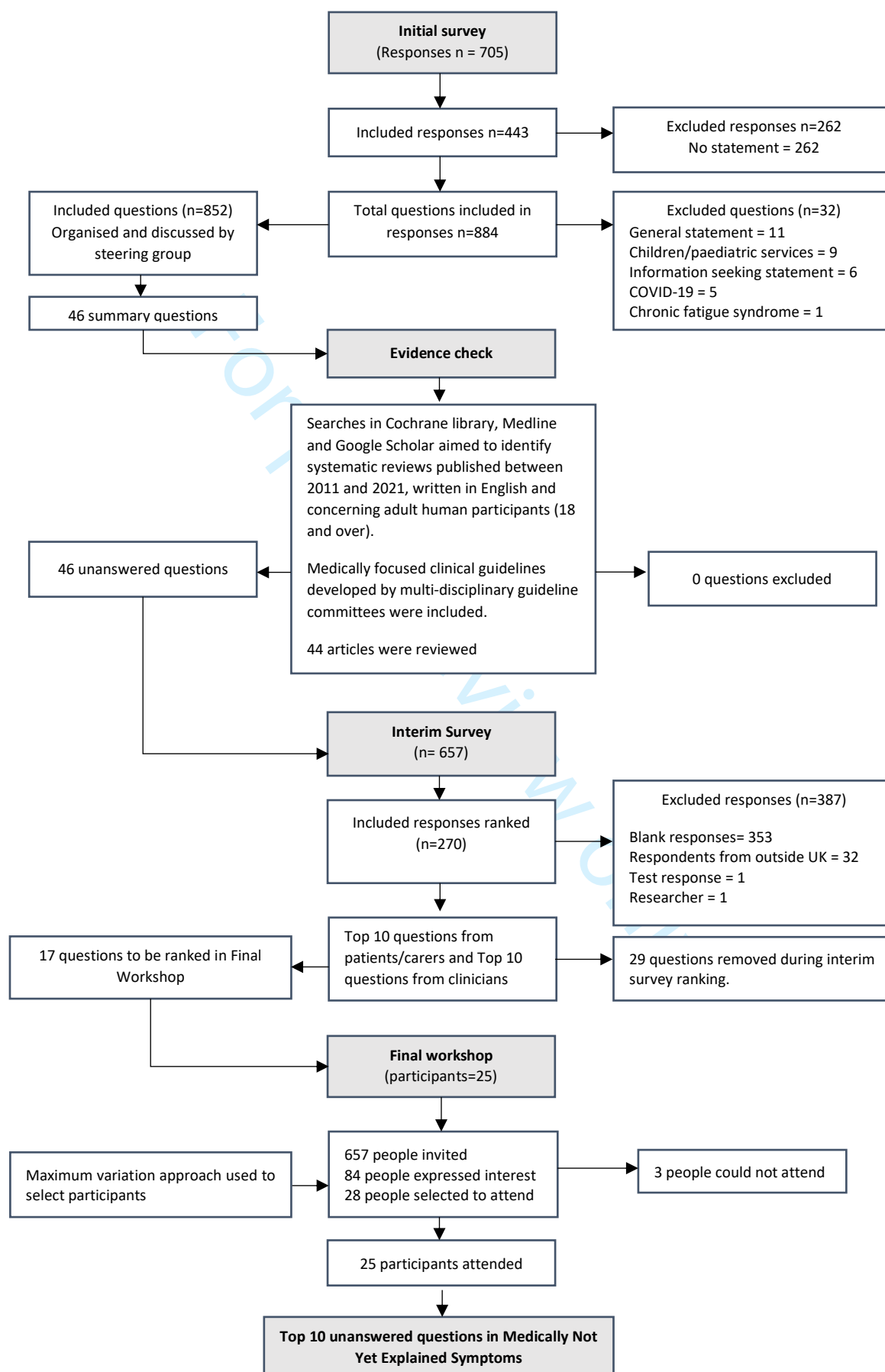
1. Patel M, James K, Moss-Morris R, Husain M, Ashworth M, Frank P, Ferreira N, Mosweu I, McCrone P, Hotopf M, David A, Landau S, Chalder T. Persistent physical symptoms reduction intervention: a system change and evaluation (PRINCE)-integrated GP care for persistent physical symptoms: protocol for a feasibility and cluster randomised waiting list, controlled trial. *BMJ Open*. 2019 Jul 23;9(7):e025513. doi: 10.1136/bmjopen-2018-025513.
2. Hoedeman R, Blankenstein AH, van der Feltz-Cornelis CM, Krol B, Stewart R, Groothoff JW. Consultation letters for medically unexplained physical symptoms in primary care. *Cochrane Database of Systematic Reviews*. 2010(12).
3. Van Hemert AM, Hengeveld MW, Bolk JH, Rooijmans HG, Vandenbroucke JP. Psychiatric disorders in relation to medical illness among patients of a general medical outpatient clinic. *Psychological medicine*. 1993;23(1):167-73.
4. Kirmayer LJ, Groleau D, Looper KJ, Dao MD. Explaining medically unexplained symptoms. *The Canadian journal of psychiatry*. 2004;49(10):663-72.
5. van der Leeuw G, Gerrits MJ, Terluin B, Numans ME, van der Feltz-Cornelis CM, van der Horst HE, Penninx BW, van Marwijk HW. The association between somatization and disability in primary care patients. *J Psychosom Res*. 2015 Aug;79(2):117-22. doi: 10.1016/j.jpsychores.2015.03.001. Epub 2015 Mar 11. PMID: 25824596.
6. den Boeft M, Twisk JW, Hoekstra T, Terluin B, Penninx BW, van der Wouden JC, Numans ME, van der Horst HE. Medically unexplained physical symptoms and work functioning over 2 years: their association and the influence of depressive and anxiety disorders and job characteristics. *BMC Fam Pract*. 2016 Apr 14;17:46. doi: 10.1186/s12875-016-0443-x. PMID: 27079909; PMCID: PMC4831095.
7. Hoedeman R, Krol B, Blankenstein N, Koopmans PC, Groothoff JW. Severe MUPS in a sick-listed population: a cross-sectional study on prevalence, recognition, psychiatric co-morbidity and impairment. *BMC Public Health*. 2009 Dec 1;9:440. doi: 10.1186/1471-2458-9-440. PMID: 19951415; PMCID: PMC2793259.
8. Escobar JI, Waitzkin H, Silver RC, Gara M, Holman A. Abridged somatization: a study in primary care. *Psychosom Med*. 1998 Jul-Aug;60(4):466-72. doi: 10.1097/00006842-199807000-00012. PMID: 9710292.
9. Salmon P, Peters S, Stanley I. Patients' perceptions of medical explanations for somatisation disorders: qualitative analysis. *Bmj*. 1999;318(7180):372-6.
10. Tolchin B, Tolchin DW, Stein MA. How Should Clinicians Minimize Harms and Maximize Benefits When Diagnosing and Treating Disorders Without Biomarkers? *AMA journal of ethics*. 2021;23(7):530-6.
11. Hatcher S, Arroll B. Assessment and management of medically unexplained symptoms. *Bmj*. 2008;336(7653):1124-8.
12. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, et al. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". *Bmj*. 2002;325(7378):1449-50.
13. Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. *Journal of Neurology, Neurosurgery & Psychiatry*. 2000;68(2):207-10.

14. Reid S, Wessely S, Crayford T, Hotopf M. Frequent attenders with medically unexplained symptoms: service use and costs in secondary care. *The British Journal of Psychiatry*. 2002;180(3):248-53.
15. Nimnuan C, Hotopf M, Wessely S. Medically unexplained symptoms: an epidemiological study in seven specialities. *Journal of psychosomatic research*. 2001;51(1):361-7.
16. James Lind Alliance. *The James Lind Alliance Guidebook Version 7*. 2018.
17. van der Feltz-Cornelis CM, Elfeddali I, Werneke U, Malt UF, Van den Bergh O, Schaefer R, et al. A European research agenda for somatic symptom disorders, bodily distress disorders, and functional disorders: results of an estimate-talk-estimate Delphi expert study. *Frontiers in psychiatry*. 2018;9:151.
18. Gill PJ, Cartwright E. *Partnering with patients in the production of evidence*. Royal Society of Medicine; 2021.
19. James Lind Alliance. *Priority Setting Partnership: Medically Not Yet Explained Symptoms 2021* [Available from: <https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/>].
20. Kellner R & Sheffield BF. The one-week prevalence of symptoms in neurotic patients and normals. *Am J Psychiatry* 1973;50:734-41
21. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, VA. 2013.
22. World Health Organization. *International Classification of Diseases-11 (ICD-11)2019*.
23. van der Feltz-Cornelis CM, Elfeddali I, Werneke U, Malt UF, Omer Van den Bergh O, Schaefer R, Kop WJ, Lobo A, Sharpe M, Söllner W, Löwe B. A European Research Agenda for Somatic Symptom Disorders, Bodily Distress Disorders, and Functional Disorders: Results of an Estimate-Talk-Estimate Delphi Expert Study. *Front Psychiatry* 2018 May 14;9:151. DOI: [10.3389/fpsy.2018.00151](https://doi.org/10.3389/fpsy.2018.00151)
24. Ding JM, Kanaan RA. What should we say to patients with unexplained neurological symptoms? How explanation affects offence. *J Psychosom Res*. 2016 Dec;91:55-60. doi: 10.1016/j.jpsychores.2016.10.012.
25. Stone J, Wojcik W, Durrance D, Carson A, Lewis S, MacKenzie L, Warlow CP, Sharpe M. What should we say to patients with symptoms unexplained by disease? The "number needed to offend". *BMJ*. 2002 Dec 21;325(7378):1449-50.
26. Van der Feltz-Cornelis C, Van Dyck R. The notion of somatization: an artefact of the conceptualization of body and mind. *Psychotherapy and psychosomatics*. 1997;66(3):117-27.
27. University of York. *Research priority setting for Medically Not Yet Explained Symptoms (MNYES) in an Anglo-Dutch partnership with the James Lind Alliance 2021* [Available from: <https://www.york.ac.uk/healthsciences/research/mental-health/projects/mnyes/>].
28. GOV.UK. *Male and female populations 2018* [Available from: <https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest>].
29. GOV.UK. *Population of England and Wales 2018* [Available from: <https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/national-and-regional-populations/population-of-england-and-wales/latest>].
30. <https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/downloads/medically-not-yet-explained-symptoms-psp-all-questions-data.doc>

- 1
2
3 31. James Lind Alliance. Medically Not Yet Explained Symptoms Top 10 priorities 2021
4 [Available from: [https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/top-10-priorities.htm)
5 [explained-symptoms/top-10-priorities.htm](https://www.jla.nihr.ac.uk/priority-setting-partnerships/medically-not-yet-explained-symptoms/top-10-priorities.htm).
6
7 32. Slade M, Amering M, Oades L. Recovery: an international perspective. *Epidemiology*
8 *and Psychiatric Sciences*. 2008;17(2):128-37.
9
10 33. Slade M. *Personal recovery and mental illness: A guide for mental health*
11 *professionals*: Cambridge University Press; 2009.
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Figure 1: Flow diagram of MNYES question prioritisation processes



Top-10 Research Priorities Medically Not Yet Explained Symptoms (MNYES)

1. What are the most effective treatment strategies for different symptoms of MNYES?
2. How can clinicians collaborate effectively to form the most appropriate care pathway and service model to offer assessment and treatment for patients with MNYES?
3. What are the most effective methods for training clinicians to diagnose and treat their patients with MNYES with compassion, empathy and respect?
4. What outcomes matter most to patients with MNYES?
5. What are the most effective ways to support patients with MNYES and their carers to live with their symptoms?
6. How can the most appropriate treatment be selected, dependent on different MNYES symptoms, that a person with MNYES is most likely to benefit from?
7. What symptoms are commonly reported by people with MNYES and what links them?
8. What factors affect outcomes for MNYES?
9. What strategies are effective at promoting awareness and up to date clinical knowledge about MNYES amongst healthcare professionals?
10. Which self-management techniques are effective in MNYES?



UNIVERSITY
of York



James
Lind
Alliance
Priority Setting Partnerships



Figure 2: Top 10 Research Priorities for Medically Not Yet Explained Symptoms

Appendix

Key words included in evidence check searches

Symptom terms	Publication focus
Medically not yet explained symptoms	Guideline
Medically unexplained symptoms (MUS)	Mechanism
Persistent Somatic Symptoms	Pathology
Somatic Symptom and Related Disorders (SSRD)	Development
Chronic pain	Assessment
Unexplained pain	Diagnosis
Fatigue	Investigation
Unexplained fatigue	Treatment
Conversion disorder	Management
Neurological conversion symptoms	Healthcare service
Functional neurological disorder	Patient care
Functional symptoms	Care pathway
Functional neurological symptom	Outcome
Functional cognitive symptom	Prognosis
Functional weakness	
Dissociative disorders	
Dissociative neurological disorder	
Dissociative syncope	
Unexplained dizziness	
Fibromyalgia	
Irritable bowel syndrome (IBS)	
Nonepileptic seizures	

Acquiring funding, international aspect, and establishing support by the James Lind Alliance

Funding for the study was acquired by the PSP lead (CFC) in November 2019. Part of the collaboration was envisioned to support setting up a parallel PSP Steering Group to explore the same question in the Netherlands, in order to have an international perspective. This article focuses on the description of the process in the UK. Support by the James Lind Alliance Priority Setting Partnership was secured in December 2019 and a JLA Advisor (JG) appointed to the project.

Box 1: Steering group composition

Clinicians: One general practitioner (GP); consultants in cardiology (1), neurology (1), endocrinology (1), clinical liaison psychiatry (3) and rheumatology (1) one stroke physician, a clinical psychologist and one physiotherapist.

Patients and caregivers: Four patients with a variety of pain, fatigue and functional neurological symptoms; one caregiver;

Other: Two information specialists and two project coordinators to facilitate the PSP working group. They prepared meeting documents, surveys, supported recruitment, completed evidence checking and analysis but did not engage in the priority setting.

The consultative process

The study followed several steps in order to establish research priorities, using a mix of online surveys and a priority setting workshop. We created a website to host the surveys (27) and sent out the website link for our partner organisations to distribute within their networks.

Gathering uncertainties

The initial survey was launched between June 2020 and January 2021 and asked patients, caregivers and healthcare professionals to indicate their priorities for future research related to MNYES (27). We promoted the survey through partner organisations' websites, and their social media platforms. In addition, the clinics of clinicians involved in the PSP Steering Group distributed the QR code to their patients. We sent out email reminders to members of professional associations, sent Twitter invitations and placed the survey on the University of York and JLA websites. Distribution of the survey was supported by the members of the PSP, several associations, networks, networking groups and charities. An overview of supporting

organisations is shown in Table 1, below. Some of them collaborated because they found that patients with unexplained symptoms often visit their websites and related specialists to assess their symptoms.

Table 1: Supporting organisations who have promoted this work

Charities	Professional networks	Other networks and Social media groups
British Thyroid Foundation	Allied Health Professional FND Networking groups	INCLUDE (University of York Disability Network)
Fibromyalgia Association UK	Clinical special interest groups	James Lind Alliance
FND Hope	Liaison psychiatry networks	People who have shared information with their friends and family
Graham Hughes International	Royal College of Psychiatrists	Individuals and organisations active on twitter
Guts UK		Special interest and support groups on facebook
Health Unlocked		
Pain UK		
POTS-UK		

We targeted patients with MNYES such as pain, bowel problems, functional neurological symptoms, or with diagnoses which comprise a set of symptoms which are medically unexplained such as postural orthostatic tachycardia syndrome (PoTS); their caregivers; and the clinicians who treat them, to participate. Survey respondents were asked whether they had experienced MYNES, in which case they were to select their symptoms from a list, or were healthcare professionals, in which case they were asked to state their profession. Anonymity was preserved in all cases accordance with General Data Protection regulations.

Data analysis and verifying uncertainties

We downloaded the online survey results through Qualtrics and exported them into Microsoft Excel. The responses to this survey were organised into summary questions and these were then checked to make sure that they had not already been answered by research.⁽¹⁶⁾ Our health information specialists (DV and JS) and PSP lead (CFC) grouped the responses into themes and each was analysed in small groups by 3 or 4 members of the Steering Group; one member of each small group was a patient or caregiver and the other members were healthcare professionals. Summary questions were developed, which encapsulated groupings of similar responses to the survey. Responses were removed if they were outside the scope

1
2
3 of the survey or general statements which would be unanswerable by research. The outputs
4 from the small group discussions were reviewed at a subsequent meeting of the full PSP
5 Steering Group.
6
7

8
9 One health information specialist (JS) checked each in-scope question with existing clinical
10 guidelines published by multi-disciplinary guideline committees and systematic reviews, to
11 ensure that the question had not been already fully answered with high-level evidence.
12
13 44 articles were shortlisted from searches conducted in the Cochrane Library, Medline and
14 Google Scholar; key words for the search used are included in the appendix. Reference lists
15 of these studies were also reviewed to identify further relevant references. Articles published
16 between 2011 and 2021 were considered relevant by the Steering Group. Each question was
17 coded to indicate whether it was 'answered'; 'partially answered' or 'unanswered' through
18 the research literature.
19
20
21
22
23
24

25 26 *Interim priority setting*

27
28 Between May and July 2021, the second online survey asked participants to select their top
29 10 priorities from the list of uncertainties presented (19). The second survey was launched
30 independently from the first survey. Questions were presented in a random order to each
31 survey participant to reduce bias. The priorities of patients and caregivers and the priorities
32 from healthcare professionals were ranked separately. The top 10 priorities identified by
33 patients and caregivers were then combined with the top 10 priorities from healthcare
34 professionals to create a shortlist of 17 priorities as there were 3 overlapping priorities.
35
36
37
38
39
40

41 *Final workshop*

42
43 The 17 top ranked questions were taken forward to the final priority setting consensus
44 meeting that took place virtually on 16th and 17th September 2021. We invited volunteers
45 from supporting organisations, two of whom joined the meeting. We also invited individuals
46 who took part in the online survey to participate in the meeting. 25 participants took part in
47 the workshop comprising 10 patients with a variety of MNYES symptoms, 1 caregiver, and 14
48 health care professionals. The workshop participants were divided into four groups, each with
49 a balanced mix of patients/caregivers and clinicians. Each group also had observers who did
50 not participate in the process, to fulfill the requirement of transparency of the JLA process.
51 Each group was asked to rank the uncertainties through group discussions using the modified
52
53
54
55
56
57
58
59
60

nominal group technique facilitated by an independent JLA Advisor. Each participant was provided with a printed and electronic copy of the different 'unanswered' questions, and the JLA Advisor leading each group shared an image containing the unanswered questions to aid the group in ranking the 17 uncertainties. The rankings from the four groups were combined and all the workshop participants then came together to discuss these rankings. Similarities and differences between the group rankings were highlighted by the JLA facilitator leading the workshop (JG) and participants were invited to comment on the initial combined ranking. Following this, participants were reallocated into four new groups, maintaining the representation of patients/caregivers and clinicians within each group, to consider the combined group ranking from the previous session. During this session, there was a specific focus placed on the ordering of uncertainties across the top 17 unanswered questions. The rankings from each of the four groups were once again combined and were presented to the whole group for discussion. By the end of the priority setting meeting, we reached consensus on the top 10 UK research priorities for MNYES.

The respondents were 77% female, 86% white; data from the 2011 census show that 51% of the England and Wales population were female (28) and 86% of the same population were White (29). Of the 884 statements, 852 were in scope and 32 out-of-scope. The out-of-scope submissions included general statements (N = 11), children/paediatric services (N = 9), information seeking statements (N = 6), or pertaining to COVID-19 (N = 5) and chronic fatigue syndrome (N = 1).

Table 2: Participant demographic information

	Initial Survey (n=443)	Interim Survey (n=270)	Final Workshop (n=25)***
Gender (%)			
Male	89 (20)	33 (12)	6 (24)
Female	339 (77)	227 (84)	18 (72)
Other	14*(3)	2** (1)	1 (4)
Ethnicity (%)			
Asian/ Asian British	12 (3)	5 (2)	-
Arab	1 (<1)	-	-
Black/ Black British	3 (1)	2 (1)	-
Mixed/ Multiple	7 (2)	7 (2)	-
White	381 (86)	242 (90)	25 (100)
Other	17 (4)	4 (1)	-
Age, mean (SD)	47.65 (12.15)	42.55 (13.26)	39.29 (13.74)
Experience (%)			
Patient	288 (65)	183 (68)	10 (40)

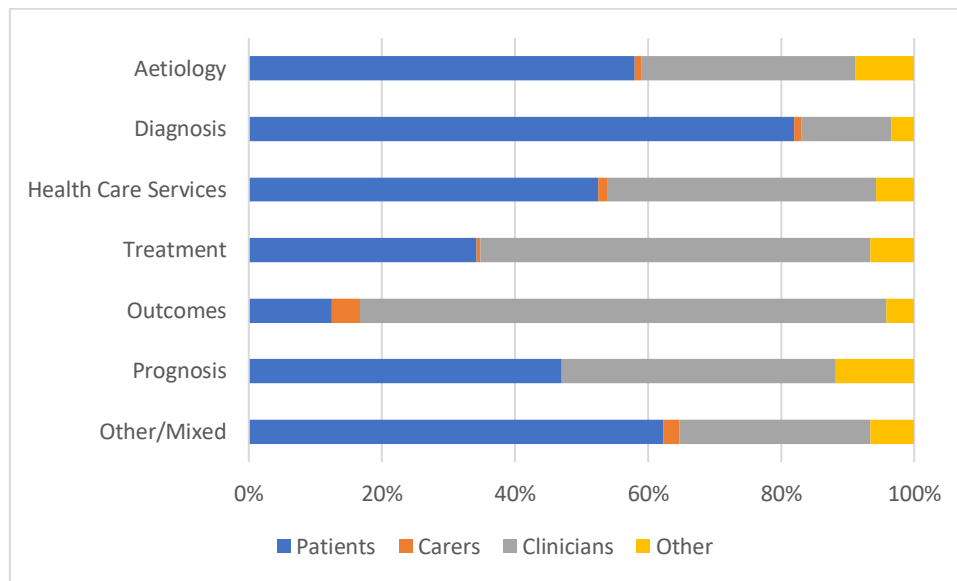
Caregiver	13 (3)	17 (6)	1 (4)
Clinician	121 (27)	65 (24)	14 (56)
Other	21 (5)	5 (2)	-
MNYES symptoms as self-described(%)			
Pain	219 (49)	147 (54)	6 (24)
Fatigue	236 (53)	146 (54)	8 (32)
Dizziness	156 (35)	91 (34)	5 (20)
Heart palpitations/fainting	134 (30)	83 (31)	5 (20)
Stomach/bowel problems	197 (44)	119 (44)	5 (20)
Problems with movement (tremors, shakes, weakness)	133 (30)	114 (42)	6 (24)
Unexplained blackouts, seizures, sudden loss of awareness	54 (12)	60 (22)	3 (12)
Other (e.g. brain fog, eye and skin problems)	126 (28)	44 (16)	4 (16)
Age when first developed MNYES, mean (SD)	31.77 (15.08)	29.89 (15.13)	-
Clinical role as self-described			
Cardiologist	-	1 (<1)	-
Consultant in emergency medicine	-	1 (<1)	-
Doctor	10 (2)	2 (1)	-
Gastroenterologist	-	-	1 (4)
GP	4 (1)	5 (2)	3 (12)
Occupational therapist	9 (2)	6 (2)	1 (4)
Neurologist	9 (2)	3 (1)	1 (4)
Neuropsychiatrist	1 (<1)	1 (<1)	-
Neuropsychologist	-	1 (<1)	-
Nurse	3 (1)	2 (1)	-
Physiotherapist	16 (4)	8 (3)	2 (8)
Psychiatrist	44 (10)	18 (7)	4 (16)
Psychologist	9 (2)	5 (2)	1 (4)
Psychotherapist	3 (1)	2 (1)	-
Other	8 (2)	1 (1)	-
Rheumatologist	1 (<1)	1 (<1)	-
Speech and language therapist	1 (<1)	4 (1)	-
Stroke specialist	-	-	1 (4)
Assistant psychologist/Support worker	3 (1)	2 (1)	-

*14 prefer not to say **1 non-binary,

Not mandatory and therefore not always provided

Figure S1 shows the proportion of original questions from each topic, which were posed by patients, caregivers, clinicians and others, who were generally individuals who met the criteria for more than one role. As can be seen, patients preferred aetiology and diagnostic questions, while clinicians emphasized treatment and outcomes. Health care services and prognosis were divided equally between patients or caregivers and clinicians.

Figure S1: The proportion of questions per domain suggested by patients, caregivers, clinicians and other



227 of the 264 (86%) people who reported gender were female and 242 of the 260 (93.1%) people who reported ethnicity, were white. The 17 resulting priorities were shortlisted for consideration at the final priority setting consensus workshop.

Box 2: research priority 11 through 17.

11. What is the relationship between mental health problems and MNYES?
12. What is the relationship over time between MNYES and known medical conditions and does that suggest some shared pathological process?
13. What is the best practice to offer optimal care for patients with MNYES?
14. What are current clinical attitudes and levels of knowledge about MNYES?
15. What are the most effective physical treatments for different symptoms of MNYES?
16. What are the most effective psychological treatments for different symptoms of MNYES?
17. Why do symptoms of MNYES fluctuate?