Multiple chemical sensitivity scoping review protocol: overview of research and MCS construct

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ABSTRACT

Introduction  Multiple chemical sensitivity (MCS) has been characterised by reported adverse responses to environmental exposures of common chemical agents (eg, perfumes, paint, cleaning products and other inhaled or ingested agents) in low doses considered non-toxic for the general population. There is currently no consensus on whether MCS can be established as a distinct disorder.

Methods and analysis  The scoping review of the literature will be guided by five questions: How is MCS defined and which diagnostic criteria have been proposed? What methods are used to report prevalence and incidence estimates of MCS? What are the characteristics of the body of scientific evidence that addresses whether MCS is a distinct disorder or syndrome? What underlying mechanisms for MCS have been proposed in the scientific literature? Which treatment and management approaches for MCS have been evaluated in empirical research studies? We will conduct a comprehensive search in 14 research databases. Citation screening will be supported by machine learning algorithms. Two independent reviewers will assess eligibility of full-text publications against prespecified criteria. Data abstraction will support concise evidence tables. A formal consultation exercise will elicit input regarding the review results and presentation. The existing research evidence will be documented in a user-friendly visualisation in the format of an evidence map.

Ethics and dissemination  Determined to be exempt from review (UP-22-00516). Results will be disseminated through a journal manuscript and data will be publicly accessible through an online data repository.

Registration details  The protocol is registered in Open Science Framework (osf.io/4a3wu).

INTRODUCTION

Multiple chemical sensitivity (MCS) has been characterised by reported adverse responses to environmental exposures of common chemical agents in low doses considered non-toxic for the general population. These may be solvents such as paint and cleaning products, odorants such as perfume and scented soaps, air pollutants such as cigarette smoke and smog, or materials such as new furnishings or new carpets. Symptoms are non-specific, involve multiple organ systems, and may include nausea, dizziness, headache, abdominal pain, fatigue and depression, among others.1-3 Responses generalise from the individual to the general population. These responses are not unique to MCS and the lack of consensus, including whether MCS should be considered a distinct disorder, hinders the...
This scoping review was prospectively registered and will be conducted according to established procedures to provide a systematic and transparent exploration of the literature. The findings of the scoping review will be presented as an evidence map. Evidence maps are an evidence synthesis tool that provide a visualisation of a large evidence base to provide readers with a concise overview. They allow a visual and user-friendly research overview suitable for a large and diverse research field, effectively mapping the existing evidence. The evidence map will document the presence and absence of research on MCS for the five questions guiding the review in a user-friendly format.

Guiding questions

The following review questions will guide the scoping review:
- GQ1: How is MCS defined and which diagnostic criteria have been proposed?
- GQ2: What methods are used to report prevalence and incidence estimates of MCS?
- GQ3: What are the characteristics of the body of scientific evidence that addresses whether MCS is a distinct disorder or syndrome?
- GQ4: What underlying mechanisms for MCS have been proposed in the scientific literature?
- GQ5: Which treatment and management approaches for MCS have been evaluated in empirical research studies?

Review aim

The review will answer the guiding questions with the identified scientific literature in a user-friendly format. A systematic evidence map will provide a visualisation of the existing evidence and research gaps.

METHODS AND ANALYSIS

The review is registered in the Open Science Framework (OSF). The scoping review will follow the steps for scoping reviews outlined by Arksey and Malloy: stage 1: identifying the research question; stage 2: identifying relevant studies; stage 3: study selection; stage 4: charting the data; stage 5: collating, summarising and reporting the results. In addition, a consultation exercise to inform and validate findings from the scoping review will be conducted. The planned duration is April 2022 to December 2023. The following outlines the steps in detail. The reporting will follow established guidelines.

Search strategy

We will search the international literature on MCS using different taxonomy and nomenclature. Literature searches will be designed, executed and documented by an experienced evidence review centre librarian. The scoping review addresses multiple aspects of MCS, and the search strategy covers multiple databases to ensure that all scientific literature relevant to MCS will be identified.
The use of multiple sources is a key method to minimise selection bias being introduced into the review. We plan on searching the following databases to obtain a diverse set of citations potentially relevant to MCS from different disciplines:

- PubMed (biomedical)
- CINAHL (nursing)
- Embase (biomedical)
- Web of Science (general scientific database)
- Scopus (health sciences)
- PsycINFO (behavioural and social sciences)
- Healthcare Administration Database (public health administration)
- Current Contents Connect (multidisciplinary)
- BIOSIS Citation Index (life sciences)
- Environment Index (environmental research)
- Environmental Science Database
- HERO (Health & Environmental Research Online)
- SciFinder (chemical literature)
- Agricultural & Environmental Science Collection (includes AGRICOLA, environmental research)

The search strategy is shown in online supplemental appendix 1. Content experts provided input regarding individual search terms and databases.

In addition, our review will be informed by existing comprehensive reviews on the topic. Reviews will be systematically identified through the systematic review filter in PubMed and the Cochrane Database of Systematic Review. We will screen the international registry PROSPERO for ongoing efforts that could inform this project during the update search period; currently, the registry includes only two ongoing efforts that address selected aspects of MCS.

For individual guiding questions, we will search additional sources, including selected and prespecified grey literature sources. For definitions and diagnostic criteria (GQ1), we will search the website of global organisations such as the WHO. Searches for prevalence research (GQ2) will reference-mine existing reviews. We will review reports identified in PubMed Health regarding consensus statements on MCS as a distinct disorder (GQ3) and regarding published suggested underlying mechanisms (GQ4). For intervention studies (GQ5), we will search repositories of practice guidelines including G-I-N and the ECRI-maintained guideline database. In addition, we will search the US trial registry clinicaltrials.gov and the International Clinical Trials Registry Platform maintained by the WHO.

In addition, we will reference-mine relevant reviews and included studies and consult with content experts to ensure that all relevant literature has been captured.

**Eligibility criteria and screening**

We will use a PICOTSO (population, intervention/exposure, comparator, outcome, timing, setting and other limiter) framework to structure the eligibility criteria. For each guiding question, we will determine detailed inclusion and exclusion criteria. The criteria, thus far, are as follows:

- **Population:**
  - Publications reporting definitions (GQ1) and studies reporting on the prevalence and incidence (GQ2) of MCS will be limited to those that explicitly state MCS, chemical intolerance or idiopathic environmental intolerance with a reference to chemical sensitivities (rather than electromagnetic sensitivity or other conditions not associated with perceived exposure to chemical agents, solvents, odors, air pollutants or materials). Publications reporting exclusively on the prevalence of individual sick building syndrome symptoms or electromagnetic hypersensitivity will be excluded.
  - Eligible populations for GQ3 and GQ4 will include those that either state MCS or those that are characterised by symptoms of idiopathic environmental intolerance or exposure to environmental factors with a reference to chemical agents, solvents, odors, air pollutants or materials. Populations will not be restricted to human participants diagnosed with MCS, and will instead include a wide range of research that may contribute to establishing MCS as a diagnosis and exploring relevant underlying mechanisms.
  - GQ5 will be limited to samples of human participants where some participants are characterised by MCS, idiopathic environmental intolerance for chemicals, the equivalent of the ICD-10-CM Code F45.9 (somatoform disorder, unspecified) or studies that report on a subgroup of the patients of interest.

- **Intervention/exposure/independent variable:**
  - We will accept definitions of MCS and descriptions that include diagnostic criteria (GQ1).
  - Prevalence and incidence measures need to state the criteria of MCS clearly to be eligible (GQ2).
  - GQ3 studies assessing whether MCS is a distinct disorder (ie, distinct from other ‘physical’ disorders or ‘psychiatric’ disorders) need to provide empirical evidence of discriminatory power to support the authors’ conclusions or need to be based on formal expert consensus methods. Opinions of individual authors will not be eligible.
  - Eligible publications suggesting underlying mechanisms (GQ4) may include evidence for the onset of MCS or the course of the disease, including TILT (toxicant-induced loss of tolerance describing an initiation and a triggering stage).
  - Studies evaluating interventions (GQ5) to prevent, manage or treat MCS will be eligible. Interventions will not be restricted by the content or treatment approach and may include interventions aiming to avoid triggers, focusing on coping with MCS symptoms, desensitisation or addressing the causes of MCS. In addition, interventions in patients diagnosed with MCS will be eligible regardless of...
the intervention focus (patient-centred rather than intervention-centred approach). Case studies of individual patients will be included if focused on intervention rather than the natural course of the condition and the description is published in a peer-reviewed scientific journal.

- Comparator: Studies will be eligible regardless of the presence of a comparator.
- Outcome: GQ1 publications will need to provide sufficiently detailed descriptions that can be operationalised as a definition or diagnostic criteria. GQ2 studies will need to report a numerical estimate of the prevalence or incidence of MCS. GQ3 and GQ4 will not be limited by reported outcomes. GQ5 studies may report on patient health (self or clinician report), physiological or psychosocial measures assessing the effect of the intervention (effectiveness as well as safety indicators); quantitative and qualitative data will be eligible. Studies reporting only on treatment uptake, patient or provider acceptability of treatments, or treatment costs will be excluded.
- Timing: GQ1 studies will be included regardless of the publication year (eg. definitions from the 1980s are eligible). GQ2 studies will be eligible regardless of the timing of the exposure or assessment (eg. childhood exposure, symptoms tested in adults). GQ3 and GQ4 studies will not be restricted by time of exposure or follow-up, and retrospective, concurrent and prospective studies will be eligible. GQ5 studies will be included regardless of the intervention duration and follow-up.
- Setting: Studies will not be restricted by setting and will be drawn from the international literature.
- Other limiters: English-language publications disseminated to a wide audience through a scientific journal will be eligible. Studies published in abbreviated form (eg. conference abstracts) will not be eligible for inclusion.

Systematic reviews and relevant narrative reviews will be retained for reference-mining. Multiple publications on the same study (ie, studies defined by the included participants) will be consolidated into one study record to ensure that a given study is not counted multiple times regardless of the number of publications reported on the study. The literature flow will be transparently documented in a citation management programme.

Inclusion screening process

We will use an online database (DistillerSR) designed for literature reviews to screen the search output. The team will design detailed citation and full-text screening forms to ensure a transparent, consistent and unambiguous approach. Citations found to be potentially relevant by at least one reviewer will be obtained as full text. Citations screening will be supported by machine learning algorithms to reduce reviewer errors and bias. All citations excluded by a human reviewer will be screened for relevance by the machine learning algorithm to ensure that no potentially relevant publication has been missed.

Full-text screening will apply the detailed eligibility criteria. Training will ensure a shared understanding of all inclusion and exclusion criteria across reviewers. Full-text publications will be screened by two independent reviewers and any discrepancies will be resolved through discussion in the review team. Dual screening reduces reviewer bias and errors and is critical for this complex topic. The screening decisions and reasons for exclusion of studies will be tracked in the online database and citation management software. This allows us to reconstruct a detailed literature flow and facilitates the documentation of included and excluded publications. Reasons for exclusion will match the exclusion criteria dimensions to orient the reader. The literature flow will be documented in a flow diagram.

Studies excluded at full text will be documented in the online supplemental appendix 1 of the review together with a reason for exclusion. We will retain background papers, that is, papers to cite or reviews to reference-mine. We will report the number of included studies and the number of publications reporting on each study across the review and for each guiding question.

Data abstraction

The data abstraction will provide a concise overview of the evidence.

For GQ1 (definitions and diagnostic criteria), we will document the suggested definitions and the approach to establish it. We will document published diagnostic criteria of MCS and for diagnostic accuracy studies, the type (eg, self-report questionnaire, objective test such as exposure chamber and challenge test) and name of the test will be recorded.

For GQ2 (prevalence and incidence), we will document the data type (eg, prevalence or incidence), the method of assessment (eg, self-report, medical record) and the operationalisation of MCS (definition, criteria). We will distinguish general, unselected populations (eg, students) from targeted samples with potentially increased risk (eg, Gulf War veterans). For each study, we will record the country, sample size and year of estimate, and identify any published prospective studies.

For GQ3 (MCS as a distinct disorder), we will document the aim of the study, the employed study design, and the analytic approach to evaluate MCS as a distinct disorder. We will record the type of research approach used to determine whether MCS should or should not be considered a distinct disorder or syndrome (eg, establishing a unique biomarker, analysing symptom clusters, documenting explained variance) and differentiate the use of direct, mechanistic and parallel evidence by the authors. We will abstract the authors’ conclusion regarding their conceptual agreement with MCS as a distinct disorder with a differential clinical diagnosis.

For GQ4 (underlying mechanisms), we will broadly categorise the study type and approach to indicate which
aspect of the condition the study addresses (eg, the
general aetiology or a specific process such as the mech-
anism of generalising across agents) and whether the
approach assumes a biological, psychological or other
(eg, multiple processes) hypothesis. For each study, we
will categorise the suggested mechanisms (eg, neurogenic
inflammation). This will involve collating and reviewing
all identified mechanisms and establishing a categorisa-
tion system based on the published literature and identi-
fied approaches. We will also establish a compendium of
frameworks and diagrams reported by the authors. For
this, figures published under a Creative Commons license
will be included in the compendium; for all others, the
publisher will be contacted to request permission to use
the figure.

GQ5 (therapy and management for MCS) will collate all
identified interventions and broadly categorise interven-
tions as prevention, management or treatment. We will
document the focus of the intervention (eg, aiming to alter
the course of the condition, coping strategies) together
with the broad therapeutic approach (removing triggers
from environment, diet, supplements, masks, devices,
(off-label) medication, psychological approaches). The
categorisation system will be built on existing reviews and
the identified empirical research. We will also abstract
the author group, publication year and country.

Data will be abstracted by one reviewer and checked by
an experienced literature review methodologist. We will
export data into tables and figures or data files for further
analysis.

Consultation exercise
The last step of the scoping review process will be a consul-
tation exercise. We will ask multidisciplinary technical
experts and stakeholders in MCS research, practice and
advocacy to review the results of the scoping review. These
reviewers will not have been involved in the review process
and will assess the review de novo. Previous experiences
have shown that this last step of stakeholder involvement
provides invaluable input and adds to the usefulness
and validity of the end product. The consultation
exercise will be conducted as an online survey sent to
participants together with the review to elicit structured
feedback on the content and presentation of the review.
The input will contribute to the presentation of the
scoping review results.

Patient and public involvement
The planned review was presented at a stakeholder
meeting organised by the funding agency that included a
patient representative. Several stakeholders are also part
of the scientific steering committee that reviewed this
protocol (see the Acknowledgement section). The results
of the review will be distributed to stakeholders in a formal
consultation exercise as outlined earlier. This step will be
instrumental in ensuring a user-friendly presentation of
results that is useful to patients and the public.

RESULT PRESENTATION
Characteristics of all studies meeting inclusion criteria
will be documented in concise evidence tables to provide
a broad documentation of the underlying evidence base.
Findings across studies will be documented in an evidence
map. This visual and user friendly research overview will
map the existing evidence on MCS.

The evidence map will use a limited number of dimen-
sions to display the existing research. Displaying the
evidence as a bubble plot, each bubble in the plot will
represent a study and the size of the bubble will repre-
sent the size of the study. The plot will use the x-axis
and the y-axis to display existing types of research studies to characterise
the evidence base further. The y-axis can be used to char-
acterise the guiding question addressed by the research.
In addition, the shape of the bubble and/or shading may
represent different study designs and methodological
characteristics. The optimal display will be selected based
on input from the consultation exercise.

The tables and figures will be accompanied by a narra-
tive that summarises the identified evidence base. This
scoping review and evidence map will provide a broad
overview of the existing research on MCS. It also aims to
facilitate a future systematic review of the literature that
will answer definitive research questions (eg, what is the
prevalence of MCS and the effectiveness of treatments
for MCS). Scoping and mapping has become increas-
ingly useful to prepare more definitive systematic reviews
that answer closed questions, in particular for large and
controversial topics. The scoping review will provide context and information on which topic areas are to date amenable to a formal systematic review of
the literature. The future systematic review will address a
narrower scope of approaches that have been identified
in this scoping review, assess the quality of evidence for
distinct topics of interest, and synthesise the evidence.
In addition to documenting the existing evidence base,
we will clearly outline gaps in the literature identified in
this scoping review. The gap presentation will use the
scoping review’s eligibility framework to transparently
document existing gaps and future research needs. The
gap analysis will make concrete recommendations to
facilitate future research.

Ethics and dissemination and data availability
The scoping review was determined to be exempt from
further review by the University of Southern California
Institutional Review Board review in July 2022 (ID UP-
00516). The results of the review will be disseminated
through a journal manuscript. Data of the scoping review
will be publicly available through an online data reposi-
tory (SRDR+).

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SH, MD, MB, JR, AIM and CP screened literature to develop this manuscript.
AnM and DT manage the data; SY conducted the literature searches; all authors contributed conceptually to the work and edited this manuscript.

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**Competing interests** None declared.

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**REFERENCES**


27. Regal Ramos RJ. Can we rule out that Fibromyalgia, chronic fatigue syndrome and multiple chemical sensitivity are psychosomatic diseases? *Semergen* 2015;41:349–53.


72 Torriani-Pasini C, Demers M, Polese JC, et al. mHealth Technologies used to capture walking and arm use behavior in adult stroke survivors: a Scoping review beyond measurement properties. Disabil Rehabil 2022;44:6094–106.
