The influence of health system change on treatment burden: a systematic review

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Manuscript Title
The influence of health system change on treatment burden: a systematic review

Short Title
Health system changes and treatment burden

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Abstract:

Background

Treatment burden is a patient-centred concept describing the effort required of people to look after their health and the impact this has on functioning and wellbeing. High treatment burden is more likely for people with multiple long-term conditions (LTCs). Validated treatment burden measures exist but have not been widely used in practice or as research outcomes.

Aim

To establish whether changes in organisation and delivery of health systems and services improves aspects contributing to treatment burden for people with multiple LTCs.

Design and setting

Systematic review of randomised controlled trials (RCTs) investigating the impact of systems-level interventions on at least one outcome relevant to previously-defined treatment burden domains among adults with two or more LTCs.

Method

Electronic databases EMBASE, Medline (OVID) and Web of Science were searched from January 2010 to July 2021 for terms related to multimorbidity, system-level change and treatment burden. Treatment burden domains were derived from validated measures and qualitative literature. Synthesis without Meta-Analysis (SWiM) methodology was used to synthesise results and study quality assessed using the Cochrane Risk of Bias Tool.

Results

Searches identified 1881 articles, with 18 meeting the inclusion criteria. Outcomes were grouped into seven domains. Studies exhibited substantial heterogeneity, limiting synthesis of results. Some concern over bias gave low confidence in results.

Conclusion

There was some evidence for effect of systems-level interventions on some domains. Adoption of a standardised outcome set incorporating validated treatment burden measures and development of standard definitions for care processes in future research would aid study comparability.

Keywords: Multimorbidity, chronic, long-term conditions, treatment burden, systems-level, healthcare organisation, minimally disruptive medicine

How this fits in

- The nature and extent of treatment burden experienced by patients with multiple long-term conditions is influenced by the way health systems are organised and
operate, but little research to date has explored the impact of systems-level change on treatment burden.

- In this systematic review of randomised trials involving a wide range of interventions that considered domains of treatment burden as outcomes, we found some evidence of an effect of interventions, particularly those operating at local organisation level.

- However, there are significant gaps in the evidence base, particularly the need to include validated treatment burden measures as outcomes in trials, and a lack of studies investigating interventions aiming to mitigate the financial impact and administrative workload for patients and carers.

- Clinicians and managers of primary care organisations should consider the impact of service organisation on patient and carer treatment burden.

Introduction

The number of people with multiple long-term conditions (LTCs) is increasing, reflecting ageing populations worldwide, which is challenging for health care systems and services operating within finite resources. Multimorbidity, often defined as the coexistence of two or more LTCs, is more common with older age, but exhibits earlier onset among people from lower socioeconomic groups. It is associated with several adverse health outcomes including poor quality of life, reduced functional ability and increased mortality. Coordination of care for patients with multiple LTCs can be challenging in health systems that are structured for individual disease management. Treatment burden describes the workload of healthcare for patients, including self-management and treatment, and the impact such demands have on wellbeing and functioning. High treatment burden can be detrimental to quality of life and health outcomes. Efforts to respond to high treatment burden may involve either increasing patients’ capacity to manage or reducing the workload imposed upon them. Uncoordinated care may lead to increased complexity for patients and contribute to health service inefficiency and ineffectiveness.

In the UK, recent health policy changes indicate movement towards collaborative, integrated care models to improve care for patients with multiple LTCs. Such system-level changes have potential to reduce treatment burden by operationalising the principles of Minimally Disruptive Medicine (MDM), focusing on outcomes that are important to patients, reducing workload and increasing capacity.

A recent systematic review explored the effectiveness of patient-level interventions in reducing treatment burden. Several studies reported positive outcomes, however...
conclusions were limited due to study heterogeneity and risk of bias\textsuperscript{11}. Even less is known about the impact of system-level change on patient experience, particularly treatment burden. Given the lack of widespread adoption of treatment burden measurement in healthcare or research, this systematic review aimed to explore the effects of systems-level change on pre-specified treatment burden domains derived from validated treatment burden measures among patients with multiple LTCs\textsuperscript{12,13}.

**Methods**

*Data sources and searches*

The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and SWiM guidelines (Supplementary Table 1). The SWiM criteria recommends a transparent, structured approach to synthesis through reporting how studies are grouped, any standardised metrics used, the synthesis method, how data are presented, a summary of findings, and limitations of the synthesis\textsuperscript{14}. The review is registered on the international prospective register of systematic reviews (PROSPERO) ID number: CRD42021265188\textsuperscript{14-16}.

The search strategy was developed with a senior librarian and searches were undertaken using EMBASE, Medline (OVID), and Web of Science during July 2021. The International Research Community on Multimorbidity (IRCMo) repository and the National Grey Literature Collection were hand searched for grey literature. Further references were requested through author follow-up and snowballing of citations identified additional relevant papers. Search terms were formulated under five domains identified from the research question (Supplementary Box 1). These domains included multiple conditions, long-term nature of disease, systems-level change in care delivery, outcome measures within previously identified domains of treatment burden, and the study design of RCTs.

Directly-measured, self-reported treatment burden could not be used as the sole outcome measure due to a lack of studies using validated treatment burden measures. Therefore, treatment burden domains were formulated a-priori using validated tools Multimorbidity Treatment Burden Questionnaire (MTBQ) and Patient Experience with Treatment and Self-Management (PETS) measures, and themes from an extensive qualitative literature review of 110 studies of patient capacity and constraints in the experience of chronic disease\textsuperscript{12,13,17}. Medical appointment load and medical expenses were included in both the PETS measure and the qualitative literature, and were therefore included as important domains a-priori\textsuperscript{12,13}. 
The MTBQ was chosen because it is a 10-item measure validated in the UK, demonstrating good reliability as a corresponding measure to quality of life and patient-centred care\textsuperscript{13}. The items cover medication number, medication adherence, collecting prescriptions, monitoring health, arranging appointments, seeing multiple health professionals, attending appointments, disease knowledge, lifestyle changes and help from family and friends. The MTBQ is limited by its lack of inclusion of financial burden, an important consideration, particularly in healthcare systems where treatment is not free at the point of use\textsuperscript{5}.

The PETS, which was validated in English in the US, was chosen because of its comprehensive nature, covering 78 items within 15 content domains, and its wide use in multimorbidity domains\textsuperscript{12}. These domains include medical information and adherence, medical appointments, monitoring health, interpersonal challenges, medical and healthcare expenses, difficulty with healthcare services, role and social activity limitations, and physical and mental exhaustion.

Using a key qualitative study synthesising 110 reports of patient capacity and constraints in their experience of chronic disease, additional domains were formulated from themes in the review in order to include further relevant studies\textsuperscript{17}. These corresponded to areas also covered in the validated tools\textsuperscript{12, 13, 17}. For example, HRQoL was identified to be relevant within the domains of treatment burden in the qualitative study\textsuperscript{17}.

**Study selection**

Studies were eligible for inclusion if they were conducted in a population of adults with multiple LTCs, when an intervention that could be defined as ‘systems-level’ was applied, and when an outcome (primary or secondary) represented at least one of the treatment burden domains. Adults were defined as those aged 18 and over. Multiple LTCs was defined as a diagnosis of two or more LTCs, confirmed by the ICD-10 codes for chronic conditions\textsuperscript{18}, or with 5 or more long-term drug prescriptions, considered to reflect patients with multiple LTCs. Eligible systems-level interventions were identified through a definition adapted from a Cochrane Review of complex interventions to improve outcomes in patients with multimorbidity in primary care settings\textsuperscript{19}. We considered systems-level to represent three levels of change: clinician-level changes in care provision (structured management plans, scheduled follow-ups); changes in local organisational structure (multidisciplinary team care, collaborative care); and higher-level changes in care models (integrated care systems)\textsuperscript{20, 21}.

The comparator was as defined in the included studies. Treatment burden domains as defined above were used as inclusion criteria for the outcomes, as an alternative to overall treatment burden measures\textsuperscript{12, 13, 17}. Two authors (KM & SR) independently screened titles.
and abstracts and applied inclusion/exclusion criteria. Disagreements were resolved by a third reviewer (SF).

Quality assessment

The quality assessment of each identified study was carried out independently by two authors (KM and SR) using the algorithm-guided electronic Cochrane Risk of Bias 2 tool for RCTs (RoB2)\(^2\). Disagreements were resolved by a third reviewer (SF).

Data synthesis

Due to heterogeneity of study populations, interventions, comparators, and outcomes, meta-analysis was not considered possible. This review used the SWiM framework to synthesise results from included papers\(^1\). Data from included studies were extracted into a standardised table. Studies were grouped according to outcomes categorised by treatment burden domains, considered as the most transparent way to report the heterogenous findings. Outcome data were summarised for each study within two domains chosen for prioritisation, due to the higher proportion of studies with primary outcomes measured within these domains (impact on HRQoL and functional status), as recommended by the SWiM criteria\(^1\). For those outcomes where synthesis was possible, the Grading of Recommendations Assessment Development and Evaluation (GRADE) approach was used to critically appraise the synthesised results and establish the confidence for the certainty of these results, therefore guiding interpretation\(^3\). However, due to study heterogeneity, and in view of the perceived risk of drawing misleading conclusions through SWiM-recommended methods (summary effect sizes, p value combination, vote counting), we did not synthesise data further. An evidence map (Figure 2) was constructed to show gaps in the evidence base, with studies mapped by outcomes to previously-identified domains, and inclusion of additional pre-identified domains to show the scope of areas with limited research.
Results

Included studies

A total of 1881 studies were identified from database searches, grey literature, and reference and author follow up (Figure 1). 466 duplicates were removed and 1415 screened by title and abstract, with 1384 excluded as not meeting the inclusion criteria. 31 full texts were assessed, of which 18 met the inclusion criteria.

[insert Figure 1.]

Figure 1 caption: PRISMA flow chart showing study selection process

Data extraction summary

A full reference list of included papers is provided in Supplementary Box 2. Supplementary Table 2 summarises included paper characteristics.

Study characteristics

There was considerable heterogeneity in included studies, limiting the potential for synthesis. The majority of studies were conducted in high-income countries with well-developed healthcare system structures. All studies were unblinded apart from one (Webel et al.) that was able to single blind participants to intervention receipt.

There was a spectrum of interventions across studies, from individual clinician level to higher-level, cross-organisational change (Table 1). Five studies implemented interventions at clinician level. At local organisation level, three studies had a multidisciplinary approach to patient care, and nine studies used an intervention which could be considered collaborative care. One study (Salisbury et al.) used a collaborative care approach across multiple providers, considered a higher-level care model change.

[Insert Table 1.]

Assessment of treatment burden outcome

Notably, just one study measured treatment burden directly, using the MTBQ\textsuperscript{24}. This was the largest study (Salisbury et al) and was considered high quality, with a complex, multi-centre collaborative care intervention, however it found no significant improvement in treatment burden in patients receiving the interventions\textsuperscript{24}. Outcome measurements most commonly covered the domains relating to impact on HRQoL and functional status, with impact on self-efficacy and social functioning also covered in a number of studies (Table 2). Five studies focused mainly on outcomes related to medication management. Outcome measurement tools were very heterogeneous across studies under each domain. For example, across the
twelve studies with outcomes relevant to the domain ‘impact on HRQoL’, seven different measurement tools were used to assess the outcome. Only some studies measured a primary outcome related to treatment burden domains. Most studies measured more than one outcome which could be placed within treatment burden domains. Table 2 demonstrates the heterogeneity of outcome measures considered and whether they were primary or secondary outcomes.

**Evidence map**
The evidence map revealed treatment burden domains considering medical costs and administrative task load at the patient level have not been investigated in any of the studies identified by this review (Figure 2).

**Quality assessment**
Most studies were considered to have ‘some concern’ for risk of bias using the Cochrane RoB2 tool\(^2^2\) (Supplementary Table 3). Intervention adherence was mentioned by 11 of 18 studies, and intervention dose was considered suboptimal in most studies, as implementation of systems-level interventions proved complex, potentially reducing intervention effectiveness. Additionally, bias was a possibility in almost all studies from difficulty in blinding study assessors and participants. Application of the GRADE approach resulted in low degree of confidence in the evidence in this review (Supplementary Table 4)\(^2^3\).

[Insert Table 2.]

**Discussion**

**Summary**
This systematic review aimed to identify and synthesise findings of studies which implemented systems-level interventions and measured outcomes relating to treatment burden domains. A total of 18 RCTs were included, with interventions ranging from medication management changes at practitioner level to national collaborative care approaches. Seven pre-defined treatment burden domains were covered by outcomes measured in included studies. Studies were heterogenous in terms of interventions and outcome measures. There were some concerns about risk of bias for most studies.

There was some evidence of effect of interventions at local organisation level, particularly interventions involving collaborative care with significant patient involvement, such as through individualised management plans. The impact was shown particularly within the
domains of HRQoL and functional status. However, the GRADE approach suggested caution should be exerted regarding interpretation of findings.

**Strengths and limitations**

This systematic review has several strengths. The protocol was registered prior to commencement with PROSPERO. SWiM and PRISMA guidelines ensured a systematic approach and methodology was documented. The Cochrane ROB2 tool was used to critically appraise studies. The GRADE approach was used to assess the confidence of the results. Broad search terms were likely sensitive enough to pick up key studies. A second reviewer independently checked included studies against inclusion criteria and performed study quality assessments using the Cochrane RoB2 tool, with disagreements resolved through a third reviewer. The use of domains allowed identification of studies with outcomes highly relevant to treatment burden which would not be considered eligible if the criteria were constrained to directly measured treatment burden. No previous systematic reviews explore intervention effects on treatment burden in this manner.

The review also had a number of limitations. Although published tools (PETS, MTBQ) and qualitative literature were used to pre-define treatment burden domains for the searches, there is possibility of exclusion of potentially relevant domains and corresponding studies. Some studies may have also been excluded if their outcome measures did not fit clearly into a domain.

Another limitation was a lack of a generally-agreed definition of 'systems-level'. Principles of systems-level changes were used instead to screen interventions for eligibility, potentially excluding studies with relevant interventions. Study heterogeneity precluded the use of meta-analysis. Despite the transparent approach to grouping by outcome, we acknowledge other groupings could have been selected. Given the heterogeneity of studies, we could not use transformation to produce standardised metrics. Consequently, the influence of interventions on the domains identified in this review could not be synthesised fully and no overall effect measures or quantitative indications of an effect could be presented. The possibility of a type two error (concluding no effect on the treatment burden domain when in fact one existed) cannot be ruled out for several of the studies as the outcome relevant to treatment burden was considered a secondary outcome. Restricting studies to those published in English may have resulted in exclusion of studies conducted in different health systems, reducing the generalisability of this review.

**Comparison with existing literature**
A recent Cochrane Review explored interventions in primary care to improve a range of outcomes for patients with multiple LTCs\textsuperscript{19}. Six of the 10 studies in the SR were considered local organisation level, involving case management and coordination\textsuperscript{19}. The results indicated interventions were more effective when targeted at specific risk factor management, but the overall conclusions of the study were limited due to heterogeneity of interventions\textsuperscript{19}. The Cochrane Review reflected issues, also identified in this systematic review, in conducting research with patients with multiple LTCs, where selection bias seems possible due to recruitment difficulties\textsuperscript{19}. For example, patients with greater capacity are more likely to participate in a trial than those with less capacity, which is directly relevant to outcomes linked to treatment burden\textsuperscript{25}. This bias may additionally reduce scope for improvement from baseline, as patients participating tend to be those experiencing less treatment burden\textsuperscript{24}.

The evidence map (Figure 2) revealed the lack of research examining intervention effects on treatment burden domains concerning medical costs and administrative task load. These domains are important to consider alongside others in their contribution towards higher levels of treatment burden in patients with multiple LTCs.

[insert Figure 2]

*Figure 2 caption: Evidence map displaying treatment burden domains identified a-priori with corresponding study IDs (as described in Table 1) which measure an outcome relevant to the displayed domain*

*Figure 2 footnote: For the purposes of this evidence map, functional status was considered to include ease of daily living, physical and mental capabilities, and difficulty with service navigation*
Implications for research and practice

Successful implementation of systems-level change to reduce treatment burden in patients with multiple LTCs requires further steps before conclusions can be drawn about the nature of systems-level interventions most likely to be successful in reducing treatment burden.

It is highly likely the way in which services are organised has a substantial impact on the experience and work of being a patient, but this is difficult to demonstrate while direct measurement of treatment burden is seldom undertaken. Our review suggests it may be beneficial for measures of treatment burden to be more routinely included in research and practice, to facilitate derivation of a standard outcome set. For example, treatment burden could be listed as a standard outcome measure investigating organisational-level interventions and multimorbidity. This requires care so a measurement tool is not, in itself, burdensome. Treatment burden is a complex concept and developing an accurate and practicable measurement tool has proved challenging. In practice, currently validated measures may be time-consuming to use. A single-item measure has been explored for use within clinical practice, to identify patients who benefit from minimising avoidable burden, however it only demonstrated moderate accuracy in comparison with more complete measures and needs further consideration, potentially as a screening tool. Further thought could be given to recruitment of patients with multiple LTCs in research, as patients may be more likely to participate when experiencing lower treatment burden levels.

Common themes arising in the risk of bias assessment included poor intervention fidelity, inadequate follow up duration, and lack of blinding of outcome assessors. Future trials could carefully consider these issues in study design to reduce risk of bias.

A broader understanding of health systems beyond the biomedical sphere may be generated by integration of complexity science in multimorbidity research to identify potential systems-level improvements. Systems-level research may benefit from the development of a standard definition for each type of care intervention. This might allow greater comparison between studies and the impact of such interventions on treatment burden. Further research on treatment burden domains not addressed by studies identified in this review could help to give a broader understanding of treatment burden. All studies included in this review were based in a primary care setting. This may reflect where the majority of people with multiple long-term conditions are managed but may also indicate there is opportunity for further research on multimorbidity and treatment burden research in secondary care.

Patient-level approaches of care in integrated systems are likely to be helpful in reducing treatment burden for people with multiple LTCs. The movement of healthcare systems towards digital care may, however, exacerbate treatment burden as care responsibility is
increasingly placed with patients, and may further disadvantage some population groups, widening health inequalities.\(^{30}\)

**Conclusion**

System-level interventions have great potential to reduce treatment burden for people with multimorbidity, but more evidence is needed to inform this process, including development and adoption of standard definitions and treatment burden outcome measures.

**Competing interests**

The authors declare that they have no competing interests.

**Funding:** The authors did not receive any funding to complete this review.

**Ethics approval:** Not applicable to this review

**Contributions:** KM and SF contributed to the conception and design of the review. KM & SR completed literature search and screening. KM extracted data from included studies and KM and SR assessed the quality of studies. KM drafted the manuscript and SF contributed editing. All authors read and approved the final manuscript.

**Acknowledgements:** We thank Paula Sands, Health Services librarian for her support with developing the search strategies.
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5. Mair FS and May CR. Thinking about the burden of treatment. *BMJ* 2014; 349: g6680. DOI: 10.1136/bmj.g6680 [Accessed 10th June 2021].


Box 1: Health-related quality of life and functional status

Of twelve studies measuring outcomes related to the HRQoL domain, four showed a statistically significant difference between intervention and control group for changes in HRQoL, with all favouring the intervention group (Supplementary Table 5). Only one study considered HRQoL as a primary outcome. Of twelve studies measuring outcomes related to functional status, five showed a statistically significant difference between intervention and control group for changes in functional status, with all favouring the intervention group. Four studies out of five showing a statistically significant improvement following intervention measured functional status as a primary outcome (Supplementary Table 6). A variety of different measures were used across HRQoL and functional status domains, for example EQ-5D (HRQoL), WHO-QOL (HRQoL), SF-12 physical and mental component summaries (functional status), HeiQ (functional status), therefore it was difficult to directly compare results and further inferences were not made.
<table>
<thead>
<tr>
<th>Source (date) (study ID)</th>
<th>Country</th>
<th>Number of participants</th>
<th>Intervention** and comparator</th>
<th>Treatment burden domains covered by outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coventry (2015) (1)</td>
<td>UK</td>
<td>387</td>
<td>Local organisation level</td>
<td>HRQoL, functional status, self-efficacy, social functioning</td>
</tr>
<tr>
<td>Fortin (2021) (2)</td>
<td>Canada</td>
<td>294</td>
<td>Local organisation level</td>
<td>HRQoL, functional status*, self-efficacy</td>
</tr>
<tr>
<td>Gillis (2014) (3)</td>
<td>United States</td>
<td>102</td>
<td>Local organisation level</td>
<td>Functional status*, social functioning*</td>
</tr>
<tr>
<td>Jager. (2017) (4)</td>
<td>Germany</td>
<td>273</td>
<td>Clinician level</td>
<td>Social functioning, medication-related</td>
</tr>
<tr>
<td>Kalt (2010) (5)</td>
<td>United States</td>
<td>214</td>
<td>Local organisation level</td>
<td>HRQoL</td>
</tr>
<tr>
<td>Kölle-Neu (2016) (6)</td>
<td>Germany</td>
<td>162</td>
<td>Clinician level</td>
<td>Functional status, social functioning, medication-related*</td>
</tr>
<tr>
<td>Lin (2018) (7)</td>
<td>Taiwan</td>
<td>178</td>
<td>Clinician level</td>
<td>HRQoL</td>
</tr>
<tr>
<td>Markle-Reid (2018) (8)</td>
<td>Canada</td>
<td>159</td>
<td>Local organisation level</td>
<td>HRQoL*, functional status*, self-efficacy</td>
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<tr>
<td>Miskovic (2020) (9)</td>
<td>Canada</td>
<td>132</td>
<td>Local organisation level</td>
<td>Functional status*, self-efficacy</td>
</tr>
<tr>
<td>Muth (2018) (10)</td>
<td>Germany</td>
<td>505</td>
<td>Clinician level</td>
<td>HRQoL, functional status, medication-related*</td>
</tr>
<tr>
<td>Rose (2018) (11)</td>
<td>Canada</td>
<td>470</td>
<td>Local organisation level</td>
<td>HRQoL*, self-efficacy, treatment adherence*</td>
</tr>
<tr>
<td>Salisbury (2018) (12)</td>
<td>United Kingdom</td>
<td>1546</td>
<td>Local organisation, higher health services level †</td>
<td>HRQoL*, functional status, medication-related, treatment burden</td>
</tr>
<tr>
<td>Siau (2017) (13)</td>
<td>Singapore</td>
<td>411</td>
<td>Local organisation level</td>
<td>Functional status</td>
</tr>
<tr>
<td>Stewart (2021) (14)</td>
<td>Canada</td>
<td>163</td>
<td>Local organisation level</td>
<td>HRQoL, functional status*, self-efficacy</td>
</tr>
<tr>
<td>Vera (2010) (15)</td>
<td>Puerto Rico</td>
<td>179</td>
<td>Local organisation level</td>
<td>Social functioning</td>
</tr>
<tr>
<td>Von Korff (2011) (16)</td>
<td>United States</td>
<td>214</td>
<td>Clinician level, local organisation level †</td>
<td>HRQoL*, functional status</td>
</tr>
<tr>
<td>Zechmann (2020) (18)</td>
<td>Switzerland</td>
<td>336</td>
<td>Clinician level</td>
<td>HRQoL, medication-related</td>
</tr>
</tbody>
</table>

HRQoL: Health-related Quality of Life

*primary outcome measured within identified domain

**three levels have been identified within systems-level interventions: at the level of the individual clinicians e.g. structured training regarding medication management; at the level of local healthcare providers e.g. multidisciplinary case conferences as part of collaborative care for patients with LTCs; at higher health services level e.g. multi-location collaborative care intervention

***Comparator was usual care in all studies

† Study deemed to cover more than one category regarding level of intervention
Table 2. Domains relating to treatment burden considered as outcomes among the included studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Domains (origin) related to treatment burden covered by outcome measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HRQoL (qualitative literature&lt;sup&gt;17&lt;/sup&gt;)</td>
</tr>
<tr>
<td>1</td>
<td>X↔</td>
</tr>
<tr>
<td>2</td>
<td>X↔</td>
</tr>
<tr>
<td>3</td>
<td>O↑</td>
</tr>
<tr>
<td>4</td>
<td>X↔</td>
</tr>
<tr>
<td>5</td>
<td>X↑</td>
</tr>
<tr>
<td>6</td>
<td>X↔</td>
</tr>
<tr>
<td>7</td>
<td>X↑</td>
</tr>
<tr>
<td>8</td>
<td>O↑</td>
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<tr>
<td>9</td>
<td>O↔</td>
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<tr>
<td>10</td>
<td>X↔</td>
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<tr>
<td>11</td>
<td>O↔</td>
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<tr>
<td>12</td>
<td>O↔</td>
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<tr>
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<td>X↑</td>
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<tr>
<td>14</td>
<td>X↔</td>
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<tr>
<td>16</td>
<td>O↑</td>
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<tr>
<td>17</td>
<td>O↔</td>
</tr>
<tr>
<td>18</td>
<td>X↔</td>
</tr>
</tbody>
</table>

O = Primary outcome  
X = Secondary outcome  
↑ = statistically significant improvement in outcome following intervention (p≤0.05)  
↔ = no statistically significant effect of intervention on outcome measure (p>0.05)

HRQoL = Health Related Quality of Life  
PETS = Patient Experience of Treatment Survey  
MTBQ = Multimorbidity Treatment Burden Questionnaire

Study ID corresponds to Supplementary Table 2

Figure titles

Figure 1. PRISMA flow chart showing study selection process

Figure 2. Evidence map displaying treatment burden domains identified a-priori with corresponding study IDs (as described in Table 1) which measure an outcome relevant to the displayed domain

Figure 2 footnote: for the purposes of this evidence map, functional status was considered to include ease of daily living, physical and mental capabilities, and difficulty with service navigation
Figure 1. PRISMA flow chart demonstrating study selection process

190x338mm (96 x 96 DPI)
Figure 2. Evidence map displaying treatment burden domains identified a-priori with corresponding study IDs (as described in Table 1) which measure an outcome relevant to the displayed domain.

Footnote: for the purposes of this evidence map, functional status was considered to include ease of daily living, physical and mental capabilities, and difficulty with service navigation.