Evidence on health inequities experienced by the rare disease community with regards to receipt of a diagnosis and access to health and social care services: protocol for a scoping review

Authors: Simon Briscoe,[1] Ruth Garside,[1] Hassanat Lawal,[1] G.J. Melendez-Torres,[1] Noreen Orr,[1] Liz Shaw,[1] Katy Sutcliffe,[2] James Thomas,[2] Jo Thompson Coon[1]

[1]Exeter PRP Evidence Review Facility, University of Exeter Medical School, University of Exeter, St Lukes Campus, Exeter, Devon, EX1 2LU.

[2]London-York PRP Evidence Review Facility, EPPI Centre, Social Research Institute, University College London, 11 Woburn Square, London, WC1H 0NS.

Rationale

Health inequities are systematic, avoidable and unfair differences in health between populations or population subgroups.[1] The England 2023 Rare Disease Action Plan is committed to addressing inequities associated with rare diseases.[2] This builds on the UK Rare Diseases Framework, which sets out four priorities including: ensuring patients get the right diagnosis faster; increasing awareness of rare diseases among healthcare professionals; better coordination of care; and improving access to specialist care, treatments and drugs.[3] In particular, the England 2023 Rare Disease Action Plan commits to gathering the evidence needed to evaluate whether rare diseases should be incorporated into the 'PLUS' category of NHS England's Core20PLUS5 framework, enabling integrated care systems (ICS) to develop targeted actions to reduce inequalities. ICSs were developed to improve care for people with complex and long term conditions, such as the rare disease community.[4] The Core20PLUS5 framework aims to support ICSs to reduce health inequities for people with complex and long term conditions at a local and national level – the 'PLUS' category refers to population groups that are likely to experience poorer than average health access, outcomes or experiences. These people require support from a range of different health care professionals who are situated across primary, secondary and specialist care settings which requires effective co-ordination to meet their needs.[5] ICSs bring together NHS organisations, social care, local authorities and the voluntary and charitable sectors to collaborate on providing effective and equitable care.

Although there is evidence that health inequity is experienced by specific groups within the rare disease community, there is no overall understanding of the extent of the evidence of health inequity across the rare disease community.[6] This includes whether there is evidence of health inequity *within*

the rare disease community, and also *between* the rare disease community and the general population. As highlighted in the UK Rare Diseases Framework, two areas where health inequity may be experienced are, firstly, obtaining a diagnosis and, secondly, access to services.[3] Inequities around diagnosis and service access can arise due to lack of clinician training and education on how to diagnose rare diseases and the services that are available.[7] However, there are also examples where people with relatively well-known rare diseases experience a lack of understanding amongst health care professionals when accessing services.[8] For example, people accessing care for sickle cell disease have reported dismissive attitudes from clinicians.[9]

Aim

To identify and summarise evidence on health inequities experienced within the rare disease community or between the rare disease community and general population with regards to receipt of a diagnosis and access to health and social care services.

Research question

What are the key characteristics and extent of evidence on health inequities experienced within the rare disease community or between the rare disease community and the general population with regards to receipt of a diagnosis and access to health and social care services?

Specific research objectives

- To carry out a scoping review which will systematically identify and describe the available evidence on health inequities experienced within the rare disease community or between the rare disease community and general population with regards to receipt of a diagnosis and access to health and social care services.
- To draw out findings relevant to the UK context.

Methods

This scoping review will follow established guidance.[10] Scoping reviews aim to "systematically identify and map the breadth of evidence available on a particular topic, field, concept, or issue, often irrespective of source (i.e., primary research, reviews, non-empirical evidence) within or across particular contexts."[11] We anticipate that this project will take approximately 20 weeks full-time working to complete.

Inclusion and exclusion criteria

We summarise the inclusion and exclusion criteria using the PICo framework below (Population, phenomenon of Interest and Context), in addition to providing criteria for geographic, study design, date and language limits.[12]

Population

Include

People or carers of people with a rare disease, defined according to European Union legislation as a disease affecting less than 1 in 2000 people.[13] Specific types of disease include:

- Rare diseases listed on the Orphanet website (c. 7000).[14]
    - To ensure we include all relevant diseases, in cases of uncertainty we will use the Rare Disease Research Landscape search protocol as a check for rare disease names when conducting title/abstract screening, which specifies c. 24,000 descriptive terms for rare diseases derived from the Orphanet website.[15] We will also consult stakeholders if necessary.

Carers including (but not limited to):

- Family carers
- Unpaid carers

Exclude

Rare disease which fall outside of the UK Rare Diseases Landscape report, namely:[16]

- Rare cancers
    - However, we will *not* exclude rare diseases which manifest as non-malignant tumours or which increase the risk of developing cancer.
- Rare infectious diseases.
- Diseases which do not meet the definition of rare disease above, i.e. diseases affecting more than 1 in 2000 people.

Phenomenon of interest

Include

Data on health inequities as described in the PROGRESS Plus framework:[17]

- PROGRESS criteria:
    - Place of residence
    - Race/ethnicity/culture/language

    - Occupation
    - Gender/Sex
    - Religion
    - Education
    - Socioeconomic status
    - Social capital
- Plus criteria
    - Personal characteristics associated with discrimination (e.g. age, disability, including both visible and invisible disabilities)
    - Features of relationships (e.g. smoking parents, excluded from school)
    - Time-dependent relationships (e.g. leaving the hospital, respite care, other instances where a person may be temporarily at a disadvantage

Researchers have argued that PROGRESS-Plus criteria by themselves are not sufficient for identifying potential health inequity.[18] Thus, we will also include studies which describe inequity which is not explicitly stated in the PROGRESS-Plus criteria, for example:

- Clinician education/awareness of rare disease services
- Health literacy

A list of potential inequities identified following full-text screening will be considered in discussion with the topic expert group.

Exclude

Inequities related to the cost of treatment, e.g. the relative cost of making medicines for rare diseases available via the NHS compared to medicines for diseases which are not rare.

Context

Include

EITHER:

1. Data on **obtaining a diagnosis**, e.g.
    - Accuracy of diagnosis
    - Misdiagnosis
    - Clinician understanding of diagnostic criteria
    - Counselling or support received with diagnosis
    - Time to diagnosis

OR:

2. Data on **access to health and social care services, or services more broadly (including voluntary and charitable sector) if these are commissioned by ICSs**:
    - Health care service include:
        - Primary care services (e.g. general practice, pharmacy services, opticians)
        - Secondary care services (e.g. mental health services)
        - Tertiary care services (e.g. specialised care, including highly specialised services)
    - Social care services include (but are not limited to):
        - Social services
    - Other services if commissioned by ICSs include:
        - Charitable sector
        - Voluntary sector
    - Issues relating to access include (but are not limited to):
        - Regional access to services
        - Timeliness of service access
        - Other barriers to service access, e.g. gender, socioeconomic status, etc.

Exclude

- Voluntary organisations when not commissioned by ICSs
- Charitable organisations when not commissioned by ICSs

Note: We are not including data on inequity arising from services provided by voluntary or charitable organisations which are not commissioned by ICSs because inequities at this level cannot be directly addressed by DHSC.

Study design

Include

Any primary study design and systematic reviews, specifically:

- Systematic reviews can include:
    - Systematic reviews
    - Meta analyses
    - Scoping reviews
    - Rapid reviews
    - Mapping reviews

    - Qualitative evidence syntheses
- All systematic reviews except for scoping and mapping reviews must meet the DARE criteria.[19]

Exclude

- Narrative reviews
- Systematic reviews which do not meet the DARE criteria.[19]

Geographic location

Include

- UK primary studies only
- No country limit for systematic reviews.

Exclude

- Non-UK primary studies.

Date

Include

- Studies published from 2010 to date of search.

Language

Include

- Studies written in English language only.

Search for studies

The search for studies will combine bibliographic database searches with various supplementary searches.

Bibliographic database searches

The bibliographic database search strategy will include generic search terms for rare diseases, in addition to generic terms for genetic diseases which are 99% comprised of rare diseases.[20] Search terms for rare diseases will be based on the search terms used in the Rare Disease Research Landscape project, specifically, the rare disease constructs which are available in Annex 3 of the web report.[15] The purpose of including genetic disease terminology alongside rare disease terminology in the search is not to privilege genetic rare diseases, but due to the fact that our background reading suggests that genetic rare diseases are not routinely described as rare in the literature. As such, we need to use genetic terminology to retrieve studies of rare genetic diseases, e.g. “genetic disease”, “genetic condition”, “genetic disorder”. Other than this, we will not search for specific types of rare

diseases owing to the large volume of diseases in scope for this project and the logistical problem of how to enter the relevant terminology into a bibliographic database. We have also ascertained that studies which meet our eligibility criteria typically either use generic rare disease or genetic disease terminology to describe the population of interest in the title and abstract or controlled vocabulary (e.g. MeSH in MEDLINE), in addition to any descriptive terms for specific rare diseases which are used. We have tested this on a sample set of studies which meet our eligibility criteria, which were identified from scoping searches and from expert solicitation.

Search terms for rare diseases will be combined with search terms which describe access to services and search terms for health equity. Search terms which describe access to services are partly derived from a pre-identified test set of studies which discuss service access for rare diseases. These are supplemented with relevant synonyms. Search terms for equity are partly derived from an existing search filter.[21] These have been supplemented with search terms which describe equity issues which are apparent in the rare diseases community based on reading the available literature. These include terms such as 'knowledge', 'education', 'information', 'communication', 'literacy' and 'unmet need', which describe how there is limited knowledge and understanding about rare diseases amongst clinicians which impacts on their ability to signpost patients to services, and the need for better information for rare disease patients and carers.[8] We also add additional terms such as 'geography' and 'regional' which reflects how equity issues sometimes relate to lack of access to services based on geographic or regional location.[22]

Finally, we will apply two separate filters to identify UK primary studies and systematic reviews. For UK primary studies, we will use a validated UK geographic search filter for databases where this is available.[23] We will not use any study type filter for primary studies. For systematic reviews, we will combine the search results with an appropriate selection of descriptive terms for systematic reviews, including "systematic review*", "evidence synthes?s" and "scoping review*".

We anticipate searching the following bibliographic databases which cover both health and social care services literature:

- ASSIA (via ProQuest)
- CINAHL (via EBSCO)
- Embase (via Ovid)
- HMIC (via Ovid)
- MEDLINE (via Ovid)
- Social Policy and Practice (via Ovid)

A draft MEDLINE search is presented in Appendix A.

Supplementary searches

We will carry out supplementary search methods. This will include checking the reference lists of included studies and conducting forward citation searches of either key or included studies. We will also search the websites of relevant organisations, including organisations recommended by our expert advisory group. This will be with a view to identifying grey literature, although we also included any journal articles identified from searching websites. Websites we will search include:

- Beacon https://www.rarebeacon.org/
- Breaking Down Barriers https://breaking-down-barriers.org.uk/
- Genetic Alliance UK https://geneticalliance.org.uk/
- Medics 4 Rare Diseases https://www.m4rd.org/
- Rare Disease UK https://www.raredisease.org.uk/
- Rare Minds https://www.rareminds.org

We will also search Google Search, primarily but not exclusively with a view to identifying grey literature which is not identified in the bibliographic database searches.

We will carry out hand searching of the Orphanet Journal of Rare Diseases, which we have pre-identified as containing a high number of potentially relevant studies.

Study selection

Titles and abstracts will be exported to EPPI Reviewer 6.0 (EPPI Centre Software, Social Science Research Unit, Institute of Education, University of London, London) and de-duplicated. Search results for UK primary studies and systematic reviews will either be retained in separate libraries or combined, depending on which approach is most appropriate with the time and resources that are available.

As an initial calibration exercise of inclusion judgments and the clarity of our inclusion criteria, all reviewers will apply inclusion and exclusion criteria to the same sample of search results at title and abstract level. Decisions will be discussed in a group meeting to ensure consistent application of criteria. Where necessary, inclusion and exclusion criteria will be revised to enable more consistent reviewer interpretation and judgement. The revised inclusion and exclusion criteria will then be applied to the title and abstract of citations independently by two reviewers until they reach ≥90% agreement, after which we will screen with one reviewer. The level of agreement between reviewers will be calculated by EPPI Reviewer 6.0. We will also use the priority screening function in EPPI Reviewer 6.0. When using the priority screening function, a machine classifier is 'trained' using a

subset of known includes and excludes, the classifier then lists the references to be screened in order of their likely relevance, with the less relevant ones moved towards the end of the list. As reviewers continue to screen the list of references the classifier incorporates the new information to increase accuracy. Screening ceases when a given stopping criterion is reached.[24]

The full text of title and abstract includes will then be sought and assessed for inclusion by two independent reviewers. We will undertake a similar screening calibration exercise to that detailed for title and abstract screening prior to screening full-texts.

Charting the data

Data extraction for a scoping review is referred to as 'charting the data'.[10] We will take a broad and inclusive approach to extracting data which might be relevant to answering the research question, extending across a range of study designs.[10]

This will include:

- First author
- Data of publication
- Study design
- Aims
- Inclusion criteria, including:
    - Population
    - Disease
    - Context (i.e. service access or diagnosis)
- Types of health inequity considered
- Summary of findings

Data charting will be carried out by one reviewer and checked by a second reviewer.

Quality appraisal

As this is a scoping review which seeks to identify and summarise evidence rather than assess evidence we are not planning to undertake quality appraisal.

Presentation of data

We will present data both narratively and in a tabulated format. Data will be categorised and presented using appropriate headers which be determined inductively based on the available data. We do not anticipate categorising data by individual disease type due to the high number of diseases which are eligible for inclusion. However, we may present data according to types of rare disease,

patient pathway from diagnosis to service access, and types of inequity. From the international literature identified via systematic reviews, we will draw out findings which are relevant to the UK context, e.g. based on data from studies set in countries with comparable health care systems.

Policy relevance

This scoping review has been designed to address a research request from the rare diseases policy team at the Department of Health and Social Care.

Stakeholder input

We have convened a topic expert group who have met with us to inform the development of this protocol. This group consists of UK-based rare disease experts from academic and charitable settings, and NHS England. We plan to invite members of the topic expert group to reconvene for the duration of the project once the project timelines have been finalised. Input from the topic expert group during the scoping review will include discussion of potential inequities identified following full-text screening.

PPIE input

We plan to convene a patient and public involvement and engagement (PPIE) group with lived experience of rare diseases for the duration of the project. Details of the project were also discussed with the PERSPEX PPIE group, who are a standing PPIE group for the Exeter PRP Evidence Review Facility, for the development of this protocol.

Resources

We anticipate that the project will take approximately 20 weeks full-time working but may take longer if the project team needs to resource other reviews concurrently which are not currently scheduled.

Dissemination

The scoping review will be sent to stakeholders and will we make the final report publicly available on our institutional repositories. We may also publish the findings in journal article format depending on the timelines and resources required for any follow up work related to this project, e.g. evidence syntheses which are commissioned following the completion of the report.

References

1. McCartney G, Popham F, McMaster R, Cumbers A. Defining health and health inequalities. *Public Health*. 2019;172:22-30.
2. Department of Health and Social Care. England Rare Diseases Action Plan 2023: main report. 2023.

3. Department of Health and Social Care. The UK Rare Diseases Framework. 2021.
4. Charles A. Integrated care systems explained: making sense of systems, places and neighbourhoods Kings Fund2022 [Available from: https://www.kingsfund.org.uk/publications/integrated-care-systems-explained.
5. Castro R, Senecat J, de Chalendar M, Vajda I, Dan D, Boncz B. Bridging the Gap between Health and Social Care for Rare Diseases: Key Issues and Innovative Solutions. *Adv Exp Med Biol*. 2017;1031:605-27.
6. Kole A, Faurisson F. Rare diseases social epidemiology: analysis of inequalities. *Adv Exp Med Biol*. 2010;686:223-50.
7. Tumiene B, Peters H, Melegh B, Peterlin B, Utkus A, Fatkulina N, et al. Rare disease education in Europe and beyond: time to act. *Orphanet J Rare Dis*. 2022;17(1):441.
8. Specialised Healthcare Alliance. Rare diseases, common inequalities: Briding rare disease into the health inequalities agenda. 2023.
9. Thalassemia APPGoSCa. No One's Listening: An inquiry into the avoidable deaths and failures of care for sickle cell patients in secondary care. All Party Parliamentary Group on Sickle Cell and Thalassemia; Sickle Cell Society; 2021.
10. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. *Int J Evid Based Healthc*. 2015;13(3):141-6.
11. Campbell F, Tricco AC, Munn Z, Pollock D, Saran A, Sutton A, et al. Mapping reviews, scoping reviews, and evidence and gap maps (EGMs): the same but different- the "Big Picture" review family. *Syst Rev*. 2023;12(1):45.
12. Stern C, Jordan Z, McArthur A. Developing the review question and inclusion criteria. *Am J Nurs*. 2014;114(4):53-6.
13. Haendel M, Vasilevsky N, Unni D, Bologa C, Harris N, Rehm H, et al. How many rare diseases are there? *Nat Rev Drug Discov*. 2020;19(2):77-8.
14. Orpha.net. Alphabetical list 2023 [Available from: https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&search=Disease_Search_List.
15. Rare Diseases Research Landscape Project. Rare Diseases Research Landscape Project 2023 [Available from: https://nihr.opendatasoft.com/explore/dataset/rare-diseases-research-landscape-project/information/.
16. Department of Health and Social Care, Medical Research Council, National Institute for Health and Care Research. Rare Diseases Research Landscape Project Report. 2023.
17. Cochrane Methods Equity. PROGRESS-Plus 2023 [Available from: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus.
18. Kunonga TP, Hanratty B, Bower P, Craig D. A systematic review finds a lack of consensus in methodological approaches in health inequality/inequity focused reviews. *J Clin Epidemiol*. 2023;156:76-84.
19. Centre for Reviews and Dissemination. Database of Abstracts of Reviews of Effects (DARE): Quality-assessed Reviews 2014 [Available from: (https://www.ncbi.nlm.nih.gov/books/NBK285222/). .
20. UK RD. What is a rare disease? 2021 [
21. Hosking J, Macmillan A, Jones R, Ameratunga S, Woodward A. Searching for health equity: validation of a search filter for ethnic and socioeconomic inequalities in transport. *Syst Rev*. 2019;8(1):94.
22. Gaito S, Aznar MC, Burnet NG, Crellin A, France A, Indelicato D, et al. Assessing Equity of Access to Proton Beam Therapy: A Literature Review. *Clin Oncol (R Coll Radiol)*. 2023;35(9):e528-e36.
23. Ayiku L, Levay P, Hudson T, Finnegan A. The NICE UK geographic search filters for MEDLINE and Embase (Ovid): Post-development study to further evaluate precision and number-needed-to-read when retrieving UK evidence. *Res Synth Methods*. 2020;11(5):669-77.

24. O'Mara-Eves A, Thomas J, McNaught J, Miwa M, Ananiadou S. Using text mining for study identification in systematic reviews: a systematic review of current approaches. *Syst Rev*. 2015;4(1):5.

Appendix 1. Draft MEDLINE search strategy

#	Searches	Results
1	(rare adj2 (autoimmune or autosomal or blood or bone or cardia* or cardio* or childhood or chromosom* or CNV or condition* or congenital or connective or contag* or "copy number variant" or derma* or develop* or disease* or disorder* or dominant or familial or frequency or gene* or genotype or haplotype or hereditary or immun* or inflammatory or inherited or kidney or liver or mendelian or metabolic or metasta* or monogenic or muscul* or mutat* or neuro* or paediatric or pathogen or pediatric or phenotype or polygenic or recessive or respira* or skeletal or skin or tumo* or uro* or variant* or "x linked" or zoono*)).tw,kw.	211196
2	"highly specialised technolog*".tw,kw.	19
3	(orphan adj2 (disease* or drug* or medicine* or medicinal)).tw,kw.	3276
4	orphanet.tw,kw.	196
5	"syndrome* without a name".tw,kw.	3
6	(("low frequency" or neglected) adj3 (condition* or disease or disorder*)).tw,kw.	5907
7	(ultraorphan or ultrarare).tw,kw.	283
8	Rare Diseases/	14295
9	Orphan Drug Production/	1456
10	or/1-9	227165
11	((gene or genes or genetic* or genomic*) adj2 (condition* or disease* or disorder* or medicine or rare)).tw,kw.	100695
12	exp Sequence Analysis, DNA/	258515
13	exp Genetic Diseases, Inborn/	735215
14	or/11-13	1035384
15	10 or 14	1215833

16	((access* or availab* or entry or referral* or pathway* or uptake or utili?ation) adj4 (care or delay* or diagnos* or healthcare or secondary or service* or specialist or support* or time)).tw.	312941
17	(diagnos* adj4 (delay* or incorrect* or missed or time or specialist* or support)).tw.	134883
18	misdiagnos*.tw.	45593
19	((healthcare or "health care" or "health service*" or information* or specialist*) adj3 (need* or support*)).tw.	84292
20	((GP* or "general practitioner*" or primary care) adj2 referral*).tw.	2330
21	exp Health Services Accessibility/	136178
22	exp "Delivery of Health Care"/	1242762
23	delayed diagnosis/	8533
24	or/16-23	1678321
25	15 and 24	40487
26	((gene or genes or genetic* or genomic* or "exome sequencing") adj4 (counsel* or diagnos* or service* or test*)).tw,kw.	131644
27	exp Genetic Services/	65279
28	or/26-27	171112
29	(access* or availab* or delay* or distribution or entry or need or needs or referral* or pathway* or receiving or uptake or utili?ation).tw.	7094133
30	exp Health Services Accessibility/	136178
31	exp "Delivery of Health Care"/	1242762
32	or/29-31	7927113
33	28 and 32	54402
34	25 or 33	89806

35	(inequalit* or inequit* or equalit* or equit* or divers* or discriminat* or disadvantage* or barrier* or obstacle* or utili*ation or unjust* or unfair* or underserved or minorit* or stigma*).tw.	2043722
36	(equit* or inequit* or inequalit* or disparit* or equality).tw.	201188
37	(ethnic* or race or racial* or racis*).tw.	311893
38	((social* or "socio-economic" or socioeconomic or economic or structural or material) adj3 (advantage* or disadvantage* or exclude* or exclusion or include* or inclusion or status or position or gradient* or hierarch* or class* or determinant*)).tw.	164646
39	(health adj3 (gap* or gradient* or hierarch*)).tw.	5711
40	Vulnerable populations/	12935
41	social stigma/	13261
42	socioeconomic factors/	172937
43	poverty/	44326
44	social class/	45205
45	Healthcare Disparities/	22664
46	Health Status Disparities/	19935
47	Poverty areas/	6710
48	Urban population/	62969
49	(SES or SEP or sociodemographic* or "socio-demographic*" or income or wealth* or literacy or poverty or education or "educational level" or "educational attainment" or "well educated" or "better educated" or unemploy* or "home owner*" or tenure or affluen* or "well off" or "better off" or "worse off").tw.	936844
50	(unmet adj3 need*).tw.	35131
51	(financial adj1 (resources or situation)).tw.	7240

52	(geograph* or regional or postcode or rural).tw.	669943
53	(communication or information or informed or knowledge).tw.	2725810
54	or/35-53	5779808
55	exp United Kingdom/	392856
56	(national health service* or nhs*).ti,ab,in.	283253
57	(english not ((published or publication* or translat* or written or language* or speak* or literature or citation*) adj5 english)).ti,ab.	52069
58	(gb or "g.b." or britain* or (british* not "british columbia") or uk or "u.k." or united kingdom* or (england* not "new england") or northern ireland* or northern irish* or scotland* or scottish* or ((wales or "south wales") not "new south wales") or welsh*).ti,ab,jw,in.	2512203
59	(bath or "bath's" or ((birmingham not alabama*) or ("birmingham's" not alabama*) or bradford or "bradford's" or brighton or "brighton's" or bristol or "bristol's" or carlisle* or "carlisle's" or (cambridge not (massachusetts* or boston* or harvard*)) or ("cambridge's" not (massachusetts* or boston* or harvard*)) or (canterbury not zealand*) or ("canterbury's" not zealand*) or chelmsford or "chelmsford's" or chester or "chester's" or chichester or "chichester's" or coventry or "coventry's" or derby or "derby's" or (durham not (carolina* or nc)) or ("durham's" not (carolina* or nc)) or ely or "ely's" or exeter or "exeter's" or gloucester or "gloucester's" or hereford or "hereford's" or hull or "hull's" or lancaster or "lancaster's" or leeds* or leicester or "leicester's" or (lincoln not nebraska*) or ("lincoln's" not nebraska*) or (liverpool not (new south wales* or nsw)) or ("liverpool's" not (new south wales* or nsw)) or ((london not (ontario* or ont or toronto*)) or ("london's" not (ontario* or ont or toronto*)) or manchester or "manchester's" or (newcastle not (new south wales* or nsw)) or ("newcastle's" not (new south wales* or nsw)) or norwich or "norwich's" or nottingham or "nottingham's" or oxford or "oxford's" or peterborough or "peterborough's" or plymouth or "plymouth's" or portsmouth or "portsmouth's" or preston or "preston's" or ripon or "ripon's" or salford or "salford's" or salisbury or "salisbury's" or sheffield or "sheffield's" or southampton or "southampton's" or st albans or stoke or "stoke's" or sunderland or "sunderland's"	1803129

	or truro or "truro's" or wakefield or "wakefield's" or wells or westminster or "westminster's" or winchester or "winchester's" or wolverhampton or "wolverhampton's" or (worcester not (massachusetts* or boston* or harvard*)) or ("worcester's" not (massachusetts* or boston* or harvard*)) or (york not ("new york*" or ny or ontario* or ont or toronto*)) or ("york's" not ("new york*" or ny or ontario* or ont or toronto*))))).ti,ab,in.	
60	(bangor or "bangor's" or cardiff or "cardiff's" or newport or "newport's" or st asaph or "st asaph's" or st davids or swansea or "swansea's").ti,ab,in.	72820
61	(aberdeen or "aberdeen's" or dundee or "dundee's" or edinburgh or "edinburgh's" or glasgow or "glasgow's" or inverness or (perth not australia*) or ("perth's" not australia*) or stirling or "stirling's").ti,ab,in.	265319
62	(armagh or "armagh's" or belfast or "belfast's" or lisburn or "lisburn's" or londonderry or "londonderry's" or derry or "derry's" or newry or "newry's").ti,ab,in.	35129
63	or/55-62	3153019
64	(exp africa/ or exp americas/ or exp antarctic regions/ or exp arctic regions/ or exp asia/ or exp australia/ or exp oceania/) not (exp United Kingdom/ or europe/)	3382992
65	63 not 64	2983353
66	34 and 54 and 65	4352
67	((systematic or Cochrane or effectiveness or qualitative or mapping or overview or realist or scoping or umbrella) adj2 review*).tw.	359048
68	(metasynthes?s or "meta synthes?s" or "meta ethnography" or "meta analys?s").tw.	289398
69	((integrative or integrated) adj1 review*).tw.	5564
70	((evidence or research) adj1 synthes?s).tw.	8643
71	systematic review.pt.	250806
72	meta-analysis.pt.	193898
73	or/67-72	524075

74	34 and 54 and 73	1001
75	66 or 74	5084
76	limit 75 to yr="2010 -Current"	3807