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TITLE

End-of-life care preferences of older patients with multimorbidity: protocol of a systematic review.

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ABSTRACT

Introduction

End-of-life care is an essential task performed by most health care providers, and often involves decision-making about how and where patients want to receive care. To provide decision support to health care professionals and patients in this difficult situation, we will systematically review an evidence cluster on the end-of-life care preferences of older patients with multimorbidity that we previously identified using an evidence map.

Methods and analysis

We will systematically search for studies reporting end-of-life care preferences of older patients (mean age ≥60) with multimorbidity (≥2 chronic conditions) in MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index, Social Sciences Citation Index Expanded, PSYNDEX and The Cochrane Library from inception. We will include all primary studies that use quantitative, qualitative and mixed methodologies, irrespective of publication date and language.

Two independent reviewers will assess eligibility, extract data and describe evidence in terms of study/population characteristics, preference assessment method, and end-of-life care elements that matter to patients (e.g. life-sustaining treatments). Risk of bias/applicability of results will be independently assessed by two reviewers using the Mixed Methods Appraisal Tool. Using a convergent integrated approach on qualitative/quantitative studies, we will synthesize information narratively and, wherever possible, quantitatively.

Ethics and dissemination

Due to the nature of the proposed systematic review, ethics approval is not required. Results from our research will be disseminated at relevant (inter-)national conferences and via publication in peer-reviewed journals. Synthesizing evidence on end-of-life care preferences of older patients with multimorbidity will improve shared decision-making and satisfaction within this final life period.

Registration

Submitted to PROSPERO (receipt number 151862); assignment in progress.

Evidence map registration: Open Science Framework (OSF): DOI 10.17605/OSF.IO/MCRWQ.

Strengths and limitations of this study

A multinational and multidisciplinary team with considerable methodological experience and skills will provide the necessary expertise.

A patient representative has been involved in designing the study to ensure that from the beginning, patient-relevant questions are assessed, and results discussed accordingly.

The main study limitations are the poor indexing of articles, and the lack of or non-standardized definition of “patient preferences”.

INTRODUCTION

Multimorbidity, or the presence of multiple coexisting diseases or conditions (1), affects the majority of older adults (2), and is associated with increased mortality and health care utilization (3–5). In addition, multimorbidity negatively impacts quality of life and increases symptom burden (6–8). Evidence is therefore required on how to best manage multimorbid patients (9, 10).

The care of patients with multimorbidity entails complex medical decision-making, especially at the end of life (EoL). EoL care refers not only to the health care services that are provided to patients in the final hours or days of their lives, but, more broadly, to those provided to all patients whose conditions have become advanced, progressive, and incurable (11, 12). EoL care must be embedded within the context of patient preferences, so the care multimorbid patients receive during the final days of their lives is concordant with the care they desire. The provision of effective EoL care to those with multimorbidity is impossible without cooperation between health care providers from palliative care, specialty care and primary care. In fact, EoL care is an essential task performed by most health care providers, and often involves decision-making about how and where patients want to receive care.

According to recent studies that were not confined to patients with multimorbidity, most adult patients' EoL care preferences (e.g. for cardiopulmonary resuscitation) are stable over time and independent of their health status (13). A systematic review of where adult patients would prefer to die revealed that most people would prefer to die at home and that such preferences are independent of changes in health status (14). These results were confirmed in another systematic review (15) on adult patients with diverse health conditions. However, it was unclear what proportion of patients preferred home when the underlying condition is taken into account (e.g. cancer *versus* non-cancer conditions) (15). Furthermore, considerable heterogeneity between and within population groups has been found, both in the proportion

of patients whose preferences change over time and in the direction of such changes (e.g. towards or away from more aggressive care) (10, 13).

Multimorbidity is positively associated with the desire not to be resuscitated, but this finding depends on the nature of the morbidities. Cognitive impairment, stroke and cancer were very positively associated with the desire not to be resuscitated, while heart diseases were not (16). However, we have no information on the preferences of patients with a mix of disabling / life-threatening conditions or an accumulation of several conditions. To the best of our knowledge, no systematic review has focused on EoL care preferences of older patients with multimorbidity.

To provide decision support to health care providers and assist this complex patient population in an emotionally difficult situation, we therefore aim to systematically review a cluster of EoL care preferences of older patients with multimorbidity that we previously identified in an evidence map we prepared on health-related preferences (17). This will allow us to synthesize current knowledge of EoL care preferences and help prioritize and guide future innovations in EoL care policy.

METHODS AND ANALYSIS

The present protocol will follow the Preferred Reporting System Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist (18) (see online additional file 1).

[About here link to: Additional file 1. Preferred Reporting System Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist]

Design

Mixed methods systematic review using the convergent integrated approach on qualitative / quantitative study designs.

Criteria for considering studies for this review

Types of studies

We will include primary studies that use quantitative (e.g. questionnaires), qualitative (e.g. interviews, focus groups) and mixed methods methodologies.

We will exclude case reports and articles, such as conference abstracts, narrative reviews and editorials, that include no detailed description of methods.

Types of participants

We will include older patients (mean or median age ≥ 60 years) with multimorbidity (two or more simultaneous conditions) (1).

Studies addressing only the preferences of caregivers, family members, and health care professionals, will be excluded. Studies confined to population-based and general public perspectives will also be excluded.

Types of outcomes

Primary outcome

Our primary outcome will focus on patients' EoL care preferences with respect to i) the use or non-use of life-sustaining treatments (e.g. percentage of patients with preferences for or against cardiopulmonary resuscitation, intubation and mechanical ventilation, intensive care, intravenous nutritional support, nasogastric tube feeding and/or dialysis withdrawal), ii) palliation of symptoms and iii) the place where EoL care is to be administered (e.g. percentage of patients that would prefer to die at home).

We will leave out studies investigating preferences for or against interventions of limited availability or whose legal status is unclear (e.g. preferences for or against euthanasia or physician-assisted suicide, which is neither legal nor available in most Western countries). We will also exclude studies exploring patients' will to live.

Table 1. Inclusion & exclusion criteria

Inclusion criteria	Exclusion criteria

⇒ Quantitative (observational & interventional) and qualitative studies addressing end-of-life care preferences from the patient's perspective ⇒ Age: average/median age of 60 or older, geriatric patients, elderly patients ⇒ Multimorbidity: two or more simultaneous acute or chronic conditions ⇒ Setting: We will not apply restrictions to geographical location, country or healthcare context ⇒ No restrictions to the date of publication or language of the study	⇒ Case reports ⇒ Articles without details of methods o Conference abstracts o Narrative reviews o Editorials ⇒ Studies investigating preferences for or against interventions that are not generally available or only legal in limited contexts (e.g. euthanasia) ⇒ Studies addressing only preferences of caregivers, family members and health care professionals ⇒ Population-based studies (public health perspective)

Search methods used to identify studies

Electronic searches

We will search the following electronic sources from inception using a combination of MESH headings and keywords: MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index, Social Sciences Citation Index Expanded, PSYNDEX and The Cochrane Library. We will not apply any restrictions to publication date or language.

We will follow the recommendations of PRESS Peer Review of Electronic Search Strategies and develop the final search strategy in collaboration with an expert medical science librarian (19).

The electronic search strategy for the MEDLINE database is provided in Table 2. This search strategy will be adapted for use in the other databases.

[About here: Table 2. Search for End-of-Life Care Preferences]

Searching other resources

We will identify potentially eligible studies that are not captured by our electronic database searches by examining the reference lists of included studies, relevant systematic reviews and meta-analyses, and by carrying out searches of cited references (forward and backward citation tracking) using the Web of Science Core Collection.

Study records

Data management

Bibliographic details of all identified references will first be uploaded to Endnote© and then converted into COVIDENCE© for title, abstract and full text screening. Duplicates will be removed.

Selection of studies

Two review authors (AIG, JN) will independently screen the title and abstract of every identified study to determine which should be assessed further. Before screening, a stepwise calibration exercise will be performed on a sample of 30 studies (20), with the aim of achieving 80% agreement between reviewers. In case 80% agreement is not reached, our inclusion and exclusion criteria will be refined, and the calibration repeated until the threshold is met. We will report any changes to the inclusion and exclusion criteria that result from the calibration exercise as deviations from the published protocol. The full text of potentially eligible papers will be then retrieved and independently assessed for eligibility by two reviewers (AIG, JN). Any discrepancy will be resolved through discussion and consensus (CS).

We will present a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow-chart of study selection (21).

Data collection

Two review authors (AIG, JN) will independently extract key study and participant characteristics from all studies that fulfil the inclusion criteria, and report data on outcomes. Any disagreement will be resolved by discussion, or by a third author (CS), if necessary. A calibration process similar to the one described above will precede data extraction.

Data items

We will stratify data extraction according to study type. Using standard extraction templates in Access datasheets, data will be extracted under the following headings: i) *Study reference* (i.e. first author, year of publication, country of study origin); ii) *Study aim;* iii) *Study setting;* iv) *Sample size;* v) *Population characteristics* (e.g. age, sex, definition of multimorbidity, patient prognosis or illness severity, cancer or non-malignant condition); vi) *Preference-assessment method* (e.g. interview or questionnaire, number of assessments, time between assessments if applicable); vii) *Context of preference* (i.e. hypothetical / real, preference-sensitive situation); viii) *Information provided by the authors on the presentation of alternatives* (e.g. negative or positive framing (22, 23)); ix) *Outcome description* (EoL care elements that patients were queried about, e.g. resuscitation preference); and x) *Results of described outcomes* (e.g. proportion of participants expressing a preference for a specific type of EoL care) (Table 3).

[About here: Table 3. Data extraction framework]

Dealing with duplicate and associated publications

In the event of multiple reports (publications) of a primary study, we will maximize the yield of information by collating all available data and using the most complete dataset, aggregated across all known publications.

Assessment of risk of bias in included studies

Two review authors (AIG, JN) will use the Mixed Methods Appraisal Tool (MMAT) and independently assess the risk of bias (RoB) and the applicability of the results for each included study (24). Assessments will be compared, and disagreements resolved through discussion and

consensus, or by consultation with a third author if necessary (CS). If appropriate, sensitivity analysis will be performed based on the results of the RoB evaluation.

Data synthesis

Should the included study pool permit quantitative information synthesis, we will conduct a mixed methods systematic review using a convergent integrated approach that i) synthesizes qualitative data by means of thematic synthesis, ii) synthesizes quantitative data, and performs meta-analysis if applicable, and in a final step, iii) synthesizes both i) and ii) following the methodology described by Sandelowski et al. and Pearson et al. (25, 26).

Descriptive analyses will be carried out if a lack of studies makes meta-analyses unfeasible, or if heterogeneity prevents quantitative information synthesis. We will first assess heterogeneity qualitatively (in terms of study design, population and outcomes). Assuming the qualitative assessment does not preclude meta-analyses of studies, we will also assess heterogeneity by means of X^2 and additional tests.

Planned sensitivity and subgroup analysis

Sensitivity analyses are planned (irrespective of the presence of heterogeneity) to determine the impact of bias by excluding studies that carry a high risk of it. If the study data allows, we plan to conduct subgroup analyses to examine whether EoL care preferences are affected by age, sex, specific life-sustaining treatment modalities, specific contexts of the preference assessment (hypothetical or real scenarios), type of advanced disease (cancer or non-malignant), patient prognosis or illness severity.

Timeline for review

At the time of this submission we have already completed electronic searches, piloted the study selection process and started formally screening search results with respect to the eligibility criteria. This systematic review is scheduled to end in August 2020.

Patient and public involvement

A patient representative (KR) from the Federal Joint Committee "Gemeinsamer Bundesausschuss (G-BA)" actively participated in the design of the systematic review. KR has considerable experience in evidence-based medicine and an understanding of the pivotal role of patients' preferences in the provision of health care. The G-BA is the ultimate decision-making body for the joint self-administration of stakeholders in the German health service, and the statutory health insurance service catalogue for over 70 million insured individuals is based on its guidelines.

ETHICS AND DISSEMINATION

Due to the nature of the proposed systematic review, ethics approval is not required. We will disseminate our study findings to health care providers and patients, and present them at relevant national and international conferences. We also aim to publish the results of the study in a peer-reviewed journal.

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DECLARATIONS

Authors' contributions

AIG wrote the initial draft of the protocol. CM is the guarantor of the review. CS and JJM provided methodological guidance and revisions of the manuscript. CS and JN assisted in the identification of databases and reviewed the search strategy. TSN, MSB, JWB, MvdA, KR, OW, TH, SES and FMG are co-supervisors of this project, provided advice at all stages of the development of the protocol, and contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data to be generated or analyzed during this study are included in the published article [and its supplementary information files].

Word count

1,871

Table 2. Search for End-of-Life Care Preferences

13.09.2019 – Medline via Ovid (medall)

1.	((advanced OR incurabl* OR progressive OR life-limiting OR fatal OR serious* OR end-stage OR terminal*) adj3 (disease OR condition OR illness OR ill OR morbid*)).ti,ab,kf.	End-of-Life
2.	(End of life OR (last days adj3 life) OR (last year* adj3 life) OR (last week* adj3 life) OR (last month* adj3 life) OR (last days adj3 live) OR (last week* adj3 live) OR (last month* adj3 live) OR (last year* adj3 live) OR imminent death OR (close adj3 death) OR before death OR palliative).ti,ab,kf.	End-of-life
3.	(Terminal Care OR Terminally Ill OR Hospice Care OR Life Support Care OR Advanced Cardiac Life Support OR Palliative Care).sh.	
4.	or/1-3	
5.	(Comorbidity OR Multimorbidity OR Multiple Chronic Conditions).sh.	Multimorbidity
6.	((comorbid* OR multiple OR several OR multi OR concurrent OR complex OR more than one) adj4 (disease* OR condition* OR illness* OR morbid*)).ti,ab,kf.	
7.	(Comorbidit* OR multimorbidit* OR multidisease* OR polymorbid* OR frail*).ti,ab,kf.	
8.	or/5-7	

9.	4 AND 8	
10.	(scale OR scaling OR ranking OR rating OR conjoint-analysis OR conjoint-analyses OR contingent valuation OR analytic hierarch* process* OR time trade off OR evidential reasoning OR multi-attribute utility OR maut OR multiattribute decision model OR madm OR electre iv OR electre is OR visual analog* scale OR score* OR scoring OR standard gamble OR EVIDEM OR paprika method OR simple additive weighting method OR weighted product method OR wpm OR technique for order preference by similarity to ideal solution OR topsis OR analytic network process OR anp OR todim OR macbeth OR smart OR focus group* OR interview* OR questionnair* OR choice).ti,ab,kf.	Methods to elicit Preferences
11.	(prefer* OR wish* OR need OR needs OR value* OR belief* OR want* OR desire* OR priorit* OR attitude* OR perception* OR evaluation* OR choice* OR experience* OR decision* OR decide* OR perspective*).ti,ab,kf.	Preferences
12.	(patient* OR women* OR men* OR elder* OR old* OR frail*).ti,ab,kf.	
13.	10 AND 11 AND 12	

14.	(Patient Satisfaction OR Patient Preference OR Health Priorities OR Needs Assessment OR Advance Care Planning OR Advance Directives).sh.	
15.	9 AND 13	
16.	9 AND 14	
17.	or/15-16	**2,176 articles retrieved**

Table 3. Data extraction framework

Bibliometrics	Description	Coding
Study identification	First Author, year of publication	(journal's description)
Study characteristics	Study aim	(authors' description)
	Geographical location	Country
	Study setting	Inpatient, outpatient
	Type of study	Observational (i.e. qualitative, quantitative cross-sectional, quantitative longitudinal, mixed methods) or interventional study
Patient characteristics	Sample size	Number of patients
	Age	(years)
	Sex	(% females)
	Definition of multimorbidity	(authors' description)
	Prognosis or illness severity indices (if applicable)	e.g. less than 6 months of life or congestive heart failure NYHA II-IV
	Type of index condition (if applicable)	Cancer or non-malignant
Methods of data collection	Type of data collection	Interview, semi-structured interview, survey, focus

		group, questionnaire (authors' description)
	Context of the preference	Hypothetical / real preference-sensitive situation*
	Presentation of information on alternatives – Framing effect**	High-risk of positive-negative framing, low risk of framing or unclear
	Number of assessments	e.g. one assessment if cross-sectional, two or more assessments if longitudinal
	Time between assessments	If applicable
Outcome	Outcome description	Type of EoL preference queried e.g. cardiopulmonary resuscitation
	Outcome results	e.g. percentage of patients for or against life-sustaining treatments (number of patients stating a preference out of all the patients included in the study)
Results / Conclusions		(authors' description)

EoL = End of Life; NYHA = New York Heart Association.

*Hypothetical preference-sensitive situation: EoL care preferences are measured by asking study participants to imagine themselves in a situation in the future that requires such care; Real preference-sensitive situation: EoL care preferences are measured by asking study participants to state their preferences in a context that actually requires them to express a preference for such care. Examining preferences using hypothetical scenarios removes the acute stress of making decisions when confronted with an EoL situation.

**Framing effect: Cognitive bias caused by the influence of the way information is presented on the choices people make.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in: Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	102-104
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-75
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	353-359
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	362-364
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	362-364
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	362-364
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	112-145
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	146-151

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	162-186 Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	187-192
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	195-197 Table 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	204-207
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	208-219
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	220-224
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	225-237 Table 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	235-237 Table 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	242-247
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	248-258
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	248-258
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	259-265
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	248-258

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	259-261
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	242-247

NA = not applicable

BMJ Open

End-of-life care preferences of older patients with multimorbidity: protocol of a mixed-methods systematic review.

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TITLE

End-of-life care preferences of older patients with multimorbidity: protocol of a mixed-methods systematic review.

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ABSTRACT

Introduction

End-of-life care is an essential task performed by most health care providers, and often involves decision-making about how and where patients want to receive care. To provide decision support to health care professionals and patients in this difficult situation, we will systematically review a knowledge cluster of the end-of-life care preferences of older patients with multimorbidity that we previously identified using an evidence map.

Methods and analysis

We will systematically search for studies reporting end-of-life care preferences of older patients (mean age ≥60) with multimorbidity (≥2 chronic conditions) in MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index, Social Sciences Citation Index Expanded, PSYNDEX and The Cochrane Library from inception to September 2019. We will include all primary studies that use quantitative, qualitative and mixed methodologies, irrespective of publication date and language.

Two independent reviewers will assess eligibility, extract data and describe evidence in terms of study/population characteristics, preference assessment method, and end-of-life care elements that matter to patients (e.g. life-sustaining treatments). Risk of bias/applicability of results will be independently assessed by two reviewers using the Mixed-Methods Appraisal Tool. Using a convergent integrated approach on qualitative/quantitative studies, we will synthesize information narratively and, wherever possible, quantitatively.

Ethics and dissemination

Due to the nature of the proposed systematic review, ethics approval is not required. Results from our research will be disseminated at relevant (inter-)national conferences and via publication in peer-reviewed journals. Synthesizing evidence on end-of-life care preferences of older patients with multimorbidity will improve shared decision-making and satisfaction in this final period of life.

Registration

PROSPERO registration number: CRD42020151862.

Strengths and limitations of this study

- This is the first systematic review on end-of-life care preferences of patients with multimorbidity and will provide an important body of evidence to support the consideration of patient-centred care in end-of-life care policy.
- A multinational and multidisciplinary team with considerable methodological experience and skills will provide the necessary expertise.
- A patient representative has been involved in designing the study to ensure that from the beginning, patient-relevant questions are assessed, and results discussed accordingly.
- The main study limitations are the poor indexing of articles, and the missing or non-standardized definition of “patient preferences”.

INTRODUCTION

Multimorbidity, or the presence of multiple coexisting chronic diseases or conditions (1), affects the majority of older adults (2), and is associated with increased mortality and health care utilization (3–5). In addition, multimorbidity negatively impacts quality of life and increases symptom burden (6–8). Evidence is therefore required on how to best manage multimorbid patients (9, 10).

The care of patients with multimorbidity entails complex medical decision-making, especially at the end of life (EoL). EoL care refers not only to the health care services that are provided to patients in the final hours or days of their lives, but, more broadly, to those provided to all patients whose conditions have become advanced, progressive, and incurable (11, 12). EoL care must be embedded within the context of patient preferences, so the care multimorbid patients receive during the final days of their lives is concordant with the care they desire. However, individuals with multimorbidity often have to make numerous and conflicting decisions and choices, which makes eliciting their preferences rather challenging. The provision of effective EoL care to those with multimorbidity is impossible without cooperation between palliative care providers, specialty care, and primary care. In fact, EoL care is an essential task performed by most health care providers, and often involves decision-making about how and where patients want to receive care.

According to recent studies that were not confined to patients with multimorbidity, most adults' EoL care preferences (e.g. for cardiopulmonary resuscitation) are stable over time and independent of their health status (13). A systematic review of where adult patients would prefer to die revealed that most people would prefer to die at home and that such preferences are independent of changes in health status (14). These results were confirmed in another systematic review (15) on adults with diverse health conditions. However, it was unclear what proportion of people preferred home when the underlying condition was taken into account (e.g. cancer *versus* non-cancer conditions) (15). Furthermore, considerable heterogeneity

between and within population groups exists, both in the proportion of patients whose preferences change over time and in the direction of such changes (e.g. towards or away from more aggressive care) (10, 13).

Multimorbidity is positively associated with the desire not to be resuscitated, but this finding depends on the nature of the morbidities. Cognitive impairment, stroke and cancer were very positively associated with the desire not to be resuscitated, while heart diseases were not (16). However, we have no information on the preferences of patients with a mix of disabling / life-threatening conditions or an accumulation of several conditions. To the best of our knowledge, no systematic review has focused on EoL care preferences of older patients with multimorbidity.

To provide decision support to health care providers and assist this complex patient population in an emotionally difficult situation, we aim to systematically review EoL care preferences of older patients with multimorbidity. We will base the review on a knowledge cluster of EoL care preferences that we identified in an evidence map we previously developed on health-related preferences in older patients with multimorbidity (17). The systematic review is the natural next step and will allow us to synthesize current knowledge of EoL care preferences and help prioritize and guide future innovations in EoL care policy.

METHODS AND ANALYSIS

The present protocol will follow the Preferred Reporting System Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist (18) (see online additional file 1).

[About here link to: Additional file 1. Preferred Reporting System Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist]

Design

Mixed-methods systematic review using the convergent integrated approach in which data is transformed in such a way that quantitative and qualitative data can be combined, and the synthesis of quantitative and qualitative studies simultaneously occurs (19).

Criteria for considering studies for this review

Types of studies

We will include primary studies that use quantitative (e.g. questionnaires), qualitative (e.g. interviews, focus groups) and mixed-methods methodologies. Systematic reviews and meta-analyses will not be included, but if a systematic review is relevant to our topic we will screen its reference list for potentially eligible studies that were not identified in our systematic literature searches (see the section on search methods used to identify studies).

We will exclude case reports and articles, such as conference abstracts, narrative reviews and editorials.

Types of participants

We will include older patients (mean or median age ≥ 60 years (20)) with multimorbidity (two or more simultaneous chronic conditions) (1). Studies focusing on patients with one chronic disease will be included when authors have reported on at least one additional chronic condition in the majority of the study population.

Studies addressing only the preferences of caregivers, family members, and health care professionals, will be excluded. Studies confined to population-based and general public perspectives will also be excluded.

Phenomenon of interest

Our phenomenon of interest will focus on EoL care preferences, defined as preferences related to the care that should be provided in the final period of life, regardless of whether it may, in some cases, be provided for months or even years (12). EoL care preferences will comprise i) willingness to receive life-sustaining treatments (e.g. percentage of people with preferences for or against cardiopulmonary resuscitation, intubation and mechanical ventilation, intensive

care, intravenous nutritional support, nasogastric tube feeding and/or dialysis withdrawal), ii) willingness to opt for palliation of symptoms, iii) the place where patients would prefer to receive EoL care (e.g. percentage of people that would prefer to die at home), and iv) interest in participating in a shared decision-making process related to EoL care.

We will exclude studies investigating preferences for or against interventions of limited availability or whose legal status is unclear (e.g. preferences for or against euthanasia or physician-assisted suicide) as such approaches are deemed outside the scope of this review. We will also exclude studies exploring patients' will to live.

(see Table 1)

Table 1. Inclusion & exclusion criteria

Inclusion criteria	**Exclusion criteria**
⇒ Quantitative (observational & interventional) and qualitative studies addressing end-of-life care preferences from the patient's perspective ⇒ Age: average/median age of 60 or older, geriatric patients, elderly patients ⇒ Multimorbidity: two or more simultaneous chronic conditions	⇒ Case reports ⇒ Articles without details of methods ○ Conference abstracts ○ Narrative reviews ○ Editorials ⇒ Studies investigating preferences for or against interventions that are not generally available or only legal in limited contexts (e.g. euthanasia) ⇒ Studies only addressing preferences of caregivers, family members and health care professionals

⇒ Setting: We will not apply restrictions to geographical location, country or healthcare context ⇒ No restrictions to the date of publication or language of the study	⇒ Population-based studies (public health perspective)

Search methods used to identify studies

Electronic searches

We will search the following electronic sources from inception using a combination of MESH headings and keywords: MEDLINE, CINAHL, PsycINFO, Social Sciences Citation Index, Social Sciences Citation Index Expanded, PSYNDEX and The Cochrane Library. To avoid publication bias, we will not apply any restrictions to publication date or language.

We will follow the recommendations of PRESS Peer Review of Electronic Search Strategies and develop the final search strategy in collaboration with an expert medical science librarian (21). The electronic search strategy for the MEDLINE database from inception to September 2019 is provided in Table 2. This search strategy will be adapted for use in the other databases.

[About here: Table 2. Search for End-of-Life Care Preferences]

Searching other resources

We will identify potentially eligible studies that are not captured by our electronic database searches by examining the reference lists of included studies, relevant systematic reviews and meta-analyses, and by carrying out searches of cited references (forward and backward citation tracking) using the Web of Science Core Collection.

Study records

Data management

Bibliographic details of all identified references will first be uploaded to Endnote© and then converted into COVIDENCE© for title, abstract and full text screening. Duplicates will be removed.

Selection of studies

Each of the two review authors (AIG, JN) will independently screen the title and abstract of each identified study to determine which should be assessed further. Before screening, a stepwise calibration exercise will be performed on a sample of 30 studies (22), with the aim of achieving 80% agreement between reviewers. In case 80% agreement is not reached, our inclusion and exclusion criteria will be refined, and the calibration repeated until the threshold is met. We will report any changes to the inclusion and exclusion criteria that result from the calibration exercise as deviations from the published protocol. The full text of potentially eligible papers will then be retrieved and independently assessed for eligibility by two reviewers (AIG, JN). Any discrepancy will be resolved through discussion and consensus (CS). We will present a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow-chart of study selection (23).

Data collection

One review author (AIG) will extract key study and participant characteristics from all studies that fulfil the inclusion criteria, and report data on the phenomenon of interest. The second review author (CS) will cross-check the extracted data. Any disagreement will be resolved by discussion, or, if necessary, by a third author (CM).

Data items

We will stratify data extraction according to study type. Using standard extraction templates in Access datasheets, data will be extracted under the following headings: *Study reference* (i.e. first author, year of publication, country of study origin); *Study aim; Study setting; Sample size; Population characteristics* (e.g. age, sex, definition of multimorbidity, prognosis or illness severity, cancer or non-malignant condition); *Preference-assessment method* (e.g. interview or

questionnaire, number of assessments, time between assessments if applicable); *Context of preference* (i.e. hypothetical / real, preference-sensitive situation); *Information provided by the authors on the presentation of alternatives* (e.g. negative or positive framing (24, 25); *Description of phenomenon of interest* (EoL care elements that study participants were queried about, e.g. resuscitation preference); and *Results concerning the described phenomenon of interest* (e.g. proportion of participants expressing a preference for a specific type of EoL care) (Table 3).

[About here: Table 3. Data extraction framework]

Dealing with duplicate and associated publications

In the event of multiple reports (publications) of a primary study, we will maximize the yield of information by collating all available data and using the most complete dataset, aggregated across all known publications.

Assessment of risk of bias in included studies

A risk of bias assessment will be conducted using the Mixed-Methods Appraisal Tool (MMAT) (26), whereby one author (AIG) will apply the MMAT criteria and a second author (CS) will verify the assessments. Both authors will discuss the impact of the RoB assessments on further analyses and involve a third author (CM) in cases of dissent. If an important RoB is detected, sensitivity analyses will be performed that exclude studies with a high RoB.

Data synthesis

We will conduct a mixed-methods systematic review using a convergent integrated approach in accordance with Joanna Briggs Institute methodology (19) that will i) synthesize qualitative data by means of thematic synthesis, ii) synthesize quantitative data, and perform meta-analysis if applicable, and in a final step, iii) synthesize and integrate both i) and ii) following the methodology described by Sandelowski et al. and Pearson et al. (27, 28). More specifically, the approach will include the following steps:

i) Qualitative analysis and synthesis: Both reviewers (AIG, CS) will independently analyse the extracted data and provide thematic codes. In order to derive a matrix structure, both reviewers will discuss coding and identify overarching thematic issues and categories with the help of MaxQDA18© software (29, 30).

ii) Quantitative analysis: Data from interventional and observational studies will be analysed separately. The meta-analysis of data will be considered in studies that have provided comparable and sufficiently homogeneous outcomes. We will first assess heterogeneity qualitatively (in terms of study design, population and the phenomenon of interest). Assuming the qualitative assessment does not preclude meta-analyses of studies, we will also assess heterogeneity by means of X^2 and additional tests. If a meta-analysis is impossible, a descriptive analysis will be carried out.

iii) Mixed-methods data synthesis (integrated synthesis methodology (27, 28)): To synthesize qualitative and quantitative data, three reviewers (AIG, CS, CM) will decide which is the most promising compatible format based on the results of i) and ii), whereby the decision will depend mainly on the number of qualitative and quantitative studies that are eligible for inclusion (27, 28)). Afterwards (27), data will either be classified according to subject matter (resulting in data synthesis by means of meta-aggregation), or by converting qualitative data into a numerical format (resulting in a quantitative synthesis using meta-analytical approaches) (31, 32, 28).

Planned sensitivity and subgroup analysis

If the available data allows, we will conduct sensitivity analyses that exclude studies at high risk of bias in order to determine its impact. In addition, we plan to conduct subgroup analyses to examine whether EoL care preferences are affected by sex, specific preference assessment contexts (hypothetical or real scenarios), the type of advanced disease (cancer or non-malignant) and patient prognosis or illness severity. If the included studies do not permit

quantitative synthesis, we will descriptively report on evidence relating to the above-mentioned aspects.

Timeline for review

At the time of this submission we have already completed electronic searches, piloted the study selection process and started formally screening search results with respect to the eligibility criteria. This systematic review is scheduled to end in August 2020.

Patient and public involvement

A patient representative (KR) from the Federal Joint Committee "Gemeinsamer Bundesausschuss (G-BA)" actively participated in the design of the systematic review. He was involved in defining the research question, selecting the methodology to be used and the data to be collected, as well as selecting the phenomenon of interest. KR will also be involved in the analysis and interpretation of the findings, crafting the overall message, the development of recommendations and in the dissemination of the results. KR has considerable experience in evidence-based medicine and an understanding of the pivotal role of patients' preferences in the provision of health care. The G-BA is the ultimate decision-making body for the joint self-administration of stakeholders in the German health service, and the statutory health insurance service catalogue for over 70 million insured individuals is based on its guidelines.

ETHICS AND DISSEMINATION

Due to the nature of the proposed systematic review, ethics approval is not required. We will disseminate our study findings to health care providers and patients, and present them at relevant national and international conferences. We also aim to publish the results of the study in a peer-reviewed journal.

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DECLARATIONS

Authors' contributions

AIG wrote the initial draft of the protocol. CM is the guarantor of the review. CS and JJM provided methodological guidance and revisions of the manuscript. CS and JN assisted in the identification of databases and reviewed the search strategy. TSN, MSB, JWB, MvdA, KR, OW, TH, SES and FMG are co-supervisors of this project, provided advice at all stages of the development of the protocol, and contributed to the revision of the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

All data to be generated or analysed during this study are included in the published article [and its supplementary information files].

Word count

2,284

Table 2. Search for End-of-Life Care Preferences

13.09.2019 – Medline via Ovid (medall)

1.	((advanced OR incurabl* OR progressive OR life-limiting OR fatal OR serious* OR end-stage OR terminal*) adj3 (disease OR condition OR illness OR ill OR morbid*)).ti,ab,kf.	End-of-Life
2.	(End of life OR (last days adj3 life) OR (last year* adj3 life) OR (last week* adj3 life) OR (last month* adj3 life) OR (last days adj3 live) OR (last week* adj3 live) OR (last month* adj3 live) OR (last year* adj3 live) OR imminent death OR (close adj3 death) OR before death OR palliative).ti,ab,kf.	End-of-life
3.	(Terminal Care OR Terminally Ill OR Hospice Care OR Life Support Care OR Advanced Cardiac Life Support OR Palliative Care).sh.	
4.	or/1-3	
5.	(Comorbidity OR Multimorbidity OR Multiple Chronic Conditions).sh.	Multimorbidity
6.	((comorbid* OR multiple OR several OR multi OR concurrent OR complex OR more than one) adj4 (disease* OR condition* OR illness* OR morbid*)).ti,ab,kf.	
7.	(Comorbidit* OR multimorbidit* OR multidisease* OR polymorbid* OR frail*).ti,ab,kf.	
8.	or/5-7	

9.	4 AND 8	
10.	(scale OR scaling OR ranking OR rating OR conjoint-analysis OR conjoint-analyses OR contingent valuation OR analytic hierarch* process* OR time trade off OR evidential reasoning OR multi-attribute utility OR maut OR multiattribute decision model OR madm OR electre iv OR electre is OR visual analog* scale OR score* OR scoring OR standard gamble OR EVIDEM OR paprika method OR simple additive weighting method OR weighted product method OR wpm OR technique for order preference by similarity to ideal solution OR topsis OR analytic network process OR anp OR todim OR macbeth OR smart OR focus group* OR interview* OR questionnair* OR choice).ti,ab,kf.	Methods to elicit Preferences
11.	(prefer* OR wish* OR need OR needs OR value* OR belief* OR want* OR desire* OR priorit* OR attitude* OR perception* OR evaluation* OR choice* OR experience* OR decision* OR decide* OR perspective*).ti,ab,kf.	Preferences
12.	(patient* OR women* OR men* OR elder* OR old* OR frail*).ti,ab,kf.	
13.	10 AND 11 AND 12	

14.	(Patient Satisfaction OR Patient Preference OR Health Priorities OR Needs Assessment OR Advance Care Planning OR Advance Directives).sh.	
15.	9 AND 13	
16.	9 AND 14	
17.	or/15-16	**2,176 articles retrieved**

Table 3. Data extraction framework

Bibliometrics	Description	Coding
Study identification	First Author, year of publication	(journal's description)
Study characteristics	Study aim	(authors' description)
	Geographical location	Country
	Study setting	Inpatient, outpatient
	Type of study	Observational (i.e. qualitative, quantitative cross-sectional, quantitative longitudinal, mixed methods) or interventional study
Patient characteristics	Sample size	Number of patients
	Age	(years)
	Sex	(% females)
	Definition of multimorbidity	(authors' description)
	Prognosis or illness severity indices (if applicable)	e.g. less than 6 months of life or congestive heart failure NYHA II-IV
	Type of index condition (if applicable)	Cancer or non-malignant
Methods of data collection	Type of data collection	Interview, semi-structured interview, survey, focus

		group, questionnaire (authors' description)
	Context of the preference	Hypothetical / real preference-sensitive situation*
	Presentation of information on alternatives – Framing effect**	High-risk of positive-negative framing, low risk of framing or unclear
	Number of assessments	e.g. one assessment if cross-sectional, two or more assessments if longitudinal
	Time between assessments	If applicable
Phenomenon of interest	Description	Type of EoL preference queried e.g. cardiopulmonary resuscitation
	Results	e.g. percentage of participants for or against life-sustaining treatments (number of participants stating a preference out of all the patients included in the study)
Results / Conclusions		(authors' description)

EoL = End of Life; NYHA = New York Heart Association.

*Hypothetical preference-sensitive situation: EoL care preferences are measured by asking study participants to imagine themselves in a situation in the future that requires such care; Real preference-sensitive situation: EoL care preferences are measured by asking study participants to state their preferences in a context that actually requires them to express a preference for such care. Examining preferences using hypothetical scenarios removes the acute stress of making decisions when confronted with an EoL situation.

**Framing effect: Cognitive bias caused by the influence of the way information is presented on the choices people make.

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☐	NA
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	102-104
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	5-75
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	353-359
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☐	NA
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	362-364
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	362-364
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	362-364
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	112-145
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	146-151

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	162-186 Table 1
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	187-192
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	195-197 Table 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	204-207
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	208-219
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	220-224
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	225-237 Table 3
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	235-237 Table 3
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	242-247
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	248-258
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	248-258
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	259-265
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	248-258

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	259-261
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	242-247

NA = not applicable