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Systematic Reviews to Inform Research and Treatment for Multi-Morbidities

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Final Systematic Review Report
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Final Report Instructions

Use the template below as a guide for producing the Systematic Review Report. The sections and information requested follow the Deliverables description from the Agreement Statement of Work. If any information requested below was not included in the project, include a brief description of why it was omitted.
Additional results or conclusions produced during performance of the agreement may also be included.

Please submit the Final Report in electronic format to the following individuals:

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A. Executive Summary, including objectives and main findings

Background:

As the population with multiple chronic conditions (MCC) increases, it is essential that randomized controlled trials (RCTs) include MCC to ensure the appropriateness of applying trial results to the broader population. However, previous reviews of RCTs not limited by intervention type have found that individuals with MCC are often excluded, and when MCC are reported in participant characteristics, details are sparse. A thorough systematic review of the inclusion of MCC in RCTs of behavioral and/or psychosocial interventions is needed to provide important insight into the applicability of results and to identify gaps in the design and implementation of behavioral and/or psychosocial interventions in prevention and control of chronic conditions.

Objectives:

With this review we seek to test the hypothesis that individuals with multiple chronic conditions are underrepresented in RCTs of behavioral and psychosocial interventions published in general medical, behavioral medicine, behavioral science, health psychology, social science, and public health journals.

The goals of the review are to: (1) conduct a systematic review to assess the frequency with which research participants with MCC are represented in all or a representative subset of RCTs of behavioral and psychosocial interventions published in general medical and specialized journals, published within the last decade or decade and a half, that focus on behavioral medicine and behavioral science, health psychology, social science, and public health; (2) determine whether there are significant differences by type of journal or over time in the frequency with which research participants with MCC are represented in RCTs of behavioral and psychosocial interventions.

Chronic conditions:

This review considered 20 chronic conditions. The selected conditions were taken from a list compiled by an MCC working group at the Office of the Assistant Secretary of Health (OASH) within the US Department of Health and Human Services (HHS). These chronic conditions meet the definition for chronicity, are prevalent and have potential to be modifiable by public health and/or clinical interventions.

Search methods:

A certified MLS librarian with expertise in searching for systematic reviews designed to retrieve all reported RCTs in adults regarding chronic illness in PubMed MEDLINE and EMBASE. Database supplied limits were used to limit by three year clusters, 2000-2004, 2005-2009, and 2010-2014. Searches were completed in February 2015.

Selection criteria:

Within each 5-year time period, search results were randomly ordered and selection criteria was applied by two independent reviewers until 200 articles meeting inclusion criteria were selected per time period. Selection criteria were primary reports of RCTs of behavioral and/or psychosocial interventions targeting adults with at least one specified chronic conditions of interest.

Data collection and analysis:

Data were extracted independently by two trained readers using a standardized form. Risk of bias was assessed using a modified version of the Cochrane Collaboration tool for assessing risk of bias. After extraction by each reader, records were compared and differences were adjudicated by a third party. Data was managed in REDCap.

Main results:

600 RCTs testing behavioral and/or psychosocial interventions were included. Studies were mostly from specialty journals (83.8%). and about half of studies were from North America (51.5%). The most common intervention focuses were psychological well-being (35.5%) and weight management/diet/physical activity (27.5%). Mean risk of bias score improved over time ($p<0.001$).

Targeting MCC directly was rare (4.3%). The most commonly targeted individual conditions were cancer (17.0%) and diabetes (13.0%). Exclusion criteria related to MCC were categorized as specific (naming specific conditions), general (using general terms for chronic conditions), or vague (criteria without clear definition that is likely to result in exclusion of MCC). Overall, 68.3% of trials included general, specific, or vague exclusion criteria for MCC. This did not change over time ($p=0.87$). The most common specific conditions excluded were substance abuse disorders (19.0%), dementia (16.9%), and schizophrenia (14.1%). Using a maximum age as exclusion criteria was common (27.8%), and in these trials the median maximum age was 65.0. When exclusions for MCC were reported, only 15.9% of trials identified the number of individuals excluded for these reasons during screening.

The inclusion of MCC could be identified in 35.8% of trials. Condition specific descriptions were more common than general descriptions (28.7% vs 11.3%). Of those trials that reported including MCC, the prevalence of MCC was reported in 59.5% of trials. Of trials reporting specific comorbidities of the index conditions, the mean number of additional conditions reported was 2.1. Comorbidities were considered in analysis in 5.2% of all trials, and 12.1% of trials reporting inclusion of MCC.

Authors' conclusions:

In a representative sample of RCTs testing behavioral and/or psychosocial interventions for participants with at least one chronic condition published over the last 15 years (2000-2014), trials rarely target individuals with MCC. Additionally, they frequently exclude individuals with MCC due to specific, general, or vague exclusion criteria, and exclusion criteria based on factors correlated with MCC, such as age. When MCC are used as exclusion criteria, information regarding to what extent potential participants were excluded for having MCC is usually not provided. When trials indicated that some participants did have MCC, the prevalence of MCC either by general measure or by individual conditions is often not specified. Although our results suggest that individuals with MCC are not appropriately represented in RCTs of behavioral and/or psychosocial interventions, perhaps of bigger concern is that it is often difficult to determine if and to what extent MCC are included due to the poor reporting quality of relevant information in trials. Collectively these factors limit the ability to judge the appropriateness of applying trial results to the broader population. Additionally this review identifies possible areas for further study to address the shortcomings of existing evidence of the representation of individuals with MCC in RCTs.

B. Key Personnel

Name	Title	Role
Graham Colditz, MD, DrPH	Niess-Gain Professor of Surgery; Chief, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine; Associate Director Prevention and Control, Alvin J. Siteman Cancer Center	Principal Investigator
Carolyn Stoll, MPH, MSW	Staff Scientist, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine	Study Director
Sonya Izadi, BA	Senior Public Health Research Coordinator, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine	Database Manager

C. Background, including information on the relevance of multiple chronic conditions in behavioral and psychosocial intervention research

Roughly 75 million people in the United States have multiple chronic conditions (MCC) and 65% of total health care spending in the nation is used for this quarter of the population.[1] In 2013, 17.6% of people age 18-64 and 60.8% of those 65 and older in the United States had more one chronic condition.[2] As the United States is experiencing considerable growth in its older population, the proportion of people with MCC will undoubtedly expand.[3]

However, randomized controlled trials (RCTs) frequently exclude participants with MCC.[1,4-8] In a systematic sampling of high impact general medical journals, 81% of RCTs reviewed excluded participants with MCC. Additionally, 38.5% of those trials excluded potential participants older than 65 years of age.[8] By excluding older participants, these trials are likely to exclude participants with MCC. A similar review sampling both general and specialized high impact medical journals found that participants with MCC were excluded from 63% of all RCTs and 90% of RCTs that explicitly or implicitly mentioned MCC. They also found that only 2% of RCTs explicitly included participants with MCC.[6] Furthermore, when these participants are not excluded, reporting of co-occurring chronic conditions is limited.[4,5,9] A survey of clinical trials revealed only a 44% reporting rate of participant comorbidities.[4] This inconsistency between the characteristics of eligible participants in RCTs and the characteristics of the actual population with the disease reduces confidence in applying trial results to the patient population.[4,7] Consequently, the knowledge base for multiple chronic conditions is largely limited by the reliance on clinical trials that strive to maximize internal validity by excluding participants with comorbidities.[1]

The challenge of treating patients who have MCC is further exacerbated by the large variance in how the term *chronic condition* is defined, which is problematic when comparing results across studies and attaining accurate prevalence rates. Among peer reviewed literature and public information sources, there is much

inconsistency in several dimensions of the definition, such as the duration, effect on function and well-being, and need for medical attention.[10] There is currently no standard list of diseases considered to epitomize universal chronic conditions.[11-13]

It is well established that behavioral and psychological factors play a large role in outcomes for numerous chronic conditions, such as cancer, cardiovascular disease, and diabetes.[14] In an analysis of actual causes of US deaths in the year 2000, the three leading causes were behavioral-based and largely modifiable: tobacco use (18.1%), poor diet and physical inactivity (15.2%), and alcohol consumption (3.5%).[15] These figures illuminate the importance of testing behavioral/psychosocial interventions within RCTs. Yet, the inclusion of MCC patients specifically in such trials has not been studied. As these patients account for roughly 25% of the US population, this is an area that warrants further examination.

Existing evidence

Several reviews[4,6,8,16,17] have attempted to assess the inclusion of individuals with MCC in RCTs. These reviews vary slightly in aims, focus, and methods, but all considered the generalizability of eligibility criteria in RCTs as related to MCC or to factors correlated with MCC.

In a review of 284 RCTs published in high impact journals from 1995 to 2010, Jadad found that individuals with MCC were excluded in 63% of trial reports. [6] There was no significant difference in exclusion over time.

Boyd (2012) reviewed 161 trials sampled from 11 Cochrane Reviews summarizing the effectiveness of various interventions for four major chronic diseases (diabetes, heart failure, COPD, and stroke) and assessed the inclusion of people with comorbidities as well as the reporting of comorbidities and whether comorbidities were considered as modifiers of treatment effects. This review also considered the reporting and replicability of eligibility criteria. In these 161 trials, the proportion of exclusions for comorbidities ranged from 0% to 55% for each of the four major chronic diseases they assessed, and people with common comorbidities of the index condition were frequently excluded. Additionally, 21% of all trials had an upper age exclusion of age greater than 65, 75, or 80 years. Only 43.5% of trials described the prevalence of comorbidities among participants, and among this subgroup of trials, the median number of reported comorbidities was 3. Trials rarely used comorbidities as a subgroup variable to examine comorbidities as a potential effect modifier (3.1%). In addition, replicability of eligibility criteria was only moderate, which affects the ability to adequately assess the eligibility criteria of a trial. [4]

Van Spall (2007) considered the nature and extent of exclusion criteria and the contribution of exclusion criteria to the representation of certain patient populations in 283 RCTs published between 1994 and 2006 in high impact general medical journals. Trials were not limited by condition of interest. Of those sampled, 12% of trials did not report exclusion criteria. Medical comorbidities were used in exclusion of 81.3% of trials. A third (31%) of trials did not use specific medical conditions in exclusion criteria but instead used more general terms such as “illness,” or “comorbidity.” Additionally, age was used in exclusion criteria in 72.1% of RCTs, which Van Spall concluded may impair the generalizability of RCT outcomes and result in exclusion of participants with MCC.[8]

Zulman (2011) assessed the inclusion of complex, older adults in RCTs by considering eligibility based on age as well as eligibility criteria that might disproportionately affect older adults (i.e., exclusion based on inability to give informed consent or decreased life expectancy) in 109 clinical trials published in high-

impact journals.[17] Of these trials, 20% excluded participants above a certain age. Among trials that did not exclude based on age, 46% used exclusion criteria that could disproportionately impact older adults.[17]

Schmidt (2014) considered the justification of exclusion criteria in cardiovascular trials and to what extent exclusion affected generalizability of study results.[16] Of 113 RCTs on secondary prevention of cardiovascular events, many used ambiguous exclusion criteria such as exclusion due to the opinion of the physician (25%) or physical disability (11%). Only 1 trial provided a rationale for its exclusion criteria.[16]

Contribution of the current review

Although there have been multiple reviews on this topic as summarized above, these reviews varied on the index conditions considered, the sampling techniques used, and the aspects of eligibility and inclusion of MCC assessed. Most reviews did not limit by intervention type, and there has not been a comprehensive review assessing the inclusion of individuals with MCC specifically in trials of behavioral and psychosocial interventions. Additionally, many previous reviews limited their sample to trials published in high-impact journals.[6,8,17] These trials may have a different quality of trial design or reporting, and may not be representative of the inclusion and reporting of MCC in RCTs among trials that encompass the current literature.

The current review differs from previous reviews by (a) focusing solely on RCTs testing behavioral and/or psychosocial interventions; (b) considering a previously defined list of 20 chronic conditions chosen for their chronicity, prevalence, and potential to be modifiable by public health and/or clinical interventions; (c) using a comprehensive search strategy and sampling technique to produce a large representative subset of the literature across 15 years (2000-2014); (d) evaluating a wide range of variables related to trial design, trial quality, eligibility criteria, participant selection, and consideration of comorbidities in analysis; and (e) using best practices for systematic reviews including review of search results and selection of included studies and extraction of data by two independent readers.

D. Research question(s) and study objectives

With this review we seek to test the hypothesis that individuals with multiple chronic conditions are underrepresented in RCTs of behavioral and psychosocial interventions published in general medical, behavioral medicine, behavioral science, health psychology, social science, and public health journals.

This review has the following goals:

Goal 1: Conduct a systematic review to assess the frequency with which research participants with MCC are represented in all or a representative subset of RCTs of behavioral and psychosocial interventions published in general medical and specialized journals, published within the last decade or decade and a half, that focus on behavioral medicine and behavioral science, health psychology, social science, and public health.

Goal 2: Determine whether there are significant differences by type of journal or over time in the frequency with which research participants with MCC are represented in RCTs of behavioral and psychosocial interventions.

E. Methods

Methods were specified in advance and documented in a protocol (Appendix B.1), along with a description of any changes from the original protocol (Appendix B.2).

Eligibility criteria

Eligibility criteria was designed with the goal of creating a representative sample of RCTs published in peer-reviewed literature from 2000-2014 designed to develop and/or test the efficacy or effectiveness of behavioral and psychosocial interventions to modify health behaviors, improve health-related quality of life, psychosocial functioning, and/or health outcomes. Eligibility criteria were designed to be fairly broad to produce a heterogeneous sample of the literature in terms of populations, interventions, and outcomes.

The following eligibility criteria was used for this review:

1. RCT with original data
2. Primary report (not protocols, posttrial follow-up studies, secondary or subgroup analyses, etc.)
3. Published in English
4. Targeting at least one of the chronic conditions of interest (i.e. all enrolled participants must have at least one of the 20 specified chronic conditions)
5. Had a primary goal to develop and/or test efficacy or effectiveness of a behavioral or psychosocial intervention
6. Enrolled participants and applied eligibility criteria at the individual level
7. Enrolled only adult subjects (18+)

Types of studies

All randomized controlled trials testing the efficacy or effectiveness of behavioral or psychosocial interventions to modify health behaviors, improve health-related quality of life, psychosocial functioning, and/or health outcomes. If trials included a non-randomized portion alongside an RCT, we considered only the RCT cohort.

Types of participants

Human adults (18+) with at least one chronic condition.

Types of conditions

The following 20 chronic conditions were considered as potential targets of the interventions: arthritis, asthma, autism spectrum disorder, cancer, cardiac arrhythmias, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, dementia (including Alzheimer's and other senile dementias), depression, diabetes, hepatitis, human immunodeficiency virus, hyperlipidemia, hypertension, osteoporosis, schizophrenia, stroke, substance abuse disorders (drug and alcohol) (Table 1).

There is much inconsistency in several dimensions of the definition of chronic condition.[10] Therefore, in order to establish consistency, the selected conditions were taken from a list compiled by an MCC working group at the Office of the Assistant Secretary of Health (OASH) within the US Department of Health and Human Services (HHS). These chronic conditions meet the definition for chronicity, are prevalent and have

potential to be modifiable by public health and/or clinical interventions. Specifically, OASH defined chronic illnesses as conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living.[10]

Additionally, interventions that targeted chronic conditions in general (using such terms as "chronic condition" or "chronic illness") were included.

TABLE 1. **Chronic conditions of interest***
Arthritis
Asthma
Autism spectrum disorder
Cancer
Cardiac arrhythmias
Chronic kidney disease
Chronic obstructive pulmonary disease
Congestive heart failure
Coronary artery disease
Dementia (including Alzheimer's and other senile dementias)
Depression
Diabetes
Hepatitis
Human immunodeficiency virus (HIV)
Hyperlipidemia
Hypertension
Osteoporosis
Schizophrenia
Stroke
Substance abuse disorders (drug and alcohol)

**OASH list of chronic conditions[10]*

Types of interventions

For the purpose of this review, "behavioral or psychosocial intervention" was defined as any intervention that is non-pharmacological and non-surgical and includes at least one behavior change technique.[18] Additionally, there must be some aspect of direct communication with an individual (or small group) whether this is in person, by phone, by internet, etc. This ensured that participants were enrolled at the individual level, and interventions are not performed at the level of a community, campus, etc.

Comparison groups could be usual care, pharmacological interventions, surgical interventions, or a lesser dose of the treatment. Interventions could include a behavioral or psychosocial intervention in addition to a drug or surgery, as long as the comparison group did not receive the same behavioral or psychosocial intervention.

Types of outcome measures

Eligibility was not limited by outcome measure.

Search methods for identification of studies

The librarian designed search strategies to retrieve, as thoroughly as possible, all reported randomized controlled trials in adults regarding chronic illness in PubMed Medline and Embase. Database supplied limits were used to limit by three year clusters, 2000-2004, 2005-2009, and 2010-2014. Chronic illness was defined using general terms for chronic conditions and specific conditions specified by the Centers for Disease Control including arthritis, asthma, autism spectrum disorder, all cancer except non-melanoma skin, cardiac arrhythmias, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, dementia including Alzheimer's and other senile dementias, depression, all non-gestational diabetes, hepatitis, human immunodeficiency virus, hyperlipidemia, hypertension, osteoporosis, schizophrenia, stroke, and drug and alcohol related substance abuse disorders. Searches were completed in February 2015. Results were sent to EndNote and the software-provided duplicate finder was used and assumed to correctly identify duplicates. Full search strategies are available in Appendix B.3.

Data collection and analysis

Selection of studies

Sampling strategy
Three separate literature searches (using identical keywords and in the same databases) were performed within the defined time periods (2000-2004, 2005-2009, 2010-2014). Within each time period, search results were randomly ordered using the RAND function in Microsoft Excel (2013). The study selection process (application of eligibility criteria onto each article) was performed on the randomly ordered results until studies meeting selection criteria were identified for extraction (200 per time period for a total of 600 articles). Selection was stratified by time period to ensure that an adequate number of studies per time period were selected to allow for analysis over time.

Selection process
Two reviewers performed study selection to reduce the possibility that relevant reports were missed.[19] Titles were examined for eligibility criteria and more obviously irrelevant results were removed. Abstracts of remaining results were then screened for eligibility. Finally, full text of the potentially eligible results were retrieved and examined for eligibility criteria. At each level of screening, excluded articles and one reason for exclusion were documented. Once full texts were selected, results were compared between the two reviewers, and any disagreement was resolved by discussion. Reviewers assessing study eligibility were not blinded to the names of the authors, journals, and other publication details. Reviewers performed study selection independently on at least 1250 citations before comparing results. The number of search results screened in each time period was kept even (i.e., the first 5000 results from each time period were screened before screening the second 5000 results from each time period) to ensure that any potential drift in application of eligibility criteria by reviewers throughout the selection process would not bias results over time periods.

Data extraction and management

Data management
Study data were collected and managed using REDCap electronic data capture tools hosted in the Biostatistics Division of Washington University School of Medicine. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing:

1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[20]

REDCap was chosen because it is uniquely suited to meet the needs of an effective and efficient data extraction process. It allows form creators to require specific entry formats for individual questions (ensuring reviewers input data in a consistent format), allows for multiple types of response formats (dropdown menus, select all, select only one, open-ended text entry, etc), and performs data validation to improve accuracy of extraction. In addition, REDCap has a built in "Data Comparison Tool" feature, which allows for the differences in two records to be identified automatically.

Development of extraction form

The extraction form was designed to ensure consistency, accuracy, and efficiency of the data extraction process. The extraction form was tested for item clarity, item comprehensiveness, and form usability. Additionally, throughout the data extraction process the form was constantly evaluated to make sure it was performing as planned. The structure of REDCap allowed for easy editing of the form, such as adding variables, adding answer options, combining answer options, changing entry formats, etc.

Reader training

Readers were Master of Public Health students or had equivalent experience. Their previous experience included managing behavioral research projects, delivering behavioral and/or psychosocial interventions, and clinical experience treating chronic conditions. Readers went through an extensive training process before they began extracting data. Training focused on relevant background material and important concepts such as background information on MCC, systematic review methods, RCT methods, RCT reporting, and assessment of bias in RCTs, as well as the specific extraction items and process for this review. Readers were assessed for accuracy and completeness of extraction on multiple test articles before beginning to extract included articles so that any learning curve did not affect the quality of the data. Further details of reader training materials are included in Appendix B.4.

Extraction of data

Each article was extracted independently by two reviewers. This method was chosen as systematic review best practices recommend that independent data extraction by more than one reader can minimize errors and reduce potential biases being introduced by readers.[21-23] After both extractions were complete, any differences were identified using the REDCap Data Comparison Tool. Disagreements were resolved by a third party with graduate training in public health and four years of experience and expertise in extraction of data from published reports, the design and implementation of systematic reviews, and the goals and objectives of this review. This continuous comparison reduced error in the database, and allowed the monitoring of any systematic errors by readers, which helped to ensure the high quality of the extraction process and of the data.

Order of extraction

Readers were assigned articles to extract and the order of extraction was designed to ensure that number of articles extracted was kept constant within time periods to minimize any bias created by extraction over a long period of time. Additionally, as two readers were required per article for double extraction, readers were shuffled in regards to which additional reader they were matched with in order to better identify inconsistencies across readers.

Study measures and variables extracted

The variables extracted were designed to assess inclusion and reporting of MCC in all phases of a trial—eligibility criteria, participant screening, participant selection and reporting of characteristics, and study analysis. A thorough review of relevant peer-reviewed literature, including reviews of a similar nature or those that assessed the inclusion criteria of RCTS, was performed to identify key variables previously used to evaluate inclusion of specific populations in RCTs.[4,8,16,17,24-28]

For each trial, the items extracted were intended to determine if participants with MCC were represented. This determination for each trial was complex and involved answering several more specific questions (Table 2).

TABLE 2. **Key questions to be answered for each trial**
Does the RCT explicitly exclude MCC?
Is the RCT likely to have excluded MCC due to exclusion criteria regarding other factors?
To what extent are potential participants excluded for MCC?
Does the RCT select participants with MCC?
What is the prevalence of MCC among participants?
Are MCC considered in analysis?

A final version of the extraction form codebook is in Appendix B.5.

Briefly, the items extracted consisted of basic study characteristics (author, title, journal, journal type, year, region, study registration, sample size), intervention details, eligibility information, participant selection details, study outcomes, and risk of bias assessment.

Assessment of risk of bias in included studies

The risk of bias of each included study was assessed for the purposes of describing and evaluating the body of evidence that conclusions are based on, and assessing if study quality and inclusion of MCC are associated. This risk of bias was assessed using a modified version of the Cochrane Collaboration's Risk of Bias tool.[29] The Risk of Bias tool (Table 3) includes six domains: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias.[21] For each item the reader categorizes the article as low risk of bias, high risk of bias, or unclear risk of bias. The unclear risk of bias option allows the reader to indicate when the article has not provided enough information to make a judgement, which helps to separate out issues of study reporting quality from actual study quality.

The Cochrane Collaboration's Risk of Bias tool was adapted slightly for use in this review. Specifically, the "other bias" domain was removed as this element was unnecessary under the scope of this review. The inclusion of this domain is beneficial when considering more specialized studies, therefore it was not necessary for our generalized approach. For attrition bias, readers made judgements on whether attrition was appropriately reported and explained but they did not assess the actual amount of attrition. As this review encompassed studies on a wide variety of populations, interventions, and outcomes, it was not feasible for readers to have enough domain specific knowledge to adequately assess how the amount of attrition in each study may have affected the outcome.

TABLE 3. Cochrane Collaboration's Risk of Bias tool

Domain	Support for judgment	Review authors' judgement
Selection bias.		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias.		
Blinding of participants and personnel	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias.		
Blinding of outcome assessment	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias.		
Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias.		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias.		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool.	Bias due to problems not covered elsewhere in the table.

Often in a systematic review it is more useful to use a quality measure adapted for the specific review topic that takes into account which quality domains are likely to actually affect the outcomes being assessed in the review. However, for this review, the goal was to see how overall trial quality as measured using a broad tool was related to inclusion of MCC or reporting regarding MCC. The GRADE scoring process[30-33] was determined to be inappropriate for this review, as it is intended for evaluating the strength of a body of evidence for specific recommendations. GRADE classifies the quality of evidence into four levels (high, moderate, low, and very low) and the strength of the recommendation as strong or weak. Since the purpose of this review was to describe the existing literature, the Cochrane Collaboration's Risk of Bias tool was more suitable for our heterogeneous sample.

We created a risk of bias score (range -6 to 6) for each article by combining the six risk of bias items (low risk of bias = -1, unclear risk of bias = 0, high risk of bias = 1).

Dealing with missing data and duplicate studies

As a key part of this review was to assess the reporting of information regarding MCC, no attempts were made to contact authors for additional information. For each extraction item there was an option to list it as "not reported." Duplicate studies were not included, and only one primary report of trials was used.

Data synthesis

Analyses performed were determined by specifics of data extracted (both type and volume) from selected studies. Basic study characteristics were summarized to describe the studies, populations, interventions, and outcomes reported and to verify that a representative sample was created. Exploratory data analysis using summary statistics such as mean, proportion, and frequency was performed to assess inclusion of participants with MCC and based on summarizing the key questions for each trial (Table 3). Statistical tests (ANOVA or t-tests) were performed to assess the impact of time period or journal type on key outcomes. No meta-analyses were performed, thus statistical measures of heterogeneity were unnecessary.[34] The potential impact of publication bias was considered.[35]

Analysis was performed using SAS 9.4 (SAS Institute, Cary, NC).

F. Main results of the review in answering the initial research question(s)

Description of studies

Results of the search

In total we identified 343,123 records through database searching (PubMed, Embase). After removing all duplicate records we were left with 190,554 records to assess for eligibility. We conducted a two-phase screening process. The first screening phase involved reading the titles/abstracts of these records, which left us with 41,186 articles that could proceed to the full-text screening phase. During this phase we identified 39,728 articles that were not eligible, which left 1,458 articles to enter the final screening phase. After this 858 were excluded, which left 600 articles included in our study, with 200 from each intended time period. Our study flow is presented in Figure 1.

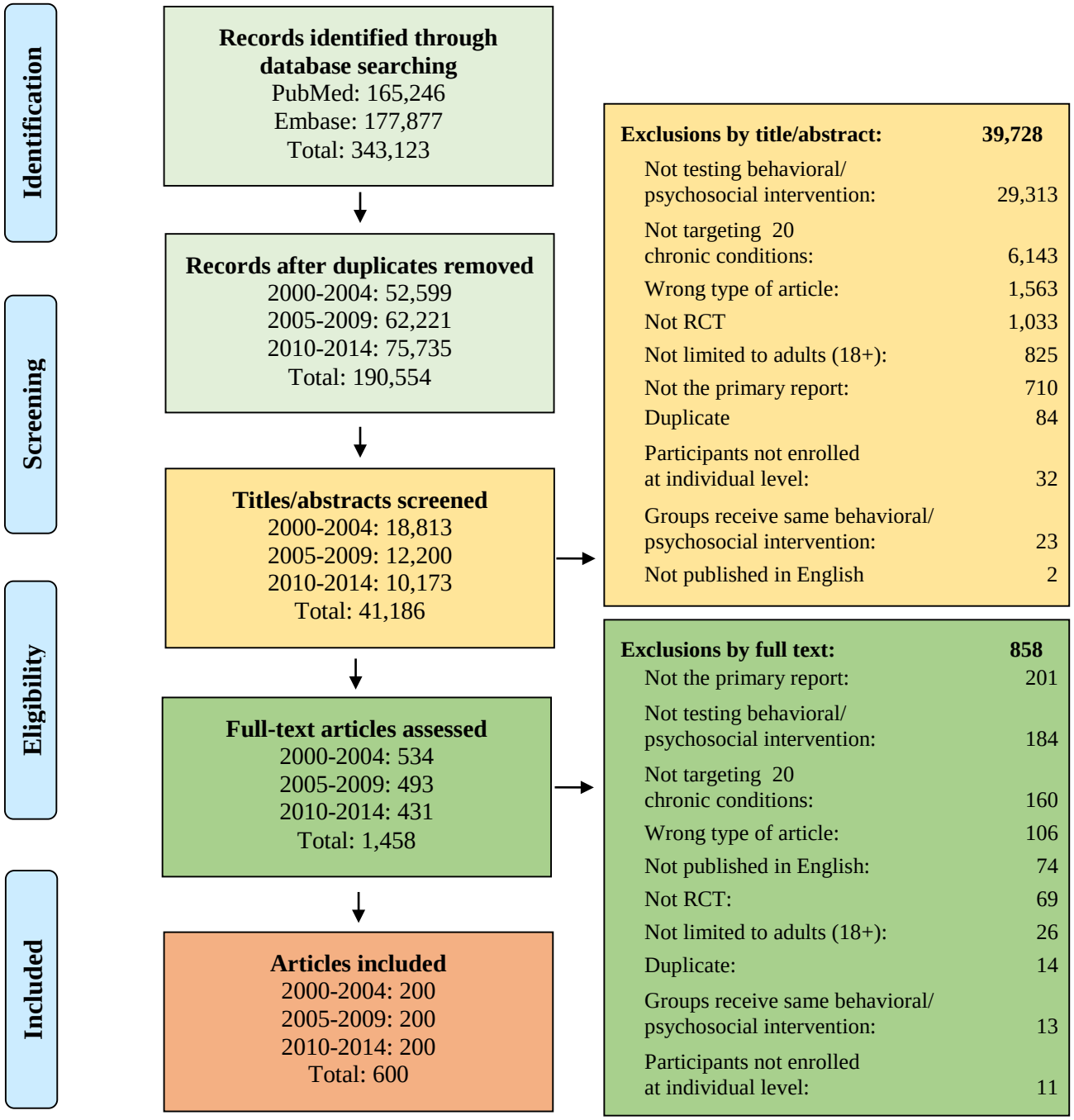

Figure 1 Flow Diagram

Excluded studies

In total there were 40,586 studies excluded during the screening process and extraction processes. 39,728 of these were excluded during the first phase of screening with the majority of articles excluded because they were not testing behavioral/psychosocial interventions (29,313) or they were not targeting at least one of our 20 chronic conditions (6,143). In many cases, these were trials testing drugs or surgery. During the second phase of screening, which occurred during full-text article assessment, 858 articles were excluded predominantly for the article not being the primary report (201) or the intervention assessed in the article was not behavioral/psychosocial in nature (184). All exclusions are listed in Figure 1. Although all included and excluded articles were confirmed by two reviewers, the reasons for exclusion were not adjudicated and the flow diagram represents only one reviewer's reasons for exclusion.

Included studies

A list of the 600 included studies can be found in Appendix B.6. A summary of the basic study characteristics of all 600 included studies is presented in Table 4 with each category stratified by time period. We found that while registration reporting generally increased over time, only 97 out of our 600 trials were registered on clinicaltrials.gov or some other registry. We also found that the number of trials with interventions related to weight management/diet/physical activity increased over time with 27.5% of all trials focusing on this intervention. Sample size of included trials varied greatly (from 8-8,517) and the median was 104.5 participants.

We examined how study quality varied over time based on the Cochrane risk of bias tool (Table 5). Surprisingly, we found that only allocation sequence concealment and selective outcome reporting increased in the number of trials with low risk of bias in these categories and decreased in the number of trials with high risk of bias. Additionally, random sequence generation and incomplete outcome data quality assessments showed an increase in the number of trials with a high risk of bias and a decrease in the number of trials with a low risk of bias between the 2005-2009 and the 2010-2014 categories. Furthermore, overall mean risk of bias score (range -6 to 6, with a lower score indicating lower risk of bias) changed from -2.2 (1.7) in the first time period to -2.8 (1.8) in the final time period, which was a significant decrease in risk of bias over time ($p<0.001$). In all time periods a large percentage of trials were categorized as unclear risk of bias in various risk categories, indicating that the trial did not report adequate information to assess the risk of bias.

We speculated that trial registration and mean risk of bias score may vary by journal type (general vs specialty). Reporting of trial registration occurred in 14.3% of specialty journals and 25.8% of general medical journals and risk of bias score was higher in specialty journals (-2.6 (1.7)) compared to general medical journals (-2.8 (1.7)) (Table 6). However, this result was not significant ($p=0.92$).

We also explored intervention focus by the top targeted conditions (Tables 7-10).

TABLE 4. **Study characteristics**

	2000-2004 (N=200)	2005-2009 (N=200)	2010-2014 (N=200)	Total (N=600)
Journal Type[a]				
General Medicine	29 (14.5)	38 (19.0)	30 (15.0)	97 (16.2)
Specialty	171 (85.5)	162 (81.0)	170 (85.0)	503 (83.8)
Funding Source[b]				
Industry	23 (11.6)	13 (6.5)	12 (6.0)	48 (8.0)
Non-Industry	145 (72.9)	153 (76.5)	160 (80.0)	458 (76.5)
Not reported	31 (15.6)	34 (17.0)	28 (14.0)	93 (15.5)
Region				
North America	121 (60.5)	101 (50.5)	87 (43.5)	309 (51.5)
Europe	50 (25.0)	55 (27.5)	61 (30.5)	166 (27.7)
Middle East	2 (1.0)	1 (0.5)	6 (3.0)	9 (1.5)
Asia/Pacific	23 (11.5)	34 (17.0)	41 (20.5)	98 (16.3)
Latin America	4 (2.0)	5 (2.5)	3 (1.5)	12 (2.0)
Africa	0 (0.0)	4 (2.0)	2 (1.0)	6 (1.0)
Registered[c]				
No	200 (100.0)	174 (87.0)	129 (64.5)	503 (83.8)
Yes - clinicaltrials.gov	0 (0.0)	14 (7.0)	47 (23.5)	61 (10.2)
Yes - other registry	0 (0.0)	12 (6.0)	24 (12.0)	36 (6.0)
Intervention focus				
Weight management/ diet/physical activity	49 (24.5)	57 (28.5)	59 (29.5)	165 (27.5)
Tobacco habits	4 (2.0)	3 (1.5)	5 (2.5)	12 (2.0)
Adherence to disease management	45 (22.5)	52 (26.0)	41 (20.5)	138 (23.0)
Psychological well-being	82 (42.0)	66 (33.0)	63 (31.5)	213 (35.5)
Other	18 (9.0)	22 (11.0)	32 (16.0)	72 (12.0)
Sample size (N=596) median (range)	112 (8 – 2957)	110 (14 – 3522)	96.5 (10 – 8517)	104.5 (8 – 8517)

TABLE 5. **Study quality**

Risk of Bias	2000-2004 (N=200)	2005-2009 (N=200)	2010-2014 (N=200)	Total (N=600)
Random sequence generation (selection bias)				
Low risk of bias	81 (40.5)	105 (52.5)	100 (50.0)	286 (47.7)
High risk of bias	11 (5.5)	6 (3.0)	12 (6.0)	29 (4.8)
Unclear risk of bias	108 (54.0)	89 (44.5)	88 (44.0)	285 (47.5)
Allocation sequence concealment (selection bias)				
Low risk of bias	50 (25.0)	61 (30.5)	86 (43.0)	197 (32.8)
High risk of bias	8 (4.0)	5 (2.5)	7 (3.5)	20 (3.3)
Unclear risk of bias	142 (71.0)	134 (67.0)	107 (53.5)	383 (63.8)
Blinding of participants and personnel (performance bias)				
Low risk of bias	16 (8.0)	20 (10.0)	48 (24.0)	84 (14.0)
High risk of bias	36 (18.0)	35 (17.5)	38 (19.0)	109 (18.2)
Unclear risk of bias	148 (74.0)	145 (72.5)	114 (57.0)	407 (67.8)
Blinding of outcome assessment (detection bias)				
Low risk of bias	78 (39.0)	103 (51.5)	114 (57.0)	295 (49.2)
High risk of bias	17 (8.5)	8 (4.0)	25 (12.5)	50 (8.3)
Unclear risk of bias	105 (52.5)	89 (44.5)	61 (30.5)	255 (42.5)
Incomplete outcome data (attrition bias)				
Low risk of bias	153 (76.5)	169 (84.5)	154 (77.0)	476 (79.3)
High risk of bias	30 (15.0)	20 (10.0)	34 (17.0)	84 (14.0)
Unclear risk of bias	17 (8.5)	11 (5.5)	12 (6.0)	40 (6.7)
Selective outcome reporting (reporting bias)				
Low risk of bias	181 (90.5)	187 (93.5)	189 (94.5)	557 (92.8)
High risk of bias	18 (9.0)	12 (6.0)	11 (5.5)	41 (6.8)
Unclear risk of bias	1 (0.5)	1 (0.5)	0 (0.0)	2 (0.4)
Mean risk of bias score	-2.2 (1.7)	-2.8 (1.7)	-2.8 (1.8)	-2.6 (1.7)

TABLE 6. **Trial registration and mean risk of bias score by time**

	General Medicine N (%)	Specialty N (%)
Registered		
No	72 (74.2)	431 (85.7)
Yes – clinicaltrials.gov	12 (12.4)	49 (9.7)
Yes – other registry	13 (13.4)	23 (4.6)
Mean quality score	-2.8 (1.7)	-2.6 (1.7)

TABLE 7. **Targeted condition and intervention focus, 2000-2004**

	Cancer	Diabetes	Depression	CVD[a]
Weight/diet/PA	4	15	0	12
Tobacco habits	1	0	0	0
Adherence to disease management	1	2	8	4
Psychological well-being	27	0	19	2
Other	5	1	1	3
Total	38 (19.0)	18 (9.0)	28 (14.0)	21 (10.5)

[a]composite of hypertension, CAD, and CHF

TABLE 8. **Targeted condition and intervention focus, 2005-2009**

	Cancer	Diabetes	Depression	CVD[a]
Weight/diet/PA	9	16	1	13
Tobacco habits	0	0	1	1
Adherence to disease management	0	11	4	8
Psychological well-being	20	1	15	6
Other	5	3	0	2
Total	34 (17.0)	31 (15.5)	21 (10.5)	30 (15.0)

[a]composite of hypertension, CAD, and CHF

TABLE 9. **Targeted condition and intervention focus, 2010-2014**

	Cancer	Diabetes	Depression	CVD[a]
Weight/diet/PA	7	13	2	11
Tobacco habits	0	0	1	0
Adherence to disease management	1	8	3	7
Psychological well-being	17	2	16	1
Other	5	6	1	2
Total	30 (15.0)	29 (14.5)	23 (11.5)	21 (10.5)

[a]composite of hypertension, CAD, and CHF

TABLE 10. **Targeted condition and intervention focus, 2000-2014**

	Cancer	Diabetes	Depression	CVD[a]
Weight/diet/PA	20	44	3	36
Tobacco habits	1	0	2	1
Adherence to disease management	2	21	15	19
Psychological well-being	64	3	50	9
Other	15	10	2	7
Total	102 (17.0)	78 (13.0)	72 (12.0)	72 (12.0)

[a]composite of hypertension, CAD, and CHF

Eligibility

Inclusion criteria

Exploratory data analysis was performed to assess inclusion of participants with MCC and to determine the frequency with which each condition was targeted based on time period (Table 11; Table 128). We found that 95.7% of trials only targeted one condition. Targeting MCC directly was rare (4.3%), and most of these trials that targeted MCC focused on a specific set of chronic conditions. No included trials targeted MCC generally. In considering which specific conditions were targeted, cancer was the condition of interest in 17.0% of all trials over all time periods and was the condition most targeted in each time period. The second most targeted condition was diabetes, which was the condition of interest in 13.0% of all trials. Of the 20 chronic conditions considered (Table 1), only hepatitis and autism spectrum disorders were not represented as index conditions in our sample.

TABLE 11. **MCC inclusion**

Do studies target MCC?	N (%)
No (target only 1 condition)	574 (95.7)
Yes	26 (4.3)
Specific set of chronic conditions	22 (3.7)
Any combination of chronic conditions within a specific set of conditions	4 (0.7)
Multiple chronic conditions	0 (0.0)

TABLE 12. **Specific conditions targeted***

	2000-2004 (N=200)	2005-2009 (N=200)	2010-2014 (N=200)	Total (N=600)
Cancer	38 (19.0)	34 (17.0)	30 (15.0)	102 (17.0)
Diabetes	18 (9.0)	31 (15.5)	29 (14.5)	78 (13.0)
Depression	28 (14.0)	21 (10.5)	23 (11.5)	72 (12.0)
Substance abuse disorders	30 (15.0)	20 (10.0)	19 (9.5)	69 (11.5)
Arthritis	16 (8.0)	16 (8.0)	14 (7.0)	46 (7.7)
Human Immunodeficiency Virus (HIV)	13 (6.5)	13 (6.5)	10 (5.0)	36 (6.0)
Schizophrenia	13 (6.5)	8 (4.0)	12 (6.0)	33 (5.5)
Chronic Obstructive Pulmonary Disease	5 (2.5)	9 (4.5)	13 (6.5)	27 (4.5)
Hypertension	4 (2.0)	11 (5.5)	11 (5.5)	26 (4.3)
Coronary Artery Disease	9 (4.5)	10 (5.0)	5 (2.5)	24 (4.0)
Congestive Heart Failure	8 (4.0)	9 (4.5)	5 (2.5)	22 (3.7)
Asthma	6 (3.0)	6 (3.0)	5 (2.5)	17 (2.8)
Stroke	3 (1.5)	5 (2.5)	9 (4.5)	17 (2.8)
Dementia	3 (1.5)	3 (1.5)	7 (3.5)	13 (2.2)
Chronic Kidney Disease	0 (0.0)	1 (0.5)	4 (2.0)	5 (0.8)
Hyperlipidemia	2 (1.0)	0 (0.0)	2 (1.0)	4 (0.7)
Osteoporosis	2 (1.0)	2 (1.0)	0 (0.0)	4 (0.7)
Chronic condition (General)	0 (0.0)	1 (0.5)	2 (1.0)	3 (0.5)
Cardiac arrhythmias	2 (1.0)	0 (0.0)	0 (0.0)	2 (0.3)

**OASH list of chronic conditions[10]*

Exclusion criteria

Exploratory analyses were also performed to evaluate exclusion criteria of participants with MCC by specific or general criteria, presence of exclusion justification, specific conditions excluded, and exclusion based on age.

Chronic conditions

We assessed exclusion criteria for all 600 trials and categorized criteria related to chronic conditions as specific (mentioned individual conditions by name or diagnostic criteria), general (used a general term), or vague (criteria that likely resulted in exclusion of specific conditions) (Table 13). Over all time periods, 68.3% of trials used a general, specific, or vague exclusion criteria (Table 14). This did not change over time (p=0.87). Although the overall use of specific, general, or vague exclusions did not change, general exclusions increased over time (from 4.5% in 2000-2004 to 8.5% in 2010-2014) and vague exclusions have decreased over time (from 51.5% in 2000-2004 to 43.5% in 2010-2014). Of those trials that mentioned specific, general or vague exclusion criteria, we considered if a justification was provided. We found that over all time periods 31.2% of trials with exclusions for specific, general, or vague exclusions justified these exclusions by citing an individual's ability to perform the intervention or otherwise mentally or physically participate in the trial (Table 15).

TABLE 13. **Definitions and examples of exclusion categories**

Type of exclusion	**Definition**	**Examples**
Specific	exclusion of individual conditions by name or diagnostic criteria	Type 2 diabetes, HbA1c > 7%
General	exclusion of MCC by general term	chronic disease, additional comorbidities
Vague	exclusion criteria that is likely to result in exclusion of specific conditions, but do not provide enough information to determine which conditions would be excluded	serious medical problems, acute medical complications, unstable medical conditions, mental illness, too ill

TABLE 14. **Exclusion of MCC**

	2000-2004 N=200	2005-2009 N=200	2010-2014 N=200	All years N=600
Specific exclusion	82 (41)	89 (44.5)	84 (42.0)	255 (42.5)
General exclusion	9 (4.5)	14 (7.0)	17 (8.5)	40 (6.7)
Vague exclusion	103 (51.5)	99 (49.5)	86 (43.0)	288 (48.0)
Specific OR general exclusion	85 (42.5)	94 (47.0)	91 (45.5)	270 (45.0)
Specific OR general OR vague exclusion	137 (68.5)	134 (67.0)	139 (69.5)	410 (68.3)

TABLE 15. **Exclusions justified by ability to perform/participate**

	2000-2004	2005-2009	2010-2014	All years
Specific exclusion	14 (17.1)	10 (11.2)	14 (16.7)	38 (14.9)
General exclusion	3 (33.3)	3 (21.4)	4 (23.5)	10 (25.0)
Vague exclusion	39 (37.9)	37 (37.4)	31 (36.0)	107 (37.2)
Specific OR general exclusion	15 (17.6)	12 (12.8)	15 (16.5)	42 (15.6)
Specific OR general OR vague exclusion	44 (32.1)	44 (32.8)	40 (28.8)	128 (31.2)

Additionally, we assessed which conditions were excluded most often when conditions were named specifically (Table 16). We found that substance abuse disorders (19.0%), dementia (16.9%), and schizophrenia (14.1%) were the most common specific exclusions named explicitly.

We considered if specific exclusions were for a narrowed version of that condition. For example, a trial could specifically exclude any form of hypertension, or could only exclude class II hypertension. We characterized specific exclusions as narrowed by severity when the exclusion specified or suggested that only certain levels of that condition were excluded. In all, 37.9% of exclusions for specific conditions were narrowed by severity. Trials sometimes used specific diagnostic criteria to narrow by severity (such as *class II hypertension*) but often times used more general terms to narrow (such as *severe dementia*). This created difficulty in assessing what levels of the condition were likely to be excluded.

TABLE 16. **Specific conditions excluded**

	Trials exclude this condition	Exclusions for this condition narrowed by severity N=94
Substance Abuse Disorders	47 (19.0)	3 (9.0)
Dementia	42 (16.9)	7 (87.5)
Schizophrenia	35 (14.1)	0 (0.0)
Stroke	21 (8.5)	1 (10.0)
Congestive Heart Failure	20 (8.1)	6 (66.7)
Chronic Kidney Disease	18 (7.3)	20 (74.1)
Cancer	16 (6.5)	10 (41.7)
Chronic Obstructive Pulmonary Disease	13 (5.2)	2 (66.7)
Coronary Artery Disease	12 (4.8)	6 (26.1)
Depression	10 (4.0)	13 (81.3)
Diabetes	8 (3.2)	3 (42.9)
Cardiac Arrhythmias	1 (0.4)	1 (14.3)
Asthma	1 (0.4)	3 (75.0)
Arthritis	1 (0.4)	1 (33.3)
Hepatitis	1 (0.4)	1 (50.0)
Human Immunodeficiency Virus (HIV)	1 (0.4)	1 (100.0)
Hyperlipidemia	1 (0.4)	0 (0.0)
Hypertension	0 (0.0)	16 (84.2)
Autism Spectrum Disorder	0 (0.0)	0 (0.0)
Osteoporosis	0 (0.0)	0 (0.0)
All conditions	**255 (42.5)**	**94 (36.9)**

Age

We evaluated the use of a maximum age as exclusion in trials, as the prevalence of MCC increases with age,[2] so excluding by age may indirectly exclude MCC. We found that 27.8% of trials had exclusions based on a maximum age and in these trials the median age used for exclusions was only 65.0 years (Table 17). The use of a maximum age in exclusion decreased very slightly over time with 26.5% of trials in 2010-2014 excluding participants over a certain age, compared to 28.5% of trials published in both 2000-2004 and 2005-2009 excluding participants based on a maximum age (Table 18). This difference was not significant (p=0.15).

TABLE 17. **Age exclusion**

N= 600	N (%)
Maximum age	
No	433 (72.2)
Yes	167 (27.8)
Maximum age (years)	
Mean	66.8
Median	65.0
Range	25 - 89

TABLE 18. **Age exclusion over time**

	2000-2004	2005-2009	2010-2014
Maximum age			
No	143 (71.5)	143 (71.5)	147 (73.5)
Yes	57 (28.5)	57 (28.5)	53 (26.5)
Mean age limit (years)	65.8	66.1	68.8

Behavioral risk factors

We also examined behavioral risk factors or conditions used in exclusion criteria that may have resulted in exclusion of MCC. Specifically, 86 (14.3%) of trials used any behavioral factor for exclusion criteria, with 36 trials excluding participants based on criteria related to physical activity (Table 19). Exclusions based on these risk factors may have been likely to exclude people at higher risk for MCC (e.g., smoked >10 packs a year) but also in some cases excluded those with lower risk of MCC (e.g., “already performing >150 min of moderate vigorous exercise per week”).

TABLE 19. **Behavioral risk factor exclusion**

Exclusions for behavioral factors	N (%)
Any behavioral factor	86 (14.3)
Physical activity	36 (6.0)
Smoking or tobacco use	24 (4.0)
Weight	23 (3.8)
Other substance abuse	17 (2.9)
Alcohol use	10 (1.7)
Diet	2 (0.3)

Participant screening

As we found that some trials were reporting general or specific exclusion criteria related to MCC, we questioned if the number of potential participants excluded for having MCC was reported. Only 15.9% of

trials that excluded participants using either general or specific criteria actually reported the number of people excluded for this reason (Table 20). This could be because the trial did not report the number of people excluded during screening, or because numbers given were only for combined eligibility criteria (such as number of people meeting exclusion criteria overall).

TABLE 20. **Participant screening**

General OR specific exclusions (N=270)	N (%)
General exclusions, # reported	8 (3.0)
Specific exclusions, # reported	35 (13.0)
General OR specific exclusions, # reported	43 (15.9)

Participant characteristics

We considered MCC information reported in participant characteristics to determine if trials actually included participants with MCC, and if so, could the prevalence of MCC in the trial be determined. We categorized a trial as reporting the presence of MCC if there was any information given from which it could be determined that conditions additional to the index condition existed. This was further categorized into general description (a measure related to chronic conditions in general, such as mean number of comorbidities, percentage of participants with specific number of comorbidities, etc.) or specific description (a measure related to a specific comorbidity). Overall, 35.8% of trials reported the presence of comorbidities through a specific or general description. There was no significant change in this over time (p=0.07) (Table 21). Condition specific descriptions were more common than general descriptions (28.7% vs. 11.3%).

Of those trials that reported including MCC, the prevalence of MCC (by general measure or by prevalence of specific conditions) was reported in 59.5% of trials. Of trials reporting specific comorbidities of the index conditions, the mean number of additional conditions reported was 2.1 (Table 22).

TABLE 21. **Trials reporting presence of MCC (specific conditions or general measure)**

	2000-2004	2005-2009	2010-2014	Total
Condition specific description	47 (23.5)	57 (28.5)	68 (34.0)	172 (28.7)
General description	22 (11.0)	20 (10.0)	26 (13.0)	68 (11.3)
Specific OR general description	61 (30.5)	71(35.5)	83 (80.7)	215 (35.8)

TABLE 22. **Additional specific conditions are reported**

	N (%)
Report prevalence of MCC (general or specific)	128 (59.5)
Number of conditions reported (N=179)	
Mean	2.1
Median	2
Range	0 - 7

Of the 68 trials that gave a general description of the presence of MCC, 95.6% reported some measure of MCC (Table 23). These measures were most often the mean number of MCC per participant (44.6%) or the number of or percentage of participants with MCC (43.1%). The Charlson Comorbidity Index (CCI), which predicts the ten-year mortality for a patient who may have a range of comorbid conditions,[36] provides a standardized way to report a general measure of MCC and may be more useful than reporting individual specific conditions. However, the CCI was reported less often than other general measures of MCC (15.4%).

TABLE 23. **General measures of MCC**

General description reported (n=68)	N (%)
Any type of measure used	65 (95.6)
Mean number of MCC per participant	29 (44.6)
Number or percentage of participants	28 (43.1)
Charlson Comorbidity Index	10 (15.4)

Study analysis

We assessed if presence of comorbidities was considered in the analysis of the trial outcomes. Comorbidities were considered in analysis in only 5.2% of all trials (n=600). Of trials that reported including MCC, any information related to comorbidities was used in analysis in 12.1% of trials. (Table 24).

TABLE 24. **Considering comorbidities in analysis**

Use in analysis	N (%)
All trials (n=600)	
Yes	31 (5.2)
No	569 (94.8)
Trials that include MCC (n=215)	
Yes	26 (12.1)
No	189 (87.9)

Reported challenges of recruiting individuals with MCC

We initially anticipated summarizing reported challenges of recruiting individuals with MCC; however, we did not find any relevant comments in any of our included trials.

Discussions with key informants

We consulted key informants with particular expertise to provide insight on prioritizing the shaping of analysis, as well as, reporting and presenting the data. While we requested their multifaceted feedback, we also specifically wanted to gather their reactions to our key variables and issues we planned to address with the data, have them evaluate if any items were omitted from this top level summary, and provide feedback both in general and regarding the potential informative nature of the summary. The key informants provided beneficial comments and criticisms, with the majority of their remarks suggesting consideration of the effect of varied reporting methods regarding MCC, redefining or specifying certain eligibility and selection criteria, and proposing particular analysis measures. While many of their comments were not within the scope of this

report or were suggestions we had already incorporated, we did take their additional remarks under advisement and pursued the feasibility of incorporating them into our analysis and report. Moreover, their comments confirmed that we were on the right track in our report strategy and that we were considering measures and analyses that would be the most informative to researchers. For a list of our key informants, their positions and affiliations, and a summary of their comments, see Appendix B.7.

G. Discussion and Conclusions

In this review, we found that in a representative sample of RCTs testing behavioral and/or psychosocial interventions published over the last 15 years (2000-2014), trials rarely target individuals with MCC. Additionally, they frequently exclude individuals with MCC due to specific, general, or vague exclusion criteria, and exclusion criteria based on factors correlated with MCC, such as age. When MCC are used as exclusion criteria, information regarding to what extent potential participants were excluded for having MCC is usually not provided. When trials indicated that some participants did have MCC, the prevalence of MCC either by general measure or by individual conditions is often not specified.

Our ability to answer the key questions for each trial (Table 2) was complicated by an overall lack of information given regarding MCC. When information about MCC was reported, either in eligibility criteria or participant characteristics, the level of detail given varied greatly.

We categorized MCC information as specific, general, or vague. Vague descriptions were the least informative, as it was impossible to determine how these related to MCC, and more specifically, which chronic conditions were likely to have been excluded by vague exclusion criteria.

General descriptions and specific descriptions could be more or less informative depending on their use. For example, when general exclusion criteria were used, occasionally examples of specific conditions that would meet the criteria were given, but in most cases a definition of how that criteria was used in the trial was not provided. Given that there is not an agreed upon definition of chronic condition,[10] assumptions about which conditions would be excluded under that criteria would need to be made. Specific exclusion criteria may be more informative than general exclusion criteria, but overall when information was given by specific conditions only, it was difficult to consider the relationship of conditions to each other. Particularly in participant characteristics, when information was given by individual specific conditions only, it was impossible to gain an overall picture of the presence and extent of MCC in the population. The CCI may be a more informative measure when describing the included population, but it is rarely used.

In view of the risk of bias assessment, we can see that quality of trial reporting is an overall issue not just related to MCC information. Unclear risk of bias, which suggests that the report did not provide appropriate information to judge the risk, was common and seemed to be indicative of the lack of important details given in reports of trials. Improving standards for reporting and increasing trial registration may help to standardize and improve trial performance and reporting.

Publication bias[35] must be considered in the context of this review. Given that our sample of trials is from published literature, we must assume that our sample is biased towards larger positive trials and that smaller null studies may not be appropriately represented. It is difficult to assess how this may have affected our results in terms of the inclusion of MCC. For example, if MCC were included and represented a significant portion of the trial population, for certain outcomes a larger effect may be shown as people with MCC may

start out sicker and have more room to improve. With a larger effect, the trial may be more likely to get published. Alternatively, the presence of MCC within the trial population may act as a confounder and reduce the likelihood of an intervention showing an effect if it is not accounted for appropriately, which would reduce the likelihood of the trial getting published.

Our review confirms results from previous reviews that comorbidities are often used as exclusion criteria in trials.[4,6,8] Maximum age limits are common.[4,17] General terms rather than specific conditions are used in eligibility often,[8] and vague or ambiguous terms are used as well.[16] Trials often do not describe the presence of comorbidities in the population, and consideration of comorbidities in analysis is rare.[4]

The strengths of this review include the large volume of RCTs assessed (n=600). This is a much larger sample size than previous reviews. Our sample was created from a comprehensive search performed in multiple databases with extensive search terms performed by a medical librarian with expertise in systematic reviews. By not limiting inclusion to higher impact journals as previous reviews have done, we ensured that our sample was representative of the literature. Our sampling strategy resulted in a broad sample of the literature over the past 15 years that varied in population addressed, conditions considered, intervention component, and study risk of bias, which gave us a wide view of behavioral and/or psychosocial interventions. Additionally, we considered a defined list of 20 conditions instead of limiting to a smaller number of conditions as previous reviews have done. In all aspects of this review we followed established best methods for systematic reviews.[21] This included an appropriate and replicable search strategy, screening of results for inclusion by two independent reviewers to ensure no relevant reports were missed, and extraction of data from each article by two independent reviewers to ensure quality of data. We assessed the inclusion of MCC in a new population of trials by focusing on behavioral and/or psychosocial interventions specifically, and confirmed that our results were similar to reviews of other intervention types. We extracted a large volume of information from each trial and developed a framework for assessing the inclusion and reporting of MCC in eligibility, screening, selection, and analysis.

Limitations of our review include the fact that we focused on trials targeting a chronic condition. In order to evaluate inclusion based on multiple conditions, it was necessary to first know that all participants had at least one conditions and then assess for presence of further conditions due to the fact that trials so often report information of exclusion or inclusion only by individual specific conditions. Many behavioral and/or psychosocial interventions are often focused on prevention and may therefore include populations that are only at risk of chronic conditions. Our requirement that trials include participants with a chronic condition may limit the generalizability of our results to the broader behavioral and/or psychosocial intervention literature.

Although focusing on a specific list of 20 chronic conditions was a strength of our review, it may have resulted in the inability to consider information from trials presented in ways that did not correspond with our conditions. For example, if trials reported participant characteristics using more broad or vague categories of conditions that we could not link to the 20 conditions or to an overall measure of MCC, we may have missed relevant information. However, we believe that this was a rare occurrence. Additionally, we were limited in the analyses that we were able to perform. We were limited to broad sample statistics rather than more sophisticated analyses or meta-analysis due to the variation in the amount and format of relevant information in these trials.

Based on the results of this review, trials of behavioral and/or psychosocial interventions often exclude MCC, and this has not improved over time. Although our results suggest that individuals with MCC are not

appropriately represented in RCTs of behavioral and/or psychosocial interventions, perhaps of bigger concern is that it is often difficult to determine if and to what extent MCC are included due to the poor reporting quality of relevant information in trials. Collectively these factors make it difficult to judge the appropriateness of applying trial results to the broader population. We recommend that behavioral and psychosocial research that both considers individuals with MCC and reports the involvement of MCC appropriately should emerge as an NCI priority.

H. Implications for further research

In the process of this review, several additional research questions were identified as necessary to address the shortcomings of existing evidence of the representation of individuals with MCC in RCTs. We suggest that the following topics would be among the next steps in evaluating the inclusion of MCC in behavioral and psychosocial trials.

Developing recommendations for reporting MCC and other relevant characteristics in the literature

This review found that even when MCC or other relevant participant characteristics are reported, they are reported in heterogeneous ways that are not always helpful in understanding to what sort of population the results are applicable. An exploration of the most informative ways of reporting this information and development of recommendations for trial reporting would help to address the shortcomings of existing evidence of the representation of MCC in RCTs of behavioral and/or psychosocial interventions.

Potential impact of race/ethnicity

Additional variables considered to be correlated with the presence of MCC were evaluated in this review (age, behavioral risk factors) to determine if inclusion related to these factors may have impacted inclusion of MCC. While this review did not consider race or ethnicity, significant differences in the prevalence of MCC stratified by race/ethnicity have been shown.[37] Evaluating reporting of race/ethnicity information in participant characteristics of these trials may provide further information regarding the inclusion of MCC.

Inclusion of MCC in specific condition populations

This review encompasses trials targeting a broad range of chronic conditions; however, it is likely that the inclusion of MCC differs based on the targeted population of each trial. Therefore, it would be important to consider inclusion of MCC within specific areas of study. For example, conducting a similar review of only trials including cancer survivors would allow for a better and more specific understanding of the current state of behavioral research for cancer survivors than the current review allows. A more focused review could include the measures of inclusion used here, but may also necessitate additional considerations regarding factors of particular importance to cancer survivors.

Effect of MCC clustering

Certain combinations of MCC are more prevalent than others,[37,38] and a focus on these clusters is a key component of the HHS MCC framework.[39] It would be of particular concern if trials considering one condition are excluding additional conditions that are often seen alongside the target condition. This would greatly limit the external validity of the trial and make it difficult for practitioners to know how the results may apply to their patients. Inclusion of MCC in trials must be explored in the context of these most

prevalent clusters to understand to what extent individuals with common clusters of MCC are being excluded from trials.

Inclusion of MCC in trials not targeting one condition

All trials included this review are targeting at least one chronic condition, meaning that every participant in the trial has at least one condition. However, many behavioral and/or psychosocial interventions are targeted at people who are at risk for conditions. A similar review should be performed on RCTs of behavioral and/or psychosocial interventions not limited to trials targeting participants with at least one chronic condition to provide a better understanding of the current state inclusion of MCC in behavioral/psychosocial research.

Inclusion of MCC in trials of specific intervention types

Inclusion of MCC may differ by intervention focus. As exclusions for MCC are often justified by limiting the ability of the individual to physically participate in the trial, it would be expected that physical activity trials may exclude MCC more often due to the physical requirements of the interventions. A more focused review on trials testing physical activity interventions would evaluate the impact of such eligibility criteria, consider if these exclusions are appropriately justified, and describe how the generalizability of the trials are affected. Similar reviews could be performed for other intervention types.

Relationship between efficacy/effectiveness of interventions and inclusion of MCC

It is unclear how inclusion of MCC may be related to efficacy and/or effectiveness of trials of behavioral and/or psychosocial interventions. A Mann-Whitney meta-analysis[40] was proposed for this review to address this relationship, but these methods were determined to not be feasible for this review due to the limited number of articles that provided sufficient outcome data for analysis and reporting of MCC. Narrowing down the sample to articles that provide appropriate information for this analysis or developing new methodology as needed would allow for an evaluation of the relationship between efficacy and/or effectiveness of interventions and inclusion of MCC. This would be essential for understanding how the inclusion of MCC is affecting the current evidence base of behavioral and/or psychosocial interventions. Additionally, describing the relationship between efficacy/effectiveness and inclusion of MCC could also help to clarify the impact of publication bias on this review.

Trial funding source correlation to inclusion of MCC

An original goal of this review was to provide evidence of research that considers individuals with MCC in order to establish if this type of research should emerge as a NCI priority. Accordingly, by assessing the inclusion of MCC in trials funded by the NCI in comparison to trials funded by the NIH as a whole or other funding sources, it would be possible to better evaluate the current state of MCC inclusion in NCI funded research.

Impact factor of journal and inclusion of MCC

Previous reviews considered trials from high impact journals only, but the current review did not limit by impact factor. It is possible that impact factor of journal may be correlated with the likelihood of the trial including MCC or with the reporting quality of the trial regarding MCC. However it may be difficult to measure over time, as impact factor changes and would be most appropriate to consider the impact factor of a journal at time of publication.

Consideration of pragmatic-explanatory trials and MCC

Exclusion of MCC may be more common in explanatory trials due to the emphasis on internal validity, while it would be expected that pragmatic trials would have less restrictive eligibility criteria. In order to confirm this hypothesis, there needs to be a way to assess where a trial falls on the pragmatic-explanatory continuum based on published reports. The PRECIS[41] and PRECIS-2[42] tools provide a framework for considering the position of a trial on the pragmatic-explanatory continuum. However, when we attempted to use a selection of these measures to evaluate trials in this review, we found that trials often did not provide appropriate information to adequately assess their position on this continuum. The development of a better method for using these measures or new measures to assess trial reports would allow for the relationship between the pragmatic-explanatory continuum and MCC to be explored. Additionally, considering reporting of participant characteristics in these trials would allow for the confirmation that broader eligibility criteria actually leads to a trial population more reflective of the general population.

Assessing general reporting of RCTs with CONSORT

A major challenge in this review was the lack of reported information regarding MCC in trials. It would be useful to consider the quality of reporting in trials in general and consider the reporting of information regarding MCC in this context. For example, CONSORT[43-45] provides a framework for reporting of trial findings and is endorsed by many journals. However, the iterations of CONSORT over time (1996, 2001, 2010) make it difficult to analyze the use of CONSORT longitudinally, as would be necessary in this review. Even when considering the same issues of reporting, the versions of CONSORT can differ in number of items and exactly what is being assessed. Additionally, it is difficult to determine at what point in time each version of CONSORT should be used, as there is no simple way to determine precisely when it was formally endorsed by individual journals. Nevertheless, the development of a framework to use CONSORT over time would contribute to the understanding of inclusion of MCC by providing a methodology for assessing overall reporting quality of RCTs.

Specific aims of trials compared to trial report

The poor reporting of primary outcomes, eligibility criteria, and additional trial information in RCTs was a major challenge in this review. It may be useful to consider the original specific aims of NIH funded research and compare those to the trial report, as well as to assess if the population included and primary outcome is reported as planned, if eligibility criteria has been altered, or if other significant differences exist.

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Appendix A: Deliverables		
Milestones/Deliverables		
Major Milestones/Deliverables	**Time Period / Due Date**	**Date competed**
Phase 1: Topic refinement, sampling and analysis plan development, protocol writing	Month 1- Month 3 (October 2014 – December 2014)	
Milestone 1: Project kick-off call	Month 1 – Month 2 (November 2014)	November 2014
Milestone 1.1.4: Finalization of PICOT topic and key questions	Month 2 (November 2014)	December 2014
Milestone 1.1.5: Finalization of inclusion/exclusion criteria	Month 2 (November 2014)	December 2014
Milestone 1.2.2: Finalization of sampling strategy	Month 1 – Month 2 (October 2014 - November 2014)	November 2014
Milestone 1.4.1: Finalization of protocol	Month 1 – Month 2 (October 2014 - November 2014)	December 2014
Phase 1 Deliverables:		
A. Monthly interim report	As indicated on cover page	
B. Background on the relevance of multiple chronic conditions in behavioral and psychosocial intervention research; process for further refinement of key scientific questions as deemed necessary and with justification	October 2014 – November 2014	October 2014
C. Summary of the discussions held with the key informants and the outcomes/impact on the project, including the list of questions asked of each informant	To be included in the Systematic Review Report, due 10/25/2015	September 2015
D. Study protocol to include key scientific questions and study objectives; methodology (search strategy for sources of evidence including databases and resources used); selection criteria (detailed study inclusion/exclusion criteria); data collection, coding schema, and analytical plans	November 2014 – December 2014	December 2014

Phase 2: Extraction forms development, development of quality assessment plan, literature search	Months 2 – 3 (November 2014 – December 2014)	
Milestone 2.1.2: Finalization of extraction form	Month 2 – Month 3 (November 2014 December 2014)	December 2014
Milestone 2.24: Finalize quality assessment tool	Month 2 – Month 3 (November 2014 December 2014)	December 2014
Milestone 2.3.1.3: Finalization of search strategy	Month 2 – Month 3 (November 2014 December 2014)	January 2015
Milestone 2.3.1.4: Performance of literature search	Month 2 – Month 3 (November 2014 December 2014)	January 2015
Phase 2 Deliverables:		
A. Monthly interim report	As indicated on cover page	
B. Extraction sheet to include examples of what and how information will be extracted	December 2014	December 2014
Phase 3: Study selection, data extraction, and quality assessment	Months 4-8 (January 2015 – May 2015)	
Milestone 3.2.3: Log of excluded studies with reasons for exclusion	Month 4 – Month 5 (January 2015 – February 2015)	July 2015
Milestone 3.2.4: Finalized list of selected studies	Month 4 – Month 5 (January 2015 – February 2015)	July 2015
Milestone 3.2.5.2: Completed database of extracted data	Month 5 – Month 8 (February 2015 – May 2015)	August 2015
Phase 3 Deliverables:		
A. Included list to reflect articles being captured by methodology and selection criteria	To be included in the Systematic Review Report, due 10/25/2015	August 2015
Phase 4: Data Synthesis and analysis	Months 8 – 10 (May 2015 – July 2015)	
Milestone 4.1.2: Table of study and patient characteristics	Month 8 – Month 10 (May 2015 – July 2015)	August 2015

Milestone 4.1.3: Table summarizing reported challenges of recruiting individuals with MMCs	Month 8 – Month 10 (May 2015 – July 2015)	August 2015
Milestone 4.2.6: Tables of figures key outcomes	Month 8 – Month 10 (May 2015 – July 2015)	August 2015
Milestone 4.3.1: Summary of study quality including GRADEing of evidence	Month 8 – Month 10 (May 2015 – July 2015)	August 2015
Phase 4 Deliverables:		
A. Monthly interim reports	As indicated on cover page	
B. Tables including GRADEing of the evidence	July 2015	July 2015
Phase 5: Formation of conclusions and reporting of recommendations	Months 10 – 12 (July 2015 – September 2015)	
Phase 5 Deliverables:		
A. Database publication per submitted plan including: • Database • Data Dictionary • Codebook • FAQ document • Hosting of Database and documents on WUSTL website	Month 12 (September 2015)	September 2015
B. Monthly interim reports	As indicated on cover page	
C. Presentation of preliminary systematic review report	July 27, 2015	July 2015
D. Draft of the systematic review report	9/4/2015	September 2015
E. Final Systematic Review Report, including responses to questions posed during NCI review	No later than 10/25/2015	October 2015

Appendix B: Additional Information

1. Protocol

BACKGROUND

There are roughly 75 million people in the United States with multiple chronic conditions (MCC), and 65% of total health care spending in the nation is used for this quarter of the population.[1] In 2010 only 32% of Medicare fee-for-service beneficiaries had zero or one chronic condition, while 32% had two or three, 25% had four or five, and 14% had six or more chronic conditions.[2]

However, randomized controlled trials (RCTs) frequently exclude patients with MCC.[1,3-7] In a systematic sampling of high impact general medical journals, 81% of RCTs reviewed excluded patients with MCC.[7] A similar review sampling both general and specialized high impact medical journals found patients with MCC were excluded from 63% of all RCTs and 90% of RCTs that explicitly or implicitly mentioned MCC. Only 2% of RCTs explicitly included patients with MCC.[5] Furthermore, when these patients are not excluded, reporting of co-occurring chronic conditions is limited.[3,4,8] An in-depth survey of clinical trials revealed only a 44% reporting rate of participant comorbidities.[3] This inconsistency between the characteristics of eligible patients in RCTs and the characteristics of the actual patient population with the disease reduces confidence in applying trial results to the patient population.[3,6] Consequently, the knowledge base for multiple chronic conditions is largely limited by the reliance on clinical trials that strive to maximize internal validity by excluding patients with comorbidities.[1]

It is well established that behavioral and psychological factors play a large role in outcomes for numerous chronic conditions, such as cancer, cardiovascular disease, and diabetes.[9] In an in depth analysis of actual causes of US deaths in the year 2000, the three leading causes were behavioral based and largely modifiable: tobacco use (18.1%), poor diet and physical inactivity (15.2%), and alcohol consumption (3.5%).[10] These figures illuminate the importance of testing behavioral/psychosocial interventions within RCTs. Yet, the inclusion of MCC patients specifically in such trials has not been studied. As these patients account for roughly 25% of the US population, this is an area that warrants further examination.

Description of the condition

The challenge of treating patients who have MCC is further exacerbated by the large variance in how chronic condition is defined, which is problematic when comparing results across studies and attaining accurate prevalence rates. Among peer reviewed literature and public information sources, there is much inconsistency in several dimensions of the definition, such as the duration, effect on function and well-being, and need for medical attention.[11] To address this issue, an MCC working group at the Office of the Assistant Secretary of Health (OASH) within the US Department of Health and Human Services (HHS) compiled a list chronic conditions that met the definition for chronicity, are prevalent and have potential to be modifiable by public health and/or clinical interventions. The definition OASH used defined chronic illnesses as conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living. This resulted in a compilation of 20 conditions (Table 1).[11]

Table 1: OASH List of Chronic Conditions
Arthritis
Asthma
Autism spectrum disorder
Cancer
Cardiac arrhythmias

Chronic kidney disease
Chronic obstructive pulmonary disease
Congestive heart failure
Coronary artery disease
Dementia (including Alzheimer's and other senile dementias)
Depression
Diabetes
Hepatitis
Human immunodeficiency virus (HIV)
Hyperlipidemia
Hypertension
Osteoporosis
Schizophrenia
Stroke
Substance abuse disorders (drug and alcohol)

Why it is important to do this review

The evaluation of representation of individuals with MCC in RCTs over the past 15 years is necessary in order to determine if behavioral and psychosocial intervention research that considers individuals with multiple chronic conditions should emerge as a research priority. We aim to perform the review, evaluation and summarization of data regarding the representation of individuals with multiple chronic conditions in RCTs of behavioral and psychosocial interventions published in general medical, behavioral medicine, behavioral science, health psychology, social science, and public health journals.

OBJECTIVES

With this review we seek to test the hypothesis that individuals with multiple chronic conditions are underrepresented in RCTs of behavioral and psychosocial interventions published in general medical, behavioral medicine, behavioral science, health psychology, social science, and public health journals. The overall goals of the project are as follows:

Goal 1: Conduct a systematic review to assess the frequency with which research participants with MCC are represented in all or a representative subset of RCTs of behavioral and psychosocial interventions published in general medical and specialized journals, published within the last decade or decade and a half, that focus on behavioral medicine and behavioral science, health psychology, social science, and public health.

Goal 2: Determine whether there are significant differences by type of journal or over time in the frequency with which research participants with MCC are represented in RCTs of behavioral and psychosocial interventions.

These goals will be accomplished with the following objectives:

Objective 1: Perform a systematic review of a representative sample of the peer-reviewed literature over the past 15 years (2000-2014) to describe, quantify, and critically appraise the inclusion of individuals with MCC in RCTs designed to develop and/or test the efficacy or effectiveness of behavioral and psychosocial interventions to modify health behaviors, improve health-related quality of life, psychosocial functioning, and/or health outcomes.

Objective 2: Describe and analyze how inclusion/exclusion of individuals with MCC in RCTs differs across time and by journal type. As appropriate, consider other factors such as components of intervention.

METHODS

Criteria for selecting studies for this review

Types of studies
All randomized controlled trials testing the efficacy or effectiveness of behavioral or psychosocial interventions to modify health behaviors, improve health-related quality of life, psychosocial functioning, and/or health outcomes.

Types of participants
All human adults (18+) with at least one chronic condition.

Types of conditions
For purposes of selecting studies, we will consider the following 20 chronic conditions as potential targets of the interventions: arthritis, asthma, autism spectrum disorder, cancer, cardiac arrhythmias, chronic kidney disease, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, dementia (including Alzheimer's and other senile dementias), depression, diabetes, hepatitis, human immunodeficiency virus, hyperlipidemia, hypertension, osteoporosis, schizophrenia, stroke, substance abuse disorders (drug and alcohol).

Types of interventions
For the purpose of this review, we define "behavioral or psychosocial intervention" to mean any intervention that is non-pharmacological and non-surgical. Additionally, there must be some aspect of direct communication with an individual (or small group) whether this is in person, by phone, by internet, etc. This ensures that participants are enrolled at the individual level, meaning that we will not include interventions that are only performed at a community, campus, etc level.

Comparison groups can be usual care, pharmacological interventions, surgical interventions, or a lesser dose of the treatment. Interventions may include a behavioral or psychosocial intervention in addition to a drug or surgery, as long as the comparison group is not receiving the same behavioral or psychosocial intervention.

Types of outcome measures

Primary outcomes

- Exclusion of individuals with multiple chronic conditions
  - Whether exclusion used names of specific conditions or used general terms such as comorbidities or coexisting disease explicitly
  - Proportion of participants excluded due to MCC
- Inclusion of individuals with multiple chronic conditions
  - Proportion of participants included with multiple chronic conditions
  - Which specific conditions were included

Secondary outcomes

- Additional details of each trial that could potentially be used in the meta-analyses, including year, type of journal (general or specialized), components of intervention, and quality of trial.

Search methods for identification of studies
The search strategy will be developed by an MLIS clinical librarian with expertise in searching for systematic reviews. We anticipate searching multiple databases (MEDLINE, EMBASE, etc) for English-language trials published from 2000 to 2014. Hand-searching will not be performed.

We will then apply our sampling strategy (see *Sampling plan* below) in order to create a representative sample of the peer-reviewed literature on RCTs designed to develop and/or test efficacy or effectiveness of behavioral and psychosocial interventions over the past 15 years.

Data collection and analysis

Sampling plan
We expect our search strategy to produce an extremely large number of results that would not be possible to manage in a reasonable amount of time. In order to reduce the number of trials to be screened we have a developed a sampling plan. This will result in a project that is manageable in the allotted time frame and provides meaningful results without imposing unnecessary restrictions on study selection and inclusion criteria that would reduce the representativeness of our sample.

Three separate literature searches (using identical keywords and in the same databases) will be done within defined time periods (2000-2004, 2005-2009, 2010-2014). Within each time-period group, search results will be randomly ordered. The study selection process (application of inclusion/exclusion onto each article) will be performed on the randomly ordered results until the desired number of studies for extraction meeting inclusion/exclusion criteria have been identified (200 per time period for a total of 600 articles).

Selection of studies
Two independent reviewers will screen the titles and the abstracts based on the following exclusion criteria:
1. Not an RCT with original data
2. Not a primary report (will not include protocols, posttrial follow-up studies, secondary subgroup analyses, etc)
3. Not published in English
4. Not targeting at least one of chronic conditions of interest (see *Types of conditions*)
5. Not testing a behavioral or psychosocial intervention or not including an accepted comparison group (see *Types of interventions*)
6. Not including patients with at least one chronic condition
7. Not enrolling participants at the individual level
8. Not human adult subjects (18+)

Excluded articles and a reason for exclusion will be carefully documented. Any disagreement between the two authors will be resolved by a third party. If the title and the abstract is not clear to determine to reject, or disagreement is not resolved by discussion, the full-text of the article will be retrieved. Reviewers assessing study eligibility will not be blinded to the names of the authors, journals, and other publication details.

Data extraction and management

Characteristics of included studies and data will be extracted independently by two reviewers using a standard abstraction form. The abstraction form will be created and used in REDCap. REDCap is uniquely suited to meet the needs of an effective and efficient data extraction process. It allows form creators to require specific entry formats for individual questions (ensuring reviewers input data in a consistent format), allows for multiple types of response formats (dropdown menus, select all, select only one, open-ended text entry, etc), and performs data validation to improve accuracy of extraction. In addition REDCap has a built in "Double Data Entry" feature, which allows multiple users to input data from a single source and automatically compares the entries and identifies differences. Disagreements that are identified by the "Double Data Entry" feature will be resolved by a third party (project manager).

Data extracted will include the following:

- Basic study characteristics (journal, journal type, journal impact factor, publication year, funding source, article title, author, country/region, trial registration, and study protocol access)
- Intervention details (enrollment/intervention duration timeframes, condition(s) targeted, number of study arms, description of comparison group including number/age/sex etc, description of intervention group including number/age/sex etc, studywide characteristics/sample size, and type/description of intervention components)
- Eligibility details (reporting of eligibility, general/specific/vague exclusion criteria, proportion of excluded patients with MCC, and justifications for exclusions)
- Patient selection details (CONSORT participant flow, MCC inclusion implicitly or explicitly, proportion of included participants with MCC, specific MCC mentioned, and how information regarding targeted and other MCC was obtained)
- Quality assessment (selection bias, performance bias, detection bias, attrition bias, and reporting bias)
- Outcomes (presence of primary outcome, type of primary outcome, how primary outcome is measured, result of primary outcome, author conclusions, subgroup analyses, and effect modification)

Assessment of methodological quality in included studies

Two reviewers will independently assess methodological quality of the trials independently. Disagreements will be resolved by a third party. The quality of the RCTs will be assessed using a modified version of the Cochrane Collaboration's Risk of Bias tool, which evaluates seven domains including selection bias, performance bias, detection bias, attrition bias, reporting bias, and 'other bias.'[12] For each domain, the trial is given a rating of low risk of bias, high risk of bias, or unclear risk of bias. We will use this information in analysis in several ways, by using individual items, domains, or overall quality. For this review we will remove the "other bias" domain as it is unnecessary for the scope of this generalized report and is better suited for more specialized studies.

Dealing with missing data and duplicate studies

As a key part of this review is to assess the reporting of information regarding MCC, no attempts will be made to contact authors for additional information. For each extraction item there will be an option to list as "not reported." Duplicate studies will not be included, and only one article will be used for each trial.

Data synthesis

Analyses will be determined by specifics of data extracted (both type and volume) from selected studies; however, we anticipate that the large scope of this review will provide enough data to perform the following analyses.

We will summarize and describe the studies, populations, interventions, and outcomes included to verify that we have a representative sample. Assessment of inclusion of patients with MCC will greatly depend on how the information is presented in included studies, but we intend to perform such analyses as (1) calculating the proportion of studies explicitly excluding patients with MCC, (2) synthesizing a list of and frequency of each chronic condition present in patients in trials, (3) performing a proportions meta-analysis to estimate average proportion of patients within a trial that have MCC when they are included.

Key outcomes regarding inclusion of patients with MCC can be stratified by time category, journal type (general vs specialized), quality of study (as measured by our original quality tool and the GRADE process) and by other key variables identified throughout the process. Additionally time can be used as continuous variables in a meta-regression.[13,14] Study quality overall score can be used in a meta-regression or individual quality categories can be used to explore relationship with inclusion of patients with MCC and address issues of bias. Study quality data will also be used to descriptively assess the body of evidence.

We will also descriptively synthesize and report any challenges of recruiting as described by the primary authors of the RCTs included in this SRMA.

Additionally, publication bias will be explored.[15]

We anticipate all meta-analyses performed will be done so with a random effects model.
Data analysis will be performed using STATA 12.0 (College Station, TX), which provides a comprehensive set of meta-analysis routines, with additional analysis in R (3.1.0) as needed.

Assessment of heterogeneity
If any meta-analyses are performed, statistical heterogeneity will be assessed with the Cochran's Q and Higgins I^2 statistic.[16] We anticipate that the amount of heterogeneity will suggest that the random effects model is appropriate.

Subgroup analysis and investigation of heterogeneity
Key outcomes regarding inclusion of patients with MCC can be stratified by time category, journal type (general vs specialized), quality of study and by other key variables identified throughout the process. If meta-analyses are performed, time can be used as a continuous variable in a meta-regression.[13,14] Study quality overall score can be used in a meta-regression or individual quality categories can be used to explore relationship with inclusion of patients with MCC and address issues of bias.

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2. Differences between protocol and report

This section summarizes the main changes in methods for our review. We found that some aspects included in our original protocol were impractical based on the scope of our report, the time restraint for completing the project, and/or another unexpected factor. For example, in our original objectives we planned to analyze how inclusion of individuals with MCC in RCTs differed across journal impact factor and if this was associated with the efficacy or effectiveness of interventions. We also planned to describe the challenges of recruiting individuals with MCC to participate in trials and identify improvements for future studies regarding reporting and inclusion of individuals with MCC. After beginning extraction we determined that we would have only a very small number of articles from high impact journals and a very large number from low/average impact journals given that we did not use impact factor in our inclusion criteria. Although previous reviews purposefully chose high impact journals, we wanted a more representative sample of RCTs. Additionally, we addressed the possibility of looking into journal impact factor, efficacy/effectiveness of interventions, challenges of recruiting individuals with MCC, and improvements for future studies regarding reporting and inclusion of individuals with MCC in our implications for future research section as these topics were better suited for a more in depth and extended review. Furthermore, we also anticipated conducting an exploratory analysis regarding the primary outcome of the trial as one of our secondary outcomes. Again, we found that this aspect would be better suited for comprehensive report, and we identified this in our future directions section.

Another change that was made was extending and specifying our data extraction parameters. Through more extensive research and input from key informants, we narrowed our criterion for data extraction to be more specific to our primary and secondary outcomes. Additionally, we originally anticipated assessing the quality of the RCTs using a modified version of the Cochrane Collaboration's Risk of Bias tool, which evaluates seven domains including selection bias, performance bias, detection bias, attrition bias, reporting bias, and 'other bias.' However, before beginning extraction we removed the "other bias" domain as this element was an unnecessary consideration under the scope of this review and is better suited for more specialized studies. This determination was also addressed in the "Assessment of risk of bias in included studies" section of our report.

We planned to stratify our key outcomes by journal impact factor and intervention components (outcomes targeted, index disease targeted, type of intervention). As stated previously, we found that these factors were not pertinent to the scope and aim of this generalized report and would be better suited in a more expansive research paper focusing on these aspects of reporting in RCTs. The possibility of including these components was addressed in our future directions section.

A Mann-Whitney meta-analysis to explore the relationship between efficacy/effectiveness of interventions and inclusion of MCC was not feasible given the small amount of trials that reported outcome information in the necessary format for this analysis.

Ultimately we determined that the changes made from our original protocol did not impact the strength of our report, and, in addition, these differences are addressed in our future directions section as aspects that should be considered in a more comprehensive report.

3. Search Strategy

PubMed

("Young Adult"[Mesh] OR "Adult"[Mesh] OR "Middle Aged"[Mesh] OR "Aged"[Mesh] OR "Aged, 80 and over"[Mesh] OR "Frail Elderly"[Mesh] OR “adult” OR “adults” OR Middle age*[tiab] OR Geriatric* OR Aged OR Elder* OR Nonagenarian* OR Octogenarian* OR Centenarian* OR “senior citizen” OR “senior citizens” OR senium OR “very old” OR “oldest old” OR “older patient” OR “older patients” OR “older people”) AND ("Controlled Clinical Trial"[Publication Type] OR "Randomized Controlled Trial"[Publication Type]) AND ("Chronic Disease"[Mesh] OR "Chronic Disease" OR “chronic illness” OR “chronic Diseases” OR “Chronic Illnesses” OR “Chronically Ill” OR "Arthritis"[Mesh] OR "Arthritis" OR “Arthritides” OR “articular tuberculosis” OR “bone joint tuberculosis” OR “joint tuberculosis” OR “osteo-articular tuberculosis” OR “osteoarticular tuberculosis” OR “tuberculosis joint” OR “osteoarticular tuberculosis” OR “Psoriasis Arthropathica” OR “Caplan's Syndrome” OR “Felty Syndrome” OR “Rheumatoid Nodule” OR “Rheumatoid Nodules” OR “Rheumatoid Nodulosis” OR “Rheumatoid Vasculitis” OR “Sjogren Syndrome” OR “Sjogrens Syndrome” OR “Sjogren's Syndrome” OR “Sicca Syndrome” OR “Adult-Onset Still's Disease” OR “Adult Onset Still's Disease” OR “Adult-Onset Stills Disease” OR “Adult-Onset Still Disease” OR “Adult Onset Still Disease” OR “Chondrocalcinoses” OR “Calcium Pyrophosphate Dihydrate Deposition” OR “Pseudogout” OR “Chondrocalcinosis” OR “Gout” OR “Gouts” OR “gouty” OR “Osteoarthritis” OR “Osteoarthritides” OR “Osteoarthrosis” OR “Osteoarthroses” OR “Periarthritis” OR “Periarthritides” OR “Rheumatic Fevers” OR “Inflammatory Rheumatism” OR “Rheumatic Fever” OR “Rheumatic Nodule” OR “Rheumatic Nodules” OR “Aschoff Bodies” OR “Aschoff Bodies” OR “Wissler's Syndrome” OR “Wissler-Fanconi Syndrome” OR “Wissler Fanconi Syndrome” OR “Subsepsis Allergica” OR “Subsepsis Hyperergica” OR “Sacroiliitis” OR “Spondylarthropathies” OR “Spondylarthropathy” OR “Bechterew Disease” OR “Bechterew's Disease” OR “Bechterews Disease” OR “Ankylosing Spondyloarthritis” OR “Rheumatoid Spondylitis” OR “Spondylarthritis Ankylopoietica” OR “Ankylosing Spondylarthritis” OR “Ankylosing Spondylarthritides” OR “Ankylosing Spondylitis” OR “Marie-Struempell Disease” OR “Marie Struempell Disease” OR “Coxarthrosis” OR “Coxarthroses” OR “hip arthrosis” OR “hip joint arthrosis” OR “cox arthrosis” OR “malum coxae senilis” OR “arthrosynovitis” OR “joint inflammation” OR “oligoarthritis” OR “antisynthetase syndrome” OR “Behcet disease” OR “Behcet's syndrome” OR “Behcet syndrome” OR “Behcets disease” OR “Behcets syndrome” OR “Blau syndrome” OR “Blau's syndrome” OR “systemic granulomatosis” OR “Jabs syndrome” OR “inflammatory joint disease” OR “polyarthritis” OR "Asthma"[Mesh] OR Asthma* OR "Child Development Disorders, Pervasive"[Mesh] OR “Pervasive Child Development Disorders” OR “Pervasive Development Disorders” OR “Pervasive Development Disorder” OR “PDD”[tiab] OR “PDDNOS”[tiab] OR Autis* OR Asperger* OR “Kanner syndrome” OR “kanner’s syndrome” OR “childhood disintegrative disorder” OR “Rett syndrome” OR “rett disease” OR “Rett's syndrome” OR “Retts syndrome” OR "Neoplasms"[Mesh] OR neoplas* OR tumor OR tumors OR tumour OR tumours OR cancer OR cancers OR cancerous OR leukemi* OR mycosis OR leukaemi* OR Leucocythaemia* OR Leucocythemia* OR Chloroma* OR incidentaloma* OR “Myeloid Sarcoma” OR “Myeloid Sarcomas” OR “Granulocytic Sarcoma” OR “Granulocytic Sarcomas” OR “blast cell crisis” OR “blast crisis” OR “blastic crisis” OR carcinoma OR adenocarcinoma OR carcinomatous OR carcinosis OR choriocarcinoma OR “chorio epithelioma” OR chorioepithelioma OR “chorion epithelioma” OR “chorioncarcinoma” OR “chorionepithelioma” OR trophocarcinoma OR cystadenocarcinoma OR cystosarcoma OR “cysto sarcoma” OR “giant fibroadenoma” OR teratocarcinoma OR lymphoma* OR “Hodgkin disease” OR “hodgkin's disease” OR “hodgkins disease” OR “lymphogranuloma malignum” OR lymphogranulomatosis OR “malignant lymphogranuloma” OR “morbus hodgkin” OR “adenolymphoma” OR “cystadenoma lymphomatosum” OR “lymphoid malignancies” OR “lymphoid malignancy” OR immunocytoma OR lymphosarcoma OR “granuloma fungoides” OR “Sezary

syndrome” OR “Sezary disease” OR “syndrome sezary” OR astrocytoma OR astroglioma OR oligoastrocytoma OR “pleomorphic xanthoastrocytoma” OR cholangiocarcinoma OR “malignant cholangioma” OR carcinogenesis OR neoplasmogenesis OR oncogenesis OR tumorigenesis OR “tumorigenic effect” OR “tumourigenesis” OR “tumourigenic effect” OR osteosarcoma OR glioma OR ependymoblastoma OR ependymoma OR glioblastoma OR gliosarcoma OR medulloblastoma OR oligodendroglioma OR subependymoma OR blastoma OR blastomere OR blastomeres OR oligodendrocytosis OR carcinoid* OR microcarcinoma OR “childhood malignancy” OR “paediatric malignancy” OR “pediatric malignancy” OR melanoma* OR “malignant lentigo” OR “dubreuilh melanosis” OR “hutchinson melanotic freckle” OR “hutchinson's melanotic freckle” OR “lentigo maligna” OR “melanosis circumscripta praecancerosa” OR “melanosis circumscripta precancerosa” OR “melanotic freckle” OR nevocarcinoma OR “melano ameloblastoma” OR “melanotic adamantinoma” OR “melanotic ameloblastoma” OR “melanotic progonoma” OR progonoma OR retinoblastoma OR neuroblastoma OR ganglioneuroblastoma OR sympathicoblastoma OR sympathicogonioma OR sympathoblastoma OR neuroepithelioma OR neurocytoma OR retinocytoma OR hepatoma OR hepatoblastoma OR hepatocarcinogenesis OR hepatocarcinoma OR “schneeberg disease” OR “Pancoast syndrome” OR “Pancoast's syndrome” OR macroglobulinemia OR mesothelioma OR celothelioma OR mesotheliomatosis OR myeloma OR myeloplaxoma OR esthesioneuroblastoma OR “nasal glial heterotopia” OR dysgerminoma OR “call exner body” OR gynandroblastoma OR “demons meigs syndrome” OR rhinopharyngioma OR pheochromocytoma OR “medullary paraganglioma” OR phaeochromocytoma OR pinealoblastoma OR pinealocytoma OR pinealoma OR pineocytoma OR “hypophyseal adenoma” OR “pituitary adenoma” OR “pituitary gland adenoma” OR “pituitary microadenoma” OR rhabdomyosarcoma OR thymoma OR leiomyosarcoma OR nephroblastoma OR "Arrhythmias, Cardiac"[Mesh] OR Arrhythmia* OR Arrythmia* OR “cardiac dysrhythmia” OR proarrhythmia OR “ectopic rhythm” OR “heart dysrhythmia” OR “heart rhythm disorder” OR tachycardia OR bradycardia OR “nodal rhythm” OR “nodal rhythms” OR brachycardia OR bradyarrhythmia OR bradycardia OR “low heart rate” OR “carotid sinus syndrome” OR “sinus reflex” OR “cardiac channelopathy” OR “cardiac channelopathies” OR “Brugada syndrome” OR “Brugada's syndrome” OR “long QT syndrome” OR “Andersen syndrome” OR “Andersen Tawil syndrome” OR “Andersen's syndrome” OR “Jervell and Lange-Nielsen syndrome” OR “Jervell Lange Nielsen syndrome” OR “Jervell Lange Nielson syndrome” OR “Jervell-Lange Nielsen syndrome” OR “Romano-Ward syndrome” OR “progressive cardiac conduction defect” OR “Lenegre disease” OR “Lenegre's disease” OR “short QT syndrome” OR “short QT interval syndrome” OR “cardiopulmonary arrest” OR “sinus node disease” OR “sinus node dysfunction” OR “sick sinus syndrome” OR “sinus arrest” OR “atrial arrest” OR “atrial asystole” OR “atrial standstill” OR “cardiac sinus arrest” OR “sinoatrial arrest” OR “sinus node arrest” OR “sinus node syndrome” OR “heart fibrillation” OR “cardiac fibrillation” OR “atrium fibrillation” OR “atrial fibrillation” OR “auricular fibrillation” OR “auricular fibrillation” OR “conduction defect” OR “conduction defects” OR “conduction disease” OR “conduction diseases” OR “conduction disorder” OR “conduction disorders” OR “conduction disturbance” OR “conduction disturbances” OR cardiopalmus OR palpitation OR proarrhythmia OR parasystole OR “hyperkinetic heart syndrome” OR "Renal Insufficiency, Chronic"[Mesh] OR “chronic kidney disorder” OR “chronic nephropathy” OR “chronic renal disease” OR “chronic kidney failure” OR “End Stage Kidney Disease” OR “End Stage Renal Disease” OR “End Stage Renal Failure” OR “Chronic Renal Failure” OR “ESRD”[tiab] OR “Frasier Syndrome” OR “Chronic Renal Insufficiencies” OR “Chronic Renal Insufficiency” OR “Chronic Kidney Insufficiency” OR “Chronic Kidney Diseases” OR “Chronic Kidney Disease” OR “Chronic Renal Diseases” OR "Pulmonary Disease, Chronic Obstructive"[Mesh] OR “COPD”[tiab] OR “Chronic Obstructive Pulmonary Disease” OR “COAD”[tiab] OR “Chronic Obstructive Airway Disease” OR “Chronic Obstructive Lung Disease” OR “Chronic Airflow Obstructions” OR “Chronic Airflow Obstruction” OR “chronic obstructive bronchitis” OR

“chronic obstructive bronchopulmonary disease” OR “chronic obstructive pulmonary disorder” OR “chronic obstructive respiratory disease” OR “Chronic Bronchitis” OR “Pulmonary Emphysema” OR “pulmonary Emphysemas” OR “Focal Emphysema” OR “Panacinar Emphysema” OR “Panlobular Emphysema” OR “Centriacinar Emphysema” OR “Centrilobular Emphysema” OR “Edema, Cardiac"[Mesh] OR "Heart Failure, Diastolic"[Mesh] OR "Heart Failure, Systolic"[Mesh] OR “cardiac congestive failure” OR “congestive cardiac failure” OR “congestive heart insufficiency” OR “congestive heart failure” OR “cor pulmonale” OR “pulmonary cardiac disease” OR “pulmonary heart disease” OR “diastolic heart failure” OR “heart failure with preserved ejection fraction” OR “heart edema” OR “cardiac edema” OR “cardiac oedema” OR “heart oedema” OR “systolic heart failure” OR "Coronary Artery Disease"[Mesh] OR “Coronary Artery Diseases” OR “Coronary Artery Disease” OR “Coronary Arteriosclerosis” OR “Coronary Atherosclerosis” OR “coronary disease” OR "Dementia"[Mesh] OR Dementia* OR Amentia* OR Alzheimer* OR CADASIL OR “Lewy body” OR “DNTC”[tiab] OR “diffuse neurofibrillary tangles with calcification” OR “frontotemporal lobar degeneration” OR “FTD”[tiab] OR “FTLD”[tiab] OR “Pick's complex”[tiab] OR “Pick complex”[tiab] OR fvFTD[tiab] OR bvFTD[tiab] OR “primary progressive aphasia” OR “Mesulam syndrome” OR “PPA”[tiab] OR tvFTD[tiab] OR “progressive nonfluent aphasia” OR “non-fluent progressive aphasia” OR “nonfluent progressive aphasia” OR “PNFA”[tiab] OR “progressive non-fluent aphasia” OR “AIDS encephalopathy” OR “HIV 1 associated cognitive motor complex” OR “HIV associated cognitive motor complex” OR “HIV associated neurocognitive disorder” OR “HIV encephalopathy” OR “HIV Encephalopathies” OR “Huntington Disease” OR “Huntington chorea” OR “chorea Huntington” OR “chronic progressive chorea” OR “hereditary chorea” OR “Huntington's chorea” OR “Huntington's disease” OR “Kluver Bucy”[tiab] OR “Kluever Bucy”[tiab] OR “Kluver-Bucy”[tiab] OR “mental deterioration” OR “cognitive deterioration” OR “mental regression” OR “neuronal ceroid lipofuscinosis” OR “amaurotic familial idiocy” OR “amaurotic idiocy” OR “Batten disease” OR “batten mayou disease” OR “familial amaurotic idiocy” OR “neuronal ceroid-lipofuscinoses” OR “neuronal ceroid-lipofuscinosis” OR “neuronal ceroidosis” OR “Pick disease” OR “pick syndrome” OR “prion disease” OR “bovine spongiform encephalopathy” OR “chronic wasting disease” OR “Creutzfeldt Jakob disease” OR “fatal familial insomnia” OR “Gerstmann Straussler Scheinker syndrome” OR “kuru” OR “scrapie” OR “transmissible mink encephalopathy” OR “transmissible neurodegenerative disease” OR “subacute spongiform” OR “transmissible spongiform encephalopathy” OR “pseudodementia” OR “Rett syndrome” OR “rett disease” OR “Retts syndrome” OR senility OR “senile confusion” OR “senile psychosis” OR tauopathy OR tauopathies OR “Kohlschutter-Tonz Syndrome” OR "Depressive Disorder"[Mesh] OR "Depression"[Mesh] OR depression* OR “depressive disease” OR “depressive disorder” OR “depressive episode” OR “depressive illness” OR “depressive personality disorder” OR “depressive state” OR “depressive symptom” OR “depressive symptoms” OR “depressive syndrome” OR Melancholia OR “depressive Disorders” OR “Depressive Neuroses” OR “Depressive Neurosis” OR “Depressive Syndrome” OR “Depressive Syndromes” OR “Involutional Psychoses” OR “Involutional Psychosis” OR “Treatment Resistant Depressive” OR “treatment Resistant Depressives” OR “Dysthymic Disorders” OR “Dysthymic Disorder” OR “Premenstrual Dysphoric Disorder” OR “Premenstrual Dysphoric Syndrome” OR “Seasonal Affective Disorder” OR “Seasonal Mood Disorder” OR “Seasonal Mood Disorders” OR “Seasonal Affective Disorders” OR “bipolar disorder” OR “bipolar affective disorder” OR “bipolar illness” OR “bipolar psychosis” OR “manic depressive” OR “bipolar mania” OR cyclothymia OR “cyclothymic depressive” OR “cyclothymic disorder” OR “cyclothymic personality” OR “rapid cycling mood disorder” OR “depressive psychosis” OR dysphoria OR dysthymia OR “depressive reaction” OR “dysthymic disorder” OR “mental anorexia” OR “mental fatigue” OR melancholy OR “unipolar disorder” OR “Perry syndrome” OR “Diabetes Mellitus, Type 1”[Mesh] OR “Diabetes Mellitus, Type 2”[Mesh] OR “insulin-Dependent Diabetes Mellitus” OR “Juvenile Onset Diabetes” OR “Type 1 Diabetes” OR “Sudden-Onset Diabetes Mellitus” OR “Diabetes

Mellitus Type I" OR "IDDM"[tiab] OR "Insulin Dependent Diabetes" OR "Brittle Diabetes" OR "Ketosis-Prone Diabetes Mellitus" OR "Autoimmune Diabetes" OR "DIDMOAD"[tiab] OR "Wolfram Syndrome" OR "NIDDM" OR "Maturity Onset Diabetes" OR "Adult Onset Diabetes" OR "Ketosis Resistant Diabetes Mellitus" OR "Non Insulin Dependent Diabetes Mellitus" OR "Stable Diabetes Mellitus" OR "MODY"[tiab] OR "Type 2 Diabetes" OR "Noninsulin Dependent Diabetes" OR "Lipoatrophic Diabetes" OR diabetic* OR "diabetes mellitus type I" OR "early onset diabetes" OR "iddm"[tiab] OR "juvenile diabetes" OR "ketoacidotic diabetes" OR "labile diabetes mellitus" OR "type I diabetes" OR "diabetes mellitus type 2" OR "diabetes mellitus type ii" OR "diabetes type 2" OR "diabetes type II" OR "insulin independent diabetes" OR "ketosis resistant diabetes" OR "type II diabetes" OR "Hepatitis, Chronic"[Mesh] OR "Chronic Hepatitis" OR "Chronic Active Hepatitis" OR "Chronic Persistent Hepatitis" OR "Chronic Delta Hepatitis" OR "Autoimmune Hepatitides" OR "Chronic Hepatitides" OR "Autoimmune Hepatitis" OR "chronic hepatopathy" OR "HIV"[Mesh] OR "AIDS Virus" OR "AIDS Viruses" OR HTLV-III OR "Human Immunodeficiency Virus" OR "Human Immunodeficiency Viruses" OR "Human T Cell Lymphotropic Virus Type III" OR "Human T Lymphotropic Virus Type III" OR "Human T-Cell Leukemia Virus Type III" OR "Human T Cell Leukemia Virus Type III" OR "Human T-Cell Lymphotropic Virus Type III" OR "Human T-Lymphotropic Virus Type III" OR "LAV-HTLV-III" OR "Lymphadenopathy-Associated Virus" OR "Lymphadenopathy Associated Virus" OR "Acquired Immune Deficiency Syndrome Virus" OR "Acquired Immunodeficiency Syndrome Virus" OR "HIV-1" OR "HIV-2" OR "aids associated retrovirus" OR "aids associated virus" OR "aids related virus" OR "immunodeficiency viruses" OR "lymphadenopathy associated retrovirus" OR "Hyperlipidemias"[Mesh] OR Hyperlipemia OR Hyperlipemias OR Hyperlipidemia OR Lipidemia OR Lipemia OR Hypercholesterolemia OR "Elevated Cholesterol" OR "Hypercholesteremia" OR hyperlipaemia OR hyperlipidaemia OR hyperlipidemias OR hyperlipidemic OR lipaemia OR lipidaemia OR cholesterolemia OR hypercholesterolaemia OR "Burger Grutz syndrome" OR hyperbetalipoproteinaemia OR hyperbetalipoproteinemia OR hypercholesterolemic OR "familial hyperlipoproteinaemia type ii" OR "familial hyperlipoproteinemia type ii" OR "hyper low density lipoproteinaemia" OR "hyper low density lipoproteinemia" OR "hypercholesterolaemic xanthomatosis" OR "hyperlipoproteinaemia type ii" OR "hyperlipoproteinemia type 2" OR "hyperlipoproteinemia type ii" OR "ldl receptor disorder" OR "tendinous xanthomatosis" OR "xanthoma tendinosum" OR "xanthoma tuberosum" OR hypertriglyceridemia OR hypertriglyceridaemia OR "triglyceride storage disease" OR triglyceridemia OR "hypertriglyceridemic waist" OR Hyperlipoproteinemias OR "Hypertension"[Mesh] OR Hypertension* OR Hypertensive OR "High Blood Pressure" OR "High Blood Pressures" OR "Goldblatt Syndrome" OR "apparent mineralocorticoid excess syndrome" OR "Gordon syndrome" OR "Gordon's syndrome" OR "Liddle syndrome" OR "Liddle's syndrome" OR "metabolic syndrome" OR "insulin resistance syndrome" OR "ocular ischaemic syndrome" OR "ocular ischemic syndrome" OR "orthostatic hypertension" OR "posterior encephalopathy" OR "posterior leucoencephalopathy" OR "posterior leucoencephalopathy" OR "posterior leukoencephalopathy" OR "posterior reversible encephalopathy" OR "posterior reversible leucoencephalopathy" OR "posterior reversible leukoencephalopathy" OR "PRES"[tiab] OR "RPLS"[tiab] OR pre-hypertension OR "goldblatt kidney" OR nephrosclerosis OR "renal arteriosclerosis" OR "renal atherosclerosis" OR "Osteoporosis"[Mesh] OR Osteoporosis OR Osteoporoses OR "Age-Related Bone Loss" OR "Age-Related Bone Losses" OR "female athlete triad" OR "Perimenopausal Bone Loss" OR "Postmenopausal Bone Loss" OR "posttraumatic osteopenia" OR "Sudeck atrophy" OR "sudeck dystrophy" OR "Sudeck Leriche syndrome" OR "Sudeck syndrome" OR "Sudeck's atrophy" OR "Schizophrenia"[Mesh] OR Schizophrenia* OR Schizophrenic* OR "Dementia Praecox" OR hebephrenia OR paraphrenia OR "Delusional Disorder" OR "Delusional Disorders" OR "schizoaffective psychosis" OR "schizo affective disorder" OR "schizo affective psychosis" OR "schizoaffective disorder" OR "schizophreniform disorder" OR "schizophreniform psychosis" OR "Shared Paranoid Disorder" OR "Shared Psychotic Disorder" OR

“Shared Psychotic Disorders” OR “Shared Paranoid Disorders” OR “Folie a Deux” OR “Folie a Trois” OR "Brain Ischemia"[Mesh] OR “Chronic stroke” OR “brain ischemia” OR “brain ischaemia” OR “cerebral blood circulation disorder” OR “cerebral circulation disorder” OR “cerebral circulatory disorder” OR “cerebral ischaemia” OR “cerebral ischemia” OR “cerebrovascular ischaemia” OR “cerebrovascular ischemia” OR “ischaemic brain disease” OR “ischaemic encephalopathy” OR “ischaemic stroke” OR “ischemic brain disease” OR “ischemic encephalopathy” OR “ischemic stroke” OR “neural ischaemia” OR “neural ischemia” OR “cerebral vasospasm” OR “intracranial vasospasm” OR “Call-Fleming syndrome” OR “brain hypoxia ischaemia” OR “brain hypoxia ischemia” OR “brain hypoxic ischemic injury” OR “cerebral hypoxia ischaemia” OR “cerebral hypoxia ischemia” OR “cerebral hypoxic ischaemic injury” OR “cerebral hypoxic ischemic damage” OR “cerebral hypoxic ischemic injuries” OR “cerebral hypoxic ischemic injury” OR “cerebral ischaemia hypoxia” OR “cerebral ischemia hypoxia” OR “hypoxic ischaemic brain damage” OR “hypoxic ischaemic brain injury” OR “hypoxic ischaemic cerebral damage” OR “hypoxic ischaemic cerebral injury” OR “hypoxic ischemic brain damage” OR “hypoxic ischemic brain injuries” OR “hypoxic ischemic brain injury” OR “hypoxic ischemic cerebral damage” OR “hypoxic ischemic cerebral injury” OR “ischaemic attack” OR “ischemic attack” OR “ischemic seizure” OR “Brain Infarction” OR “Brain Stem Infarctions” OR “Brain Stem Infarction” OR “Brainstem Infarctions” OR “Brainstem Infarction” OR “Brainstem Stroke” OR “Claude Syndrome” OR “Weber Syndrome” OR “Millard Gublar Syndrome” OR “Top of the Basilar Syndrome” OR “Foville Syndrome” OR “Lateral Medullary Syndrome” OR “Lateral Medullary Syndromes” OR “Posterior Inferior Cerebellar Artery Syndrome” OR “Wallenberg's Syndrome” OR “Wallenberg Syndrome” OR “Dorsolateral Medullary Syndrome” OR “Lateral Bulbar Syndrome” OR “Cerebral Infarction” OR “Cerebral Infarctions” OR “Subcortical Infarction” OR “Subcortical Infarctions” OR “Choroidal Artery Infarction” OR “Cerebral Artery Infarction” OR “Cerebral Artery Infarctions” OR “ACA Infarction” OR “ACA Infarctions” OR “Cerebral Artery Stroke” OR “Cerebral Artery Syndrome” OR “MCA Infarction” OR “Cerebral Artery Thrombosis” OR “PCA Infarction” OR “Substance-Related Disorders”[Mesh] OR alcoholism OR “drug dependence” OR “drug addiction” OR “Drug Habituation” OR “Drug Abuse” OR “Substance Abuse” OR “Substance Abuses” OR “Substance Dependence” OR “Substance Addiction” OR “Substance Use Disorders” OR “Substance Use Disorder” OR “Drug Dependence” OR “Drug Addiction” OR “substance abuser” OR “substance dependence” OR “amphetamine related disorders” OR “drug abuser” OR “drug problem” OR “needle sharing” OR “phencyclidine abuse” OR “alcohol addiction” OR “alcohol dependence” OR “alcohol dependents” OR “alcohol polyneuropathy” OR “alcohol dependent individual” OR “alcohol induced disorders” OR “alcohol related disorders” OR dipsomania* OR “ethanol dependence” OR “problem drinker” OR “problematic drinker” OR “analgesic abuse” OR doping OR “drug misuse” OR “inhalant abuse” OR “intravenous drug abuse” OR “intravenous drug user” OR “prescription drug diversion” OR “drug use disorder” OR “drug use disorders” OR “Alcohol Related Disorders” OR “Alcohol Related Disorder” OR “Alcohol Induced Disorders” OR “Alcohol Induced Disorder” OR “Alcohol Amnestic Syndrome” OR “Alcohol Induced Amnestic Syndrome” OR “Alcohol Induced Korsakoff Syndrome” OR “Alcohol Induced Persisting Amnestic Disorder” OR “Korsakoff Syndrome” OR “Korsakoff Psychosis” OR “Korsakoff Psychoses” OR “Alcoholic Neuropathy” OR “Alcoholic Neuropathies” OR “Alcoholic Polyneuropathies” OR “Alcoholic Polyneuropathy” OR “Alcoholic Polyneuritis” OR “Alcohol Induced Polyneuropathy” OR “Alcohol Related Polyneuropathy” OR “Alcohol Induced Peripheral Neuropathy” OR “Alcoholic Cardiomyopathy” OR “Fetal Alcohol Spectrum Disorders” OR “FASD”[tiab] OR “FASDs”[tiab] OR “Alcohol Related Birth Defects” OR “Alcohol Related Neurodevelopmental Disorder” OR “Fetal Alcohol Effects” OR “Fetal Alcohol Syndrome” OR “Alcoholic Liver Diseases” OR “Alcoholic Liver Disease” OR “Alcoholic Fatty Liver” OR “Alcoholic Steatohepatitis” OR “Chronic Alcoholic Hepatitis” OR “Alcoholic Liver Cirrhosis” OR “Alcoholic Cirrhosis” OR “Alcoholic Hepatic Cirrhosis” OR “Alcoholic Pancreatitis” OR “Alcoholic Psychoses” OR “Chronic Alcoholic

Intoxication" OR "Alcohol Abuse" OR "Amphetamine Related Disorders" OR "Amphetamine Abuse" OR "Amphetamine Addiction" OR "Amphetamine Dependence" OR "Cocaine Related Disorders" OR "Cocaine Related Disorder" OR "Cocaine Abuse" OR "Cocaine Dependence" OR "Cocaine Addiction" OR "Glue Sniffing" OR "Glue Sniffings" OR "Glue Abuse" OR "Marijuana Abuse" OR "Marihuana Abuse" OR "Hashish Abuse" OR "Cannabis Related Disorder" OR "Cannabis Abuse" OR "Cannabis Dependence" OR "Marijuana Dependence" OR "Opioid Related Disorders" OR "Opiate Dependence" OR "Opiate Addiction" OR "Narcotic Abuse" OR "Narcotic Dependence" OR "Narcotic Addiction" OR "Heroin Dependence" OR "Heroin Addiction" OR "Heroin Abuse" OR "Morphine Dependence" OR "Morphine Addiction" OR "Morphine Abuse" OR "PCP Abuse" OR "Angel Dust Abuse" OR "Substance Induced Psychoses" OR "Toxic Psychoses" OR "Drug Psychoses" OR "Intravenous Substance Abuse" OR "Parenteral Drug Abuse" OR "Tobacco Use Disorder" OR "Tobacco Use Disorders" OR "Nicotine Use Disorder" OR "Nicotine Use Disorders" OR "Tobacco Dependence" OR "Tobacco Dependences" OR "Nicotine Dependence" OR "alcoholic individual" OR "alcoholics" OR "alcoholic polyneuropathy" OR "ethanol dependence" OR "narcotic depression" OR "narcotism" OR "heroin addict" OR "heroinism" OR "morphine addict" OR "opiate addict" OR "opioid dependence" OR "opium addict" OR "opium addiction" OR "opium addiction" OR "benzodiazepine dependence" OR "benzodiazepine addiction" OR "cannabis addiction" OR "drug abuse pattern" OR "methamphetamine dependence" OR "toxicomania" OR "drug addict" OR "drug dependence" OR "drug dependency")

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'controlled clinical trial'/it OR 'randomized controlled trial'/it OR 'controlled clinical trial'/exp OR 'randomized controlled trial'/exp AND ('young adult'/exp OR 'adult'/exp OR 'middle aged'/exp OR 'aged'/exp OR 'aged hospital patient'/exp OR 'frail elderly'/exp OR 'very elderly'/exp OR 'geriatrics'/exp OR adult OR adults OR 'Middle age' OR 'middle aged' OR 'middle ages' OR geriatric* OR Aged OR Elder* OR 'Oldest Old' OR Nonagenarian* OR Octogenarian* OR Centenarian* OR 'senior citizen' OR 'senior citizens' OR senium OR 'very old' OR 'older patients' OR 'older patient' OR 'older people') AND ('chronic disease'/exp OR 'chronic disease' OR 'chronic illness' OR 'chronic Diseases' OR 'Chronic Illnesses' OR 'Chronically Ill' OR 'asthma'/exp OR asthma* OR 'arthritis'/exp OR 'Arthritis' OR 'Arthritides' OR 'arthrotuberculosis' OR 'articular tuberculosis' OR 'bone joint tuberculosis' OR 'white joint swelling' OR 'joint tuberculosis' OR 'osteo-articular tuberculosis' OR 'osteoarticular tuberculosis' OR 'tuberculosis joint' OR 'tuberculosis sacroileitis' OR 'osteoarticular tuberculosis' OR 'white swelling' OR 'Psoriasis Arthropathica' OR 'Juvenile-Onset Still Disease' OR 'Juvenile Onset Still Disease' OR 'Juvenile-Onset Stills Disease' OR 'Juvenile-Onset Stills Disease' OR 'Juvenile Onset Stills Disease' OR 'Caplan Syndromes' OR 'Caplans Syndrome' OR 'Caplans Syndrome' OR 'Felty Syndrome' OR 'Feltys Syndrome' OR 'Rheumatoid Nodule' OR 'Rheumatoid Nodules' OR 'Rheumatoid Nodulosis' OR 'Rheumatoid Noduloses' OR 'Rheumatoid Vasculitis' OR 'Rheumatoid Vasculitides' OR 'Sjogren Syndrome' OR 'Sjogrens Syndrome' OR 'Sjogrens Syndrome' OR 'Sicca Syndrome' OR 'Adult-Onset Stills Disease' OR 'Adult Onset Stills Disease' OR 'Adult-Onset Stills Disease' OR 'Adult-Onset Still Disease' OR 'Adult Onset Still Disease' OR 'Chondrocalcinoses' OR 'Calcium Pyrophosphate Dihydrate Deposition' OR 'Pseudogout' OR 'Chondrocalcinosis' OR 'Gout' OR 'Gouts' OR 'gouty' OR 'Osteoarthritis' OR 'Osteoarthritides' OR 'Osteoarthrosis' OR 'Osteoarthroses' OR 'Periarthritis' OR 'Periarthritides' OR 'Rheumatic Fevers' OR 'Inflammatory Rheumatism' OR 'Rheumatic Fever' OR 'Rheumatic Nodule' OR 'Rheumatic Nodules' OR 'Aschoff Bodies' OR 'Wisslers Syndrome' OR 'Wissler Syndrome' OR 'Wisslers Syndrome' OR 'Wissler-Fanconi Syndrome' OR 'Wissler Fanconi Syndrome' OR 'Subsepsis Allergica' OR 'Subsepsis Hyperergica' OR 'Sacroiliitis' OR 'Sacroiliitides' OR 'Spondylarthropathies' OR 'Spondylarthropathy' OR 'Bechterew Disease' OR 'Bechterews Disease' OR 'Bechterews Disease' OR 'Ankylosing Spondyloarthritis' OR 'Ankylosing Spondyloarthritides' OR 'Rheumatoid Spondylitis' OR 'Spondylarthritis Ankylopoietica' OR

‘Ankylosing Spondylarthritis’ OR ‘Ankylosing Spondylarthritides’ OR ‘Ankylosing Spondylitis’ OR ‘Marie-Struempell Disease’ OR ‘Marie Struempell Disease’ OR ‘Coxarthrosis’ OR ‘Coxarthroses’ OR ‘hip arthrosis’ OR ‘hip joint arthrosis’ OR ‘cox arthrosis’ OR ‘coxartherosis’ OR ‘hip osteo-arthritis’ OR ‘hip osteo-arthrosis’ OR ‘malum coxae senilis’ OR ‘arthrochondritis’ OR ‘arthrosynovitis’ OR ‘joint inflammation’ OR ‘oligoarthritis’ OR ‘antisynthetase syndrome’ OR ‘Behcet disease’ OR ‘Behcets syndrome’ OR ‘Behcet syndrome’ OR ‘behcet ulcer’ OR ‘Behcets disease’ OR ‘Behcets syndrome’ OR ‘Blau syndrome’ OR ‘arthrocutaneouveal granulomatosis’ OR ‘Blaus syndrome’ OR ‘Blau type familial granulomatosis’ OR ‘Blaus syndrome’ OR ‘systemic granulomatosis’ OR ‘Jabs disease’ OR ‘Jabs syndrome’ OR ‘inflammatory joint disease’ OR ‘polyarthritis’ OR ‘urate inflammation’ OR ‘arthragra’ OR 'autism'/exp OR ‘Pervasive Child Development Disorders’ OR ‘Pervasive Development Disorders’ OR ‘Pervasive Development Disorder’ OR ‘PDD’ OR ‘PDDNOS’ OR Autis* OR Asperger* OR ‘Kanner syndrome’ OR ‘kanners syndrome’ OR ‘childhood disintegrative disorder’ OR ‘Rett syndrome’ OR ‘morbus rett’ OR ‘rett disease’ OR ‘Retts syndrome’ OR 'neoplasm'/exp OR neoplas* OR tumor OR tumors OR tumour OR tumours OR cancer OR cancers OR cancerous OR leukemi* OR mycosis OR leukaemi* OR Leucocythaemia* OR Leucocythemia* OR Chloroma* OR incidentaloma* OR ‘Myeloid Sarcoma’ OR ‘Myeloid Sarcomas’ OR ‘Granulocytic Sarcoma’ OR ‘Granulocytic Sarcomas’ OR ‘blast cell crisis’ OR ‘blast crisis’ OR ‘blastic crisis’ OR carcinoma OR adenocarcinoma OR carcinomatous OR carcinosis OR choriocarcinoma OR ‘chorio epithelioma’ OR chorioepithelioma OR ‘chorion epithelioma’ OR ‘chorioncarcinoma’ OR ‘chorionepithelioma’ OR trophocarcinoma OR cystadenocarcinoma OR cystosarcoma OR ‘cysto sarcoma’ OR ‘giant fibroadenoma’ OR teratocarcinoma OR lymphoma* OR ‘Hodgkin disease’ OR ‘hodgkins disease’ OR ‘hodgkins disease’ OR ‘lymphogranuloma malignum’ OR lymphogranulomatosis OR ‘malignant lymphogranuloma’ OR ‘morbus hodgkin’ OR ‘adenolymphoma’ OR ‘cystadenoma lymphomatosum’ OR ‘lymphoid malignancies’ OR ‘lymphoid malignancy’ OR immunocytoma OR lymphosarcoma OR ‘granuloma fungoides’ OR ‘Sezary syndrome’ OR ‘Sezary disease’ OR ‘syndrome sezary’ OR astrocytoma OR astroglioma OR oligoastrocytoma OR ‘pleomorphic xanthoastrocytoma’ OR cholangiocarcinoma OR ‘malignant cholangioma’ OR carcinogenesis OR neoplasmogenesis OR oncogenesis OR tumorigenesis OR ‘tumorigenic effect’ OR ‘tumourigenesis’ OR ‘tumourigenic effect’ OR osteosarcoma OR glioma OR ependymoblastoma OR ependymoma OR glioblastoma OR gliosarcoma OR medulloblastoma OR oligodendroglioma OR subependymoma OR blastoma OR blastomere OR blastomeres OR oligodendrocytosis OR carcinoid* OR microcarcinoma OR ‘childhood malignancy’ OR ‘paediatric malignancy’ OR ‘pediatric malignancy’ OR melanoma* OR ‘malignant lentigo’ OR ‘dubreuilh melanosis’ OR ‘hutchinson melanotic freckle’ OR ‘hutchinsons melanotic freckle’ OR ‘lentigo maligna’ OR ‘melanosis circumscripta praecancerosa’ OR ‘melanosis circumscripta precancerosa’ OR ‘melanotic freckle’ OR nevocarcinoma OR ‘melano ameloblastoma’ OR ‘melanotic adamantinoma’ OR ‘melanotic ameloblastoma’ OR ‘melanotic progonoma’ OR progonoma OR retinoblastoma OR neuroblastoma OR ganglioneuroblastoma OR sympathicoblastoma OR sympathicogonioma OR sympathoblastoma OR neuroepithelioma OR neurocytoma OR retinocytoma OR hepatoma OR hepatoblastoma OR hepatocarcinogenesis OR hepatocarcinoma OR ‘schneeberg disease’ OR ‘Pancoast syndrome’ OR ‘Pancoasts syndrome’ OR macroglobulinemia OR mesothelioma OR celothelioma OR mesotheliomatosis OR myeloma OR myeloplaxoma OR esthesioneuroblastoma OR ‘nasal glial heterotopia’ OR dysgerminoma OR ‘call exner body’ OR gynandroblastoma OR ‘demons meigs syndrome’ OR rhinopharyngioma OR pheochromocytoma OR ‘medullary paraganglioma’ OR phaeochromocytoma OR pinealoblastoma OR pinealocytoma OR pinealoma OR pineocytoma OR ‘hypophyseal adenoma’ OR ‘pituitary adenoma’ OR ‘pituitary gland adenoma’ OR ‘pituitary microadenoma’ OR rhabdomyosarcoma OR thymoma OR leiomyosarcoma OR nephroblastoma OR 'heart arrhythmia'/exp OR Arrhythmia* OR Arrythmia* OR ‘cardiac dysrhythmia’ OR proarrhythmia OR proarrhythmias OR ‘ectopic heart rhythm’ OR

‘ectopic rhythm’ OR ‘heart aberrant conduction’ OR ‘heart dysrhythmia’ OR ‘heart ectopic beat’ OR ‘heart ectopic ventricle contraction’ OR ‘heart rhythm disorder’ OR tachycardia OR bradycardia OR ‘nodal rhythm’ OR ‘nodal rhythms’ OR brachycardia OR bradyarrhythmia OR bradycardy OR bradycardia OR ‘low heart rate’ OR hypoarrhythmia OR ‘carotid sinus syndrome’ OR ‘carotid cavernous syndrome’ OR ‘sinus caroticus syndrome’ OR ‘sinus reflex’ OR ‘weiss baker syndrome’ OR ‘cardiac channelopathy’ OR ‘cardiac channelopathies’ OR ‘Brugada syndrome’ OR ‘Brugadas syndrome’ OR ‘Brugadas syndrome’ OR ‘long QT syndrome’ OR ‘Andersen syndrome’ OR ‘Andersen Tawil syndrome’ OR ‘Andersen triad’ OR ‘Andersens syndrome’ OR ‘Andersens syndrome’ OR ‘Jervell and Lange-Nielsen syndrome’ OR ‘Jervell Lange Nielsen syndrome’ OR ‘Jervell Lange Nielson syndrome’ OR ‘Jervell Nielsen syndrome’ OR ‘Jervell-Lange Nielsen syndrome’ OR ‘Lange Nielson Jervell syndrome’ OR ‘Romano-Ward syndrome’ OR ‘Romano Ward ECG’ OR ‘progressive cardiac conduction defect’ OR ‘Lenegre disease’ OR ‘Lenegre syndrome’ OR ‘Lenegres disease’ OR ‘Lenegres syndrome’ OR ‘Lev Lenegre disease’ OR ‘short QT syndrome’ OR ‘short QT interval syndrome’ OR ‘cardiopulmonary arrest’ OR ‘sinus node disease’ OR ‘sinus node dysfunction’ OR ‘sick sinus syndrome’ OR ‘sinus arrest’ OR ‘atrial arrest’ OR ‘atrial asystole’ OR ‘atrial standstill’ OR ‘atrium standstill’ OR ‘cardiac sinus arrest’ OR ‘heart atrium arrest’ OR ‘sinoatrial arrest’ OR ‘sinus node arrest’ OR ‘sinus node syndrome’ OR ‘heart fibrillation’ OR ‘cardiac fibrillation’ OR ‘atrium fibrillation’ OR ‘atrial fibrillation’ OR ‘auricular fibrillation’ OR ‘auricular fibrillation’ OR ‘conduction defect’ OR ‘conduction defects’ OR ‘conduction disease’ OR ‘conduction diseases’ OR ‘conduction disorder’ OR ‘conduction disorders’ OR ‘conduction disturbance’ OR ‘conduction disturbances’ OR cardiopalmus OR palpitation OR proarrhythmia OR parasystole OR ‘hyperkinetic heart syndrome’ OR 'chronic kidney disease'/exp OR ‘chronic kidney disorder’ OR ‘chronic nephropathy’ OR ‘chronic renal disease’ OR ‘chronic kidney failure’ OR ‘End Stage Kidney Disease’ OR ‘End Stage Renal Disease’ OR ‘End Stage Renal Failure’ OR ‘Chronic Renal Failure’ OR ‘ESRD’ OR ‘Frasier Syndrome’ OR ‘Chronic Renal Insufficiencies’ OR ‘Chronic Renal Insufficiency’ OR ‘Chronic Kidney Insufficiency’ OR ‘Chronic Kidney Insufficiencies’ OR ‘Chronic Kidney Diseases’ OR ‘Chronic Kidney Disease’ OR ‘Chronic Renal Diseases’ OR 'chronic obstructive lung disease'/exp OR ‘COPD’ OR ‘Chronic Obstructive Pulmonary Disease’ OR ‘COAD’ OR ‘Chronic Obstructive Airway Disease’ OR ‘Chronic Obstructive Lung Disease’ OR ‘Chronic Airflow Obstructions’ OR ‘Chronic Airflow Obstruction’ OR ‘chronic obstructive bronchitis’ OR ‘chronic obstructive bronchopulmonary disease’ OR ‘chronic obstructive lung disorder’ OR ‘chronic obstructive pulmonary disorder’ OR ‘chronic obstructive respiratory disease’ OR ‘Chronic Bronchitis’ OR ‘Pulmonary Emphysema’ OR ‘pulmonary Emphysemas’ OR ‘Focal Emphysema’ OR ‘Focal Emphysemas’ OR ‘Panacinar Emphysema’ OR ‘Panacinar Emphysemas’ OR ‘Panlobular Emphysema’ OR ‘Panlobular Emphysemas’ OR ‘Centriacinar Emphysema’ OR ‘Centriacinar Emphysemas’ OR ‘Centrilobular Emphysema’ OR ‘Centrilobular Emphysemas’ OR 'congestive heart failure'/exp OR ‘cardiac congestive failure’ OR ‘congestive cardiac failure’ OR ‘congestive heart insufficiency’ OR ‘congestive heart failure’ OR ‘cor pulmonale’ OR corpulmonale OR ‘pulmonary cardiac disease’ OR ‘pulmonary heart disease’ OR ‘diastolic heart failure’ OR ‘heart failure with preserved ejection fraction’ OR ‘heart edema’ OR ‘cardiac edema’ OR ‘cardiac oedema’ OR ‘heart oedema’ OR ‘systolic heart failure’ OR 'coronary artery disease'/exp OR ‘Coronary Artery Diseases’ OR ‘Coronary Artery Disease’ OR ‘Coronary Arteriosclerosis’ OR ‘Coronary Arterioscleroses’ OR ‘Coronary Atheroscleroses’ OR ‘Coronary Atherosclerosis’ OR ‘coronary disease’ OR dementia/exp OR Dementia* OR Amentia* OR Alzheimer* OR CADASIL OR ‘Lewy body’ OR ‘DNTC’ OR ‘diffuse neurofibrillary tangles with calcification’ OR ‘frontotemporal lobar degeneration’ OR ‘FTD’ OR ‘FTLD’ OR ‘Picks complex’ OR ‘Pick complex’ OR fvFTD OR bvFTD OR ‘primary progressive aphasia’ OR ‘Mesulam syndrome’ OR ‘PPA’ OR tvFTD OR ‘progressive nonfluent aphasia’ OR ‘non-fluent progressive aphasia’ OR ‘nonfluent progressive aphasia’ OR ‘PNFA’ OR ‘progressive non-fluent aphasia’ OR ‘AIDS encephalopathy’ OR ‘HIV 1 associated cognitive motor complex’ OR ‘HIV associated

cognitive motor complex' OR 'HIV associated neurocognitive disorder' OR 'HIV encephalopathy' OR 'HIV Encephalopathies' OR 'Huntington Disease' OR 'Huntington chorea' OR 'chorea Huntington' OR 'chronic progressive chorea' OR 'hereditary chorea' OR 'Huntingtons chorea' OR 'Huntingtons disease' OR 'Kluver Bucy' OR 'Kluever Bucy' OR 'Kluver-Bucy' OR 'mental deterioration' OR 'cognitive deterioration' OR 'mental regression' OR 'neuronal ceroid lipofuscinosis' OR 'amaurotic familial idiocy' OR 'amaurotic idiocy' OR 'Batten disease' OR 'batten mayou disease' OR 'familial amaurotic idiocy' OR 'neuronal ceroid-lipofuscinoses' OR 'neuronal ceroid-lipofuscinosis' OR 'neuronal ceroidosis' OR 'Pick disease' OR 'pick syndrome' OR 'prion disease' OR 'bovine spongiform encephalopathy' OR 'chronic wasting disease' OR 'Creutzfeldt Jakob disease' OR 'fatal familial insomnia' OR 'Gerstmann Straussler Scheinker syndrome' OR 'kuru' OR 'scrapie' OR 'transmissible mink encephalopathy' OR 'transmissible neurodegenerative disease' OR 'subacute spongiform' OR 'transmissible spongiform encephalopathy' OR 'pseudodementia' OR 'Rett syndrome' OR 'rett disease' OR 'Retts syndrome' OR senility OR 'senile confusion' OR 'senile psychosis' OR tauopathy OR tauopathies OR 'Kohlschutter-Tonz Syndrome' OR 'depression'/exp OR depression* OR 'depressive disease' OR 'depressive disorder' OR 'depressive episode' OR 'depressive illness' OR 'depressive personality disorder' OR 'depressive state' OR 'depressive symptom' OR 'depressive symptoms' OR 'depressive syndrome' OR Melancholia OR Melancholias OR 'depressive Disorders' OR 'Depressive Neuroses' OR 'Depressive Neurosis' OR 'Depressive Syndrome' OR 'Depressive Syndromes' OR 'Involutional Psychoses' OR 'Involutional Psychosis' OR 'Involutional paraphrenia' OR 'Therapy Resistant Depressive' OR 'Therapy-Resistant Depressives' OR 'Treatment Resistant Depressive' OR 'treatment Resistant Depressives' OR 'Dysthymic Disorders' OR 'Dysthymic Disorder' OR 'Premenstrual Dysphoric Disorder' OR 'Premenstrual Dysphoric Syndrome' OR 'Seasonal Affective Disorder' OR 'Seasonal Mood Disorder' OR 'Seasonal Mood Disorders' OR 'Seasonal Affective Disorders' OR 'bipolar disorder' OR 'bipolar affective disorder' OR 'bipolar illness' OR 'bipolar psychosis' OR 'manic depressive' OR 'maniodepressive psychosis' OR 'mano depressive syndrome' OR 'bipolar mania' OR cyclothymia OR cyclophrenia OR 'cyclothymic depressive' OR 'cyclothymic disorder' OR 'cyclothymic personality' OR 'rapid cycling mood disorder' OR 'depressive psychosis' OR dysphoria OR dysforia OR dysthymia OR 'depressive reaction' OR 'dysthymic disorder' OR 'mental anorexia' OR 'mental fatigue' OR melancholy OR 'unipolar disorder' OR 'mourning syndrome' OR 'Perry syndrome' OR 'Perrys syndrome' OR 'diabetes mellitus'/exp OR 'insulin dependent diabetes mellitus'/exp OR 'non insulin dependent diabetes mellitus'/exp OR 'lipoatrophic diabetes mellitus'/exp OR 'insulin-Dependent Diabetes Mellitus' OR 'Juvenile Onset Diabetes' OR 'Type 1 Diabetes' OR 'Sudden-Onset Diabetes Mellitus' OR 'Diabetes Mellitus Type I' OR 'IDDM' OR 'Insulin Dependent Diabetes' OR 'Brittle Diabetes' OR 'Ketosis-Prone Diabetes Mellitus' OR 'Autoimmune Diabetes' OR 'DIDMOAD' OR 'DIDMOADUD' OR 'Wolfram Syndrome' OR 'NIDDM' OR 'Maturity Onset Diabetes' OR 'Adult Onset Diabetes' OR 'Ketosis Resistant Diabetes Mellitus' OR 'Non Insulin Dependent Diabetes Mellitus' OR 'Slow Onset Diabetes Mellitus' OR 'Stable Diabetes Mellitus' OR 'MODY' OR 'Type 2 Diabetes' OR 'Noninsulin Dependent Diabetes' OR 'Lipoatrophic Diabetes' OR 'Lipoatrophic Diabete' OR diabetic* OR 'diabetes mellitus type I' OR 'early onset diabetes' OR 'iddm' OR 'juvenile diabetes' OR 'ketoacidotic diabetes' OR 'labile diabetes mellitus' OR 'mckusick 22210' OR 'type I diabetes' OR 'diabetes mellitus type 2' OR 'diabetes mellitus type ii' OR 'diabetes type 2' OR 'diabetes type II' OR 'insulin independent diabetes' OR 'ketosis resistant diabetes' OR 'type II diabetes' OR 'diabetes lipoatrophic' OR 'chronic hepatitis'/exp OR 'Chronic Hepatitis' OR 'Chronic Active Hepatitis' OR 'Chronic Persistent Hepatitides' OR 'Chronic Persistent Hepatitis' OR 'Chronic Delta Hepatitis' OR 'Chronic Delta Hepatitides' OR 'Autoimmune Hepatitides' OR 'Chronic Hepatitides' OR 'Autoimmune Hepatitis' OR 'chronic hepatopathy' OR 'Human immunodeficiency virus'/exp OR 'HIV' OR 'AIDS Virus' OR 'AIDS Viruses' OR HTLV-III OR 'Human Immunodeficiency Virus' OR 'Human Immunodeficiency Viruses' OR 'Human T Cell Lymphotropic Virus Type III' OR 'Human T Lymphotropic

Virus Type III' OR 'Human T-Cell Leukemia Virus Type III' OR 'Human T Cell Leukemia Virus Type III' OR 'Human T-Cell Lymphotropic Virus Type III' OR 'Human T-Lymphotropic Virus Type III' OR 'LAV-HTLV-III' OR 'Lymphadenopathy-Associated Virus' OR 'Lymphadenopathy Associated Virus' OR 'Lymphadenopathy-Associated Viruses' OR 'Acquired Immune Deficiency Syndrome Virus' OR 'Acquired Immunodeficiency Syndrome Virus' OR 'HIV-1' OR 'HIV-2' OR 'aids associated lentivirus' OR 'aids associated retrovirus' OR 'aids associated virus' OR 'aids related virus' OR 'immunodeficiency associated virus' OR 'immunodeficiency viruses' OR 'lymphadenopathy associated retrovirus' OR 'hyperlipidemia'/exp OR Hyperlipemia OR Hyperlipemias OR Hyperlipidemia OR Lipidemia OR Lipidemias OR Lipemia OR Lipemias OR Hypercholesterolemia OR Hypercholesterolemias OR 'Elevated Cholesterol' OR 'Hypercholesteremia' OR Hypercholesteremias OR hyperlipaemia OR hyperlipidaemia OR hyperlipidemias OR hyperlipidemic OR lipaemia OR lipidaemia OR cholesteremia OR cholesterinemia OR cholesterolemia OR hypercholesterinaemia OR hypercholesterinemia OR hypercholesterolaemia OR 'Buerger Gruetz syndrome' OR 'Burger Grutz syndrome' OR hyperbetalipoproteinaemia OR hyperbetalipoproteinemia OR hypercholesterolemic OR 'familial hyperlipoproteinaemia type ii' OR 'familial hyperlipoproteinemia type ii' OR 'harbitz mueller syndrome' OR 'hyper low density lipoproteinaemia' OR 'hyper low density lipoproteinemia' OR 'hypercholesterolaemic xanthomatosis' OR 'hyperlipoproteinaemia type 2' OR 'hyperlipoproteinaemia type ii' OR 'hyperlipoproteinemia type 2' OR 'hyperlipoproteinemia type ii' OR 'ldl receptor disorder' OR 'tendinous xanthogranulomatosis' OR 'tendinous xanthomatosis' OR 'tendon xanthogranulomatosis' OR 'xanthogranulomatosis tendinosum' OR 'xanthogranulomatosis tendinous' OR 'xanthoma tendinosum' OR 'xanthoma tuberosum' OR hypertriglyceridemia OR hypertriglyceridaemia OR 'triglyceride storage disease' OR triglyceridemia OR 'hypertriglyceridemic waist' OR Hyperlipoproteinemias OR 'hypertension'/exp OR Hypertension* OR Hypertensive OR 'High Blood Pressure' OR 'High Blood Pressures' OR 'Goldblatt Syndrome' OR 'apparent mineralocorticoid excess syndrome' OR 'Gordon syndrome' OR 'Gordons syndrome' OR 'Liddle syndrome' OR 'Liddles syndrome' OR 'metabolic syndrome' OR 'insulin resistance syndrome' OR 'ocular ischaemic syndrome' OR 'ocular ischemic syndrome' OR 'orthostatic hypertension' OR 'posterior encephalopathy' OR 'posterior leucoencephalopathy' OR 'posterior leucoencephalopathy' OR 'posterior leukoencephalopathy' OR 'posterior reversible encephalopathy' OR 'posterior reversible leucoencephalopathy' OR 'posterior reversible leukoencephalopathy' OR 'PRES' OR 'RPLS' OR prehypertension OR 'pre-hypertension' OR 'goldblatt kidney' OR nephrosclerosis OR 'renal arteriosclerosis' OR 'renal atherosclerosis' OR renosclerosis OR 'osteoporosis'/exp OR Osteoporosis OR Osteoporoses OR 'Age-Related Bone Loss' OR 'Age-Related Bone Losses' OR 'pathological decalcification' OR 'osteoporotic decalcification' OR 'female athlete triad' OR 'Perimenopausal Bone Loss' OR 'Postmenopausal Bone Loss' OR 'Perimenopausal Bone Losses' OR 'posttraumatic osteopenia' OR 'Sudeck atrophy' OR 'Sudeck disease' OR 'Sudeck dystrophy' OR 'Sudeck Leriche syndrome' OR 'Sudeck syndrome' OR 'Sudecks atrophy' OR 'Suedeck dystrophy' OR 'Suedeck reflex dystrophy' OR 'schizophrenia'/exp OR Schizophrenia* OR Schizophrenic* OR 'Dementia Praecox' OR hebephrenia OR paraphrenia OR 'Delusional Disorder' OR 'Delusional Disorders' OR 'schizoaffective psychosis' OR 'schizo affective disorder' OR 'schizo affective psychosis' OR 'schizoaffective disorder' OR 'schizophreniform disorder' OR 'schizophreniform psychosis' OR 'Shared Paranoid Disorder' OR 'Shared Psychotic Disorder' OR 'Shared Psychotic Disorders' OR 'Shared Paranoid Disorders' OR 'Folie a Deux' OR 'Folie a Trois' OR 'brain ischemia'/exp OR 'Chronic stroke' OR 'brain ischemia' OR 'brain arterial insufficiency' OR 'brain circulation disorder' OR 'brain ischaemia' OR 'cerebral blood circulation disorder' OR 'cerebral blood flow disorder' OR 'cerebral circulation disorder' OR 'cerebral circulatory disorder' OR 'cerebral ischaemia' OR 'cerebral ischemia' OR 'cerebrovascular circulation disorder' OR 'cerebrovascular ischaemia' OR 'cerebrovascular ischemia' OR 'ischaemia cerebri' OR 'ischaemic brain disease' OR 'ischaemic encephalopathy' OR 'ischaemic stroke' OR 'ischemia cerebri'

OR ‘ischemic brain disease’ OR ‘ischemic encephalopathy’ OR ‘ischemic stroke’ OR ‘neural ischaemia’ OR ‘neural ischemia’ OR ‘brain vasospasm’ OR ‘cerebral vasospasm’ OR ‘intracranial vasospasm’ OR ‘Call-Fleming syndrome’ OR ‘brain hypoxia ischaemia’ OR ‘brain hypoxia ischemia’ OR ‘brain hypoxic ischaemic injuries’ OR ‘brain hypoxic ischaemic injury’ OR ‘brain hypoxic ischemic damage’ OR ‘brain hypoxic ischemic injuries’ OR ‘brain hypoxic ischemic injury’ OR ‘cerebral hypoxia ischaemia’ OR ‘cerebral hypoxia ischemia’ OR ‘cerebral hypoxic ischaemic damage’ OR ‘cerebral hypoxic ischaemic injuries’ OR ‘cerebral hypoxic ischaemic injury’ OR ‘cerebral hypoxic ischemic damage’ OR ‘cerebral hypoxic ischemic injuries’ OR ‘cerebral hypoxic ischemic injury’ OR ‘cerebral ischaemia hypoxia’ OR ‘cerebral ischemia hypoxia’ OR ‘hypoxic ischaemic brain damage’ OR ‘hypoxic ischaemic brain injuries’ OR ‘hypoxic ischaemic brain injury’ OR ‘hypoxic ischaemic cerebral damage’ OR ‘hypoxic ischaemic cerebral injuries’ OR ‘hypoxic ischaemic cerebral injury’ OR ‘hypoxic ischemic brain damage’ OR ‘hypoxic ischemic brain injuries’ OR ‘hypoxic ischemic brain injury’ OR ‘hypoxic ischemic cerebral damage’ OR ‘hypoxic ischemic cerebral injuries’ OR ‘hypoxic ischemic cerebral injury’ OR ‘circulatory epilepsy’ OR ‘epilepsy circulatory’ OR ‘ischaemic attack’ OR ‘ischemic attack’ OR ‘ischaemic seizure’ OR ‘ischemic seizure’ OR ‘Brain Infarction’ OR ‘Brain Stem Infarctions’ OR ‘Brain Stem Infarction’ OR ‘Brainstem Infarctions’ OR ‘Brainstem Infarction’ OR ‘Brainstem Stroke’ OR ‘Claude Syndrome’ OR ‘Weber Syndrome’ OR ‘Millard Gublar Syndrome’ OR ‘Top of the Basilar Syndrome’ OR ‘Benedict Syndrome’ OR ‘Foville Syndrome’ OR ‘Lateral Medullary Syndrome’ OR ‘Lateral Medullary Syndromes’ OR ‘Posterior Inferior Cerebellar Artery Syndrome’ OR ‘Wallenbergs Syndrome’ OR ‘Wallenbergs Syndrome’ OR ‘Wallenberg Syndrome’ OR ‘Dorsolateral Medullary Syndrome’ OR ‘Lateral Bulbar Syndrome’ OR ‘Cerebral Infarction’ OR ‘Cerebral Infarctions’ OR ‘Subcortical Infarction’ OR ‘Subcortical Infarctions’ OR ‘Choroidal Artery Infarction’ OR ‘Cerebral Artery Infarction’ OR ‘Cerebral Artery Infarctions’ OR ‘ACA Infarction’ OR ‘ACA Infarctions’ OR ‘Cerebral Artery Stroke’ OR ‘Heubner Artery Infarction’ OR ‘Heubners Artery Infarction’ OR ‘Heubners Artery Infarction’ OR ‘Cerebral Artery Syndrome’ OR ‘MCA Infarction’ OR ‘Cerebral Artery Thrombosis’ OR ‘Cerebral Artery Thrombotic Infarction’ OR ‘PCA Infarction’ OR ‘Cerebral Artery Embolic Infarction’ OR 'substance abuse'/exp OR 'alcoholism'/exp 'drug abuse'/exp OR 'drug dependence'/exp OR alcoholism OR ‘drug dependence’ OR ‘drug addiction’ OR ‘Drug Habituation’ OR ‘Drug Abuse’ OR ‘Substance Abuse’ OR ‘Substance Abuses’ OR ‘Substance Dependence’ OR ‘Substance Addiction’ OR ‘Substance Use Disorders’ OR ‘Substance Use Disorder’ OR ‘Drug Dependence’ OR ‘Drug Addiction’ OR ‘substance abuser’ OR ‘substance dependence’ OR ‘amphetamine-related disorders’ OR ‘chronic drug overuser’ OR ‘drug abuser’ OR ‘drug problem’ OR ‘needle sharing’ OR ‘phencyclidine abuse’ OR ‘alcohol addiction’ OR ‘alcohol dependence’ OR ‘alcohol dependents’ OR ‘alcohol polyneuropathy’ OR ‘alcohol dependent individual’ OR ‘alcohol induced disorders’ OR ‘alcohol related disorders’ OR dipsomania* OR ‘ethanol dependence’ OR ‘problem drinker’ OR ‘problematic drinker’ OR ‘analgesic agent abuse’ OR ‘analgesic abuse’ OR doping OR ‘drug misuse’ OR ‘inhalant abuse’ OR ‘intravenous drug abuse’ OR ‘intravenous drug user’ OR ‘prescription drug diversion’ OR ‘drug use disorder’ OR ‘drug use disorders’ OR ‘Alcohol Related Disorders’ OR ‘Alcohol Related Disorder’ OR ‘Alcohol Induced Disorders’ OR ‘Alcohol Induced Disorder’ OR ‘Ethanol Induced Nervous System Disorders’ OR ‘Alcohol Amnestic Disorders’ OR ‘Alcohol Amnestic Syndrome’ OR ‘Alcohol Amnestic Syndromes’ OR ‘Alcohol Induced Amnestic Psychosis’ OR ‘Alcohol Induced Amnestic Syndrome’ OR ‘Alcohol Induced Dysmnesic Syndrome’ OR ‘Alcohol Induced Dysmnesic Syndromes’ OR ‘Alcohol Induced Korsakoff Syndrome’ OR ‘Alcohol Induced Korsakoff Syndromes’ OR ‘Alcohol Induced Persisting Amnestic Disorder’ OR ‘Alcoholic Korsakoff Syndrome’ OR ‘Alcoholic Korsakoff Syndromes’ OR ‘Alcohol Induced Amnestic Psychoses’ OR ‘Alcohol Induced Dysmnesic Psychosis’ OR ‘Alcohol Induced Dysmnesic Psychoses’ OR ‘Korsakoff Syndrome’ OR ‘Korsakoff Psychosis’ OR ‘Korsakoff Psychoses’ OR ‘Alcoholic Neuropathy’ OR ‘Alcoholic Neuropathies’ OR ‘Alcohol Induced Peripheral Neuropathies’ OR

'Alcoholic Polyneuropathies' OR 'Alcoholic Polyneuropathy' OR 'Alcoholic Polyneuritides' OR 'Alcoholic Polyneuritis' OR 'Alcohol Induced Polyneuropathy' OR 'Alcohol Induced Polyneuropathies' OR 'Alcohol Related Autonomic Polyneuropathy' OR 'Alcohol Related Autonomic Polyneuropathies' OR 'Alcohol Related Polyneuropathy' OR 'Alcohol-Related Polyneuropathies' OR 'Alcohol Induced Peripheral Neuropathy' OR 'Alcoholic Axonal Neuropathy' OR 'Alcoholic Axonal Neuropathies' OR 'Alcoholic Cardiomyopathy' OR 'Fetal Alcohol Spectrum Disorders' OR 'FASD' OR 'FASDs' OR 'Alcohol Related Birth Defects' OR 'Alcohol Related Neurodevelopmental Disorder' OR 'Fetal Alcohol Effects' OR 'Fetal Alcohol Syndrome' OR 'Alcoholic Liver Diseases' OR 'Alcoholic Liver Disease' OR 'Alcoholic Fatty Liver' OR 'Alcoholic Steatohepatitis' OR 'Chronic Alcoholic Hepatitis' OR 'Chronic Alcoholic Hepatitides' OR 'Alcoholic Liver Cirrhosis' OR 'Alcoholic Cirrhosis' OR 'Alcoholic Hepatic Cirrhosis' OR 'Alcoholic Pancreatitis' OR 'Alcoholic Psychoses' OR 'Chronic Alcoholic Intoxication' OR 'Alcohol Abuse' OR 'Amphetamine Related Disorders' OR 'Amphetamine Abuse' OR 'Amphetamine Addiction' OR 'Amphetamine Dependence' OR 'Cocaine Related Disorders' OR 'Cocaine Related Disorder' OR 'Cocaine Abuse' OR 'Cocaine Dependence' OR 'Cocaine Addiction' OR 'Inhalant Abuses' OR 'Glue Sniffing' OR 'Glue Sniffings' OR 'Glue Abuse' OR 'Glue Abuses' OR 'Marijuana Abuse' OR 'Marihuana Abuse' OR 'Hashish Abuse' OR 'Cannabis Related Disorder' OR 'Cannabis Abuse' OR 'Cannabis Dependence' OR 'Marijuana Dependence' OR 'Opioid Related Disorders' OR 'Opiate Dependence' OR 'Opiate Addiction' OR 'Narcotic Abuse' OR 'Narcotic Abuses' OR 'Narcotic Dependence' OR 'Narcotic Addiction' OR 'Heroin Dependence' OR 'Heroin Addiction' OR 'Heroin Abuse' OR 'Morphine Dependence' OR 'Morphine Addiction' OR 'Morphine Abuse' OR 'Phencyclidine Abuses' OR 'PCP Abuse' OR 'Angel Dust Abuse' OR 'Phencyclidine Related Disorders' OR 'Phencyclidine Related Disorder' OR 'Substance Induced Psychoses' OR 'Toxic Psychoses' OR 'Drug Psychoses' OR 'Intravenous Substance Abuse' OR 'Parenteral Drug Abuse' OR 'Tobacco Use Disorder' OR 'Tobacco Use Disorders' OR 'Nicotine Use Disorder' OR 'Nicotine Use Disorders' OR 'Tobacco Dependence' OR 'Tobacco Dependences' OR 'Nicotine Dependence' OR 'alcoholic individual' OR 'alcoholics' OR 'alcoholic polyneuropathy' OR 'ethanol dependence' OR 'narcotic depression' OR 'narcotism' OR 'heroin addict' OR heroinism OR 'morphine addict' OR 'opiate addict' OR 'opioid dependence' OR 'opium addict' OR 'opium addiction' OR 'opium alkaloid addiction' OR 'opium addiction' OR 'benzodiazepine dependence' OR 'benzodiazepine addiction' OR 'cannabis addiction' OR 'drug abuse pattern' OR 'methamphetamine dependence' OR toxicomania OR 'drug addict' OR 'drug dependence' OR 'drug dependency')

4. Reader training materials

Along with a comprehensive review of the extraction process, the extraction form and items, and a thorough extraction testing process with sample articles, all readers carefully reviewed the following resources to gain an understanding of background material and relevant concepts.

I. Systematic Review and Meta-Analysis

a. Egger M, Smith GD, Altman D. "Chapter 1: Rationale, potentials & promise of systematic reviews." Systematic reviews in health care: meta-analysis in context. John Wiley & Sons; 2008.

II. Relevant published reviews

a. Jadad AR, To MJ, Emara M, Jones J. Consideration of multiple chronic diseases in randomized controlled trials. JAMA: the journal of the American Medical Association. 2011;306(24):2670-2672.
b. Boyd CM, Vollenweider D, Puhan MA. Informing evidence-based decision-making for patients with comorbidity: availability of necessary information in clinical trials for chronic diseases. PLoS One. 2012;7(8):e41601.
c. Van Spall HG, Toren A, Kiss A, Fowler RA. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. JAMA : the journal of the American Medical Association. Mar 21 2007;297(11):1233-1240.
d. Kenning C, Coventry PA, Bower P. Self-management interventions in patients with long-term conditions: a structured review of approaches to reporting inclusion, assessment, and outcomes in multimorbidity. 2014. 2014-08-28 2014;4(1):9.

III. Randomized Controlled Trials (RCT)

a. Overview
    i. Stolberg HO, Norman G, Trop I. Randomized controlled trials. American Journal of Roentgenology. 2004;183(6):1539-1544.
    ii. Stanley K. Design of randomized controlled trials. Circulation. 2007;115(9):1164-1169.
b. Reporting in RCT
    i. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMC medicine. 2010;8(1):18.
    ii. Sample Study
        1. http://www.consort-statement.org/examples/sample
    iii. Jun M, Zoungas S, Perkovic V, Webster AC. How to read a report of a randomized controlled trial. Nephrology. 2010;15(2):153-157.
c. Quality of RCTs and risk of bias
    i. Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. 2008. Chapter 5- Assessing the quality of randomized controlled trials

ii. Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. 2008. Chapter 8- Assessing risk of bias in included studies

5. Extraction codebook

Data Dictionary Codebook

#	Variable / Field Name	Field Label *Field Note*	Field Attributes (Field Type, Validation, Choices, Calculations, etc.)
Instrument: **Basic**			
1	record_id	Record Number	text
2	journal_type	Journal Type	dropdown 0, General Medical 1, Specialty
3	pub_year_category	Publication Year Category	dropdown 0, 2000-2004 1, 2005-2009 2, 2010-2014
4	fund_source	Funding Source	checkbox 0, fund_source___0, Industry 1, fund_source___1, Non-Industry 2, fund_source___2, Not Reported
5	region	Region	dropdown 0, North America 1, Europe 2, Middle East 3, Asia/Pacific 4, Latin America 5, Africa
6	registered	Is this study reported to be a registered clinical trial?	checkbox 0, registered___0, No 1, registered___1, Yes- clinicaltrials.gov 2, registered___2, Yes- other registry
7	basic_complete	Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete
Instrument: **Intervention**			

<table>
<tr><td>8</td><td>sample_cc_targeted</td><td>Is the trial selection targeting individuals with multiple chronic conditions?</td><td>dropdown<table><tr><td>0</td><td>No</td></tr><tr><td>1</td><td>Yes, individuals with a specific set of chronic conditions</td></tr><tr><td>2</td><td>Yes, individuals with multiple chronic conditions, regardless of conditions</td></tr><tr><td>3</td><td>Yes, individuals with any combination of chronic conditions within a specific set of conditions</td></tr></table></td></tr>
<tr><td>9</td><td>cc_list
Show the field ONLY if:
[sample_cc_targeted]="0"</td><td>Is the trial selection targeting individuals with one condition from a specific set of chronic conditions?</td><td>dropdown<table><tr><td>0</td><td>No</td></tr><tr><td>1</td><td>Yes</td></tr></table></td></tr>
<tr><td>10</td><td>sample_cc
Show the field ONLY if:
[sample_cc_targeted]="0" or [sample_cc_targeted]="1" or [sample_cc_targeted]="3"</td><td>The study sample consists of individuals with which chronic condition(s)?</td><td>checkbox<table><tr><td>1</td><td>sample_cc___1</td><td>Arthritis</td></tr><tr><td>2</td><td>sample_cc___2</td><td>Asthma</td></tr><tr><td>3</td><td>sample_cc___3</td><td>Autism spectrum disorder</td></tr><tr><td>4</td><td>sample_cc___4</td><td>Cancer</td></tr><tr><td>5</td><td>sample_cc___5</td><td>Cardiac arrhythmias</td></tr><tr><td>6</td><td>sample_cc___6</td><td>Chronic kidney disease</td></tr><tr><td>7</td><td>sample_cc___7</td><td>Chronic obstructive pulmonary disease</td></tr><tr><td>8</td><td>sample_cc___8</td><td>Congestive heart failure</td></tr><tr><td>9</td><td>sample_cc___9</td><td>Coronary artery disease</td></tr><tr><td>10</td><td>sample_cc___10</td><td>Dementia</td></tr><tr><td>11</td><td>sample_cc___11</td><td>Depression</td></tr><tr><td>12</td><td>sample_cc___12</td><td>Diabetes</td></tr><tr><td>13</td><td>sample_cc___13</td><td>Hepatitis</td></tr><tr><td>14</td><td>sample_cc___14</td><td>Human immunodeficiency virus (HIV)</td></tr><tr><td>15</td><td>sample_cc___15</td><td>Hyperlipidemia</td></tr><tr><td>16</td><td>sample_cc___16</td><td>Hypertension</td></tr><tr><td>17</td><td>sample_cc___17</td><td>Osteoporosis</td></tr><tr><td>18</td><td>sample_cc___18</td><td>Schizophrenia</td></tr><tr><td>19</td><td>sample_cc___19</td><td>Stroke</td></tr><tr><td>20</td><td>sample_cc___20</td><td>Substance abuse disorders</td></tr><tr><td>21</td><td>sample_cc___21</td><td>Chronic condition (General)</td></tr></table></td></tr>
</table>

11	number_arms	Number of experimental study arms	text (integer, Min: 1, Max: 4)
12	randomized_1	Is the number of participants randomized to this group reported?	dropdown 0 No 1 Yes
13	sample_size_1 Show the field ONLY if: [randomized_1]= "1"	Sample Size	text (integer)
14	randomized_2	Is the number of participants randomized to this group reported?	dropdown 0 No 1 Yes
15	sample_size_2 Show the field ONLY if: [randomized_2]= "1"	Sample Size	text (integer)
16	randomized_3 Show the field ONLY if: [number_arms]>1	Is the number of participants randomized to this group reported?	dropdown 0 No 1 Yes
17	sample_size_3 Show the field ONLY if: [number_arms]>1 and [randomized_3] = "1"	Sample Size	text (integer)
18	randomized_4 Show the field ONLY if: [number_arms]>2	Is the number of participants randomized to this group reported?	dropdown 0 No 1 Yes
19	sample_size_4 Show the field ONLY if:	Sample Size	text (integer)

	[number_arms]>2 and [randomized_4] = "1"		
20	randomized_5 Show the field ONLY if: [number_arms]>3	Is the number of participants randomized to this group reported?	dropdown 0, No 1, Yes
21	sample_size_5 Show the field ONLY if: [number_arms]>3 and [randomized_5] = "1"	Sample Size	text (integer)
22	randomized_total	Is the total number of participants randomized reported?	dropdown 0, No 1, Yes
23	sample_size_total Show the field ONLY if: [randomized_total] ="1"	Studywide Sample Size	text (integer)
24	sample_size_total_calc	Calculated Studywide Sample Size	calc Calculation: sum([sample_size_1],[sample_size_2],[sample_size_3],[sample_size_4],[sample_size_5])
25	intervention_behav	What is the behavioral component of the intervention?	checkbox 0, intervention_behav___0, Weight management/diet/physical activity 1, intervention_behav___1, Tobacco habits 2, intervention_behav___2, Adherence to disease management 3, intervention_behav___3, Psychological well-being 4, intervention_behav___4, Other
26	intervention_complete	Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete
Instrument: **Eligibility**			
27	elig_reported	Is eligibility criteria reported?	dropdown 0, No

			1 Yes
28	elig_criteria_behav	Were any behavioral factors/conditions are used as inclusion or exclusion criteria?	dropdown 0 No 1 Yes
29	elig_behav Show the field ONLY if: [elig_criteria_behav]="1"	Which of the following behavioral factors/conditions were reported as eligibility criteria?	checkbox 0 elig_behav___0 Alcohol use 1 elig_behav___1 Smoking or tobacco use 2 elig_behav___2 Other substance use 3 elig_behav___3 Physical activity 4 elig_behav___4 Diet 5 elig_behav___5 Weight
30	mcc_exclusion	Did trial explicitly exclude individuals with multiple chronic conditions, regardless of conditions?	dropdown 0 No 1 Yes
31	mcc_exclusion_report Show the field ONLY if: [mcc_exclusion]="1"	Is the number of individuals excluded for having comorbid chronic conditions reported?	dropdown 0 No 1 Yes
32	mcc_exclusion_just Show the field ONLY if: [mcc_exclusion]="1"	Is a justification for MCC exclusion provided?	dropdown 0 No 1 Yes
33	mcc_ability Show the field ONLY if:	Is this justification based on ability to	dropdown 0 No 1 Yes

	[mcc_exclusion_just]="1"	participate in the study?	
34	elig_charlson	Was the Charlson comorbidity index used in eligibility criteria?	dropdown 0 No 1 Yes
35	elig_vague	Are there any vague exclusions for medical or psychological conditions (not reported above)?	dropdown 0 No 1 Yes
36	vague_ability Show the field ONLY if: [elig_vague]="1"	Is this exclusion based on ability to participate in the study?	dropdown 0 No 1 Yes
37	condition_exclusion	Did trial exclude individuals with specific chronic conditions?	dropdown 0 No 1 Yes
38	condition_ability Show the field ONLY if: [condition_exclusion]="1"	Is this exclusion based on ability to participate in the study?	dropdown 0 No 1 Yes
39	conditions_excluded Show the field ONLY if: [condition_exclusion]="1"	Which chronic conditions were subject to exclusions? *Check all that apply*	checkbox 1 conditions_excluded___1 Arthritis 2 conditions_excluded___2 Asthma 3 conditions_excluded___3 Autism Spectrum Disorder 4 conditions_excluded___4 Cancer 5 conditions_excluded___5 Cardiac Arrhythmias 6 conditions_excluded___6 Chronic Kidney Disease 7 conditions_excluded___7 Chronic Obstructive Pulmonary Disease

<table>
<tr><td></td><td></td><td></td><td>
<table>
<tr><td>8</td><td>conditions_excluded___8</td><td>Congestive Heart Failure</td></tr>
<tr><td>9</td><td>conditions_excluded___9</td><td>Coronary Artery Disease</td></tr>
<tr><td>10</td><td>conditions_excluded___10</td><td>Dementia</td></tr>
<tr><td>11</td><td>conditions_excluded___11</td><td>Depression</td></tr>
<tr><td>12</td><td>conditions_excluded___12</td><td>Diabetes</td></tr>
<tr><td>13</td><td>conditions_excluded___13</td><td>Hepatitis</td></tr>
<tr><td>14</td><td>conditions_excluded___14</td><td>Human Immunodeficiency Virus (HIV)</td></tr>
<tr><td>15</td><td>conditions_excluded___15</td><td>Hyperlipidemia</td></tr>
<tr><td>16</td><td>conditions_excluded___16</td><td>Hypertension</td></tr>
<tr><td>17</td><td>conditions_excluded___17</td><td>Osteoporosis</td></tr>
<tr><td>18</td><td>conditions_excluded___18</td><td>Schizophrenia</td></tr>
<tr><td>19</td><td>conditions_excluded___19</td><td>Stroke</td></tr>
<tr><td>20</td><td>conditions_excluded___20</td><td>Substance Abuse Disorders</td></tr>
</table>
</td></tr>
<tr><td>40</td><td>exclusion_n_report_1
Show the field ONLY if:
[conditions_excluded(1)]="1"</td><td>Is the number of individuals excluded for having Arthritis reported?</td><td>dropdown
<table>
<tr><td>0</td><td>No</td></tr>
<tr><td>1</td><td>Yes</td></tr>
</table>
</td></tr>
<tr><td>41</td><td>exclusion_1
Show the field ONLY if:
[conditions_excluded(1)]="1"</td><td>Is exclusion of individuals with Arthritis narrowed?</td><td>checkbox
<table>
<tr><td>0</td><td>exclusion_1___0</td><td>No</td></tr>
<tr><td>1</td><td>exclusion_1___1</td><td>Yes- narrowed by type</td></tr>
<tr><td>2</td><td>exclusion_1___2</td><td>Yes- narrowed by severity</td></tr>
<tr><td>3</td><td>exclusion_1___3</td><td>Yes- narrowed by onset</td></tr>
<tr><td>4</td><td>exclusion_1___4</td><td>Yes- narrowed by other specification</td></tr>
</table>
</td></tr>
<tr><td>42</td><td>exclusion_n_report_2
Show the field ONLY if:
[conditions_excluded(2)]="1"</td><td>Is the number of individuals excluded for having Asthma reported?</td><td>dropdown
<table>
<tr><td>0</td><td>No</td></tr>
<tr><td>1</td><td>Yes</td></tr>
</table>
</td></tr>
<tr><td>43</td><td>exclusion_2
Show the field ONLY if:
[conditions_excluded(2)]="1"</td><td>Is exclusion of individuals with Asthma narrowed?</td><td>checkbox
<table>
<tr><td>0</td><td>exclusion_2___0</td><td>No</td></tr>
<tr><td>1</td><td>exclusion_2___1</td><td>Yes- narrowed by type</td></tr>
<tr><td>2</td><td>exclusion_2___2</td><td>Yes- narrowed by severity</td></tr>
<tr><td>3</td><td>exclusion_2___3</td><td>Yes- narrowed by onset</td></tr>
</table>
</td></tr>
</table>

			4 | exclusion_2___4 | Yes- narrowed by other specification
44	exclusion_n_report_3 Show the field ONLY if: [conditions_excluded(3)]="1"	Is the number of individuals excluded for having Autism Spectrum Disorder reported?	dropdown 0 | No 1 | Yes
45	exclusion_3 Show the field ONLY if: [conditions_excluded(3)]="1"	Is exclusion of individuals with Autism Spectrum Disorder narrowed?	checkbox 0 | exclusion_3___0 | No 1 | exclusion_3___1 | Yes- narrowed by type 2 | exclusion_3___2 | Yes- narrowed by severity 3 | exclusion_3___3 | Yes- narrowed by onset 4 | exclusion_3___4 | Yes- narrowed by other specification
46	exclusion_n_report_4 Show the field ONLY if: [conditions_excluded(4)]="1"	Is the number of individuals excluded for having Cancer reported?	dropdown 0 | No 1 | Yes
47	exclusion_4 Show the field ONLY if: [conditions_excluded(4)]="1"	Is exclusion of individuals with Cancer narrowed?	checkbox 0 | exclusion_4___0 | No 1 | exclusion_4___1 | Yes- narrowed by type 2 | exclusion_4___2 | Yes- narrowed by severity 3 | exclusion_4___3 | Yes- narrowed by onset 4 | exclusion_4___4 | Yes- narrowed by other specification
48	exclusion_n_report_5 Show the field ONLY if: [conditions_excluded(5)]="1"	Is the number of individuals excluded for having Cardiac Arrhythmias reported?	dropdown 0 | No 1 | Yes
49	exclusion_5 Show the field ONLY if: [conditions_excluded(5)]="1"	Is exclusion of individuals with Cardiac	checkbox 0 | exclusion_5___0 | No 1 | exclusion_5___1 | Yes- narrowed by type 2 | exclusion_5___2 | Yes- narrowed by severity

		Arrhythmias narrowed?	3 exclusion_5___3 Yes- narrowed by onset 4 exclusion_5___4 Yes- narrowed by other specification
50	exclusion_n_report_6 Show the field ONLY if: [conditions_excluded(6)]="1"	Is the number of individuals excluded for having Chronic Kidney Disease reported?	dropdown 0 No 1 Yes
51	exclusion_6 Show the field ONLY if: [conditions_excluded(6)]="1"	Is exclusion of individuals with Chronic Kidney Disease narrowed?	checkbox 0 exclusion_6___0 No 1 exclusion_6___1 Yes- narrowed by type 2 exclusion_6___2 Yes- narrowed by severity 3 exclusion_6___3 Yes- narrowed by onset 4 exclusion_6___4 Yes- narrowed by other specification
52	exclusion_n_report_7 Show the field ONLY if: [conditions_excluded(7)]="1"	Is the number of individuals excluded for having Chronic Obstructive Pulmonary Disease reported?	dropdown 0 No 1 Yes
53	exclusion_7 Show the field ONLY if: [conditions_excluded(7)]="1"	Is exclusion of individuals with Chronic Obstructive Pulmonary Disease narrowed?	checkbox 0 exclusion_7___0 No 1 exclusion_7___1 Yes- narrowed by type 2 exclusion_7___2 Yes- narrowed by severity 3 exclusion_7___3 Yes- narrowed by onset 4 exclusion_7___4 Yes- narrowed by other specification
54	exclusion_n_report_8 Show the field ONLY if: [conditions_excluded(8)]="1"	Is the number of individuals excluded for having Congestive Heart Failure reported?	dropdown 0 No 1 Yes

<table>
<tr><td>55</td><td>exclusion_8
Show the field ONLY if:
[conditions_excluded(8)]="1"</td><td>Is exclusion of individuals with Congestive Heart Failure narrowed?</td><td>checkbox<table><tr><td>0</td><td>exclusion_8___0</td><td>No</td></tr><tr><td>1</td><td>exclusion_8___1</td><td>Yes- narrowed by type</td></tr><tr><td>2</td><td>exclusion_8___2</td><td>Yes- narrowed by severity</td></tr><tr><td>3</td><td>exclusion_8___3</td><td>Yes- narrowed by onset</td></tr><tr><td>4</td><td>exclusion_8___4</td><td>Yes- narrowed by other specification</td></tr></table></td></tr>
<tr><td>56</td><td>exclusion_n_report_9
Show the field ONLY if:
[conditions_excluded(9)]="1"</td><td>Is the number of individuals excluded for having Coronary Artery Disease reported?</td><td>dropdown<table><tr><td>0</td><td>No</td></tr><tr><td>1</td><td>Yes</td></tr></table></td></tr>
<tr><td>57</td><td>exclusion_9
Show the field ONLY if:
[conditions_excluded(9)]="1"</td><td>Is exclusion of individuals with Coronary Artery Disease narrowed?</td><td>checkbox<table><tr><td>0</td><td>exclusion_9___0</td><td>No</td></tr><tr><td>1</td><td>exclusion_9___1</td><td>Yes- narrowed by type</td></tr><tr><td>2</td><td>exclusion_9___2</td><td>Yes- narrowed by severity</td></tr><tr><td>3</td><td>exclusion_9___3</td><td>Yes- narrowed by onset</td></tr><tr><td>4</td><td>exclusion_9___4</td><td>Yes- narrowed by other specification</td></tr></table></td></tr>
<tr><td>58</td><td>exclusion_n_report_10
Show the field ONLY if:
[conditions_excluded(10)]="1"</td><td>Is the number of individuals excluded for having Dementia reported?</td><td>dropdown<table><tr><td>0</td><td>No</td></tr><tr><td>1</td><td>Yes</td></tr></table></td></tr>
<tr><td>59</td><td>exclusion_10
Show the field ONLY if:
[conditions_excluded(10)]="1"</td><td>Is exclusion of individuals with Dementia narrowed?</td><td>checkbox<table><tr><td>0</td><td>exclusion_10___0</td><td>No</td></tr><tr><td>1</td><td>exclusion_10___1</td><td>Yes- narrowed by type</td></tr><tr><td>2</td><td>exclusion_10___2</td><td>Yes- narrowed by severity</td></tr><tr><td>3</td><td>exclusion_10___3</td><td>Yes- narrowed by onset</td></tr><tr><td>4</td><td>exclusion_10___4</td><td>Yes- narrowed by other specification</td></tr></table></td></tr>
<tr><td>60</td><td>exclusion_n_report_11
Show the field ONLY if:
[conditions_excluded(11)]="1"</td><td>Is the number of individuals excluded for having Depression reported?</td><td>dropdown<table><tr><td>0</td><td>No</td></tr><tr><td>1</td><td>Yes</td></tr></table></td></tr>
</table>

61	exclusion_11 Show the field ONLY if: [conditions_excluded(11)]="1"	Is exclusion of individuals with Depression narrowed?	checkbox 0 exclusion_11___0 No 1 exclusion_11___1 Yes- narrowed by type 2 exclusion_11___2 Yes- narrowed by severity 3 exclusion_11___3 Yes- narrowed by onset 4 exclusion_11___4 Yes- narrowed by other specification
62	exclusion_justified_11 Show the field ONLY if: [conditions_excluded(11)]="1"	Is a justification for Depression exclusion provided?	dropdown 0 No 1 Yes
63	exclusion_n_report_12 Show the field ONLY if: [conditions_excluded(12)]="1"	Is the number of individuals excluded for having Diabetes reported?	dropdown 0 No 1 Yes
64	exclusion_12 Show the field ONLY if: [conditions_excluded(12)]="1"	Is exclusion of individuals with Diabetes narrowed?	checkbox 0 exclusion_12___0 No 1 exclusion_12___1 Yes- narrowed by type 2 exclusion_12___2 Yes- narrowed by severity 3 exclusion_12___3 Yes- narrowed by onset 4 exclusion_12___4 Yes- narrowed by other specification
65	exclusion_n_report_13 Show the field ONLY if: [conditions_excluded(13)]="1"	Is the number of individuals excluded for having Hepatitis reported?	dropdown 0 No 1 Yes
66	exclusion_13 Show the field ONLY if: [conditions_excluded(13)]="1"	Is exclusion of individuals with Hepatitis narrowed?	checkbox 0 exclusion_13___0 No 1 exclusion_13___1 Yes- narrowed by type 2 exclusion_13___2 Yes- narrowed by severity 3 exclusion_13___3 Yes- narrowed by onset 4 exclusion_13___4 Yes- narrowed by other specification
67	exclusion_n_report_14	Is the number of	dropdown 0 No

	Show the field ONLY if: [conditions_excluded(14)]="1"	individuals excluded for having HIV reported?	1 Yes
68	exclusion_14 Show the field ONLY if: [conditions_excluded(14)]="1"	Is exclusion of individuals with HIV narrowed?	checkbox 0 exclusion_14___0 No 1 exclusion_14___1 Yes- narrowed by type 2 exclusion_14___2 Yes- narrowed by severity 3 exclusion_14___3 Yes- narrowed by onset 4 exclusion_14___4 Yes- narrowed by other specification
69	exclusion_n_report_15 Show the field ONLY if: [conditions_excluded(15)]="1"	Is the number of individuals excluded for having Hyperlipidemia reported?	dropdown 0 No 1 Yes
70	exclusion_15 Show the field ONLY if: [conditions_excluded(15)]="1"	Is exclusion of individuals with Hyperlipidemia narrowed?	checkbox 0 exclusion_15___0 No 1 exclusion_15___1 Yes- narrowed by type 2 exclusion_15___2 Yes- narrowed by severity 3 exclusion_15___3 Yes- narrowed by onset 4 exclusion_15___4 Yes- narrowed by other specification
71	exclusion_n_report_16 Show the field ONLY if: [conditions_excluded(16)]="1"	Is the number of individuals excluded for having Hypertension reported?	dropdown 0 No 1 Yes
72	exclusion_16 Show the field ONLY if: [conditions_excluded(16)]="1"	Is exclusion of individuals with Hypertension narrowed?	checkbox 0 exclusion_16___0 No 1 exclusion_16___1 Yes- narrowed by type 2 exclusion_16___2 Yes- narrowed by severity 3 exclusion_16___3 Yes- narrowed by onset 4 exclusion_16___4 Yes- narrowed by other specification
73	exclusion_n_report_17	Is the number of individuals	dropdown 0 No

	Show the field ONLY if: [conditions_excluded(17)]="1"	excluded for having Osteoporosis reported?	1 Yes
74	exclusion_17 Show the field ONLY if: [conditions_excluded(17)]="1"	Is exclusion of individuals with Osteoporosis narrowed?	checkbox 0 exclusion_17___0 No 1 exclusion_17___1 Yes- narrowed by type 2 exclusion_17___2 Yes- narrowed by severity 3 exclusion_17___3 Yes- narrowed by onset 4 exclusion_17___4 Yes- narrowed by other specification
75	exclusion_n_report_18 Show the field ONLY if: [conditions_excluded(18)]="1"	Is the number of individuals excluded for having Schizophrenia reported?	dropdown 0 No 1 Yes
76	exclusion_18 Show the field ONLY if: [conditions_excluded(18)]="1"	Is exclusion of individuals with Schizophrenia narrowed?	checkbox 0 exclusion_18___0 No 1 exclusion_18___1 Yes- narrowed by type 2 exclusion_18___2 Yes- narrowed by severity 3 exclusion_18___3 Yes- narrowed by onset 4 exclusion_18___4 Yes- narrowed by other specification
77	exclusion_n_report_19 Show the field ONLY if: [conditions_excluded(19)]="1"	Is the number of individuals excluded for having Stroke reported?	dropdown 0 No 1 Yes
78	exclusion_19 Show the field ONLY if: [conditions_excluded(19)]="1"	Is exclusion of individuals with Stroke narrowed?	checkbox 0 exclusion_19___0 No 1 exclusion_19___1 Yes- narrowed by type 2 exclusion_19___2 Yes- narrowed by severity 3 exclusion_19___3 Yes- narrowed by onset 4 exclusion_19___4 Yes- narrowed by other specification
79	exclusion_n_report_20 Show the field ONLY if:	Is the number of individuals excluded for	dropdown 0 No 1 Yes

	[conditions_excluded(20)]="1"	having Substance Abuse Disorders reported?	
80	exclusion_20 Show the field ONLY if: [conditions_excluded(20)]="1"	Is exclusion of individuals with Substance Abuse Disorders narrowed?	checkbox 0 exclusion_20___0 No 1 exclusion_20___1 Yes- narrowed by type 2 exclusion_20___2 Yes- narrowed by severity 3 exclusion_20___3 Yes- narrowed by onset 4 exclusion_20___4 Yes- narrowed by other specification
81	age_restrict	Were there any age restrictions for trial participants (aside from 18 years or older)?	dropdown 0 No 1 Yes
82	age_restric_type Show the field ONLY if: [age_restrict]="1"	What type of age exclusion?	checkbox 0 age_restric_type___0 Minimum Age 1 age_restric_type___1 Maximum Age
83	max_age Show the field ONLY if: [age_restric_type(1)]="1"	Excluded those above age:	text (integer)
84	eligibility_complete	Complete?	dropdown 0 Incomplete 1 Unverified 2 Complete
Instrument:**Patient Selection**			
85	mcc_reported	Are multiple chronic conditions included in the participant characteristics?	dropdown 0 No 1 Yes
86	mcc_infer	Could the inclusion of	dropdown

		individuals with multiple chronic conditions be inferred?	0 No 1 Yes 2 Extracted before 8/7/15 (DON'T SELECT)
87	mcc_reported_spec Show the field ONLY if: [mcc_reported]="1"	Is this description general or condition specific?	checkbox 0 mcc_reported_spec___0 General 1 mcc_reported_spec___1 Condition Specific
88	mcc_reported_cond Show the field ONLY if: [mcc_reported_spec(1)]="1" or [mcc_infer]="1"	Which specific conditions are reported or inferred in the participant characteristics?	checkbox 1 mcc_reported_cond___1 Arthritis 2 mcc_reported_cond___2 Asthma 3 mcc_reported_cond___3 Autism Spectrum Disorder 4 mcc_reported_cond___4 Cancer 5 mcc_reported_cond___5 Cardiac Arrhythmias 6 mcc_reported_cond___6 Chronic Kidney Disease 7 mcc_reported_cond___7 Chronic Obstructive Pulmonary Disease 8 mcc_reported_cond___8 Congestive Heart Failure 9 mcc_reported_cond___9 Coronary Artery Disease 10 mcc_reported_cond___10 Dementia 11 mcc_reported_cond___11 Depression 12 mcc_reported_cond___12 Diabetes 13 mcc_reported_cond___13 Hepatitis 14 mcc_reported_cond___14 Human Immunodeficiency Virus (HIV) 15 mcc_reported_cond___15 Hyperlipidemia 16 mcc_reported_cond___16 Hypertension 17 mcc_reported_cond___17 Osteoporosis 18 mcc_reported_cond___18 Schizophrenia 19 mcc_reported_cond___19 Stroke 20 mcc_reported_cond___20 Substance Abuse Disorders
89	mcc_infer_1 Show the field ONLY if: [mcc_reported_cond(1)]="1"	Is the total number of participants with Arthritis reported?	dropdown 0 No 1 Yes

90	mcc_infer_2 Show the field ONLY if: [mcc_reported_cond(2)]="1"	Is the total number of participants with Asthma reported?	dropdown 0 No 1 Yes
91	mcc_infer_3 Show the field ONLY if: [mcc_reported_cond(3)]="1"	Is the total number of participants with Autism Spectrum Disorder reported?	dropdown 0 No 1 Yes
92	mcc_infer_4 Show the field ONLY if: [mcc_reported_cond(4)]="1"	Is the total number of participants with Cancer reported?	dropdown 0 No 1 Yes
93	mcc_infer_5 Show the field ONLY if: [mcc_reported_cond(5)]="1"	Is the total number of participants with Cardiac Arrhythmias reported?	dropdown 0 No 1 Yes
94	mcc_infer_6 Show the field ONLY if: [mcc_reported_cond(6)]="1"	Is the total number of participants with Chronic Kidney Disease reported?	dropdown 0 No 1 Yes
95	mcc_infer_7 Show the field ONLY if: [mcc_reported_cond(7)]="1"	Is the total number of participants with Chronic Obstructive Pulmonary Disease reported?	dropdown 0 No 1 Yes
96	mcc_infer_8 Show the field ONLY if: [mcc_reported_cond(8)]="1"	Is the total number of participants with Congestive Heart Failure reported?	dropdown 0 No 1 Yes

97	mcc_infer_9 Show the field ONLY if: [mcc_reported_cond(9)]="1"	Is the total number of participants with Coronary Artery Disease reported?	dropdown 0 No 1 Yes
98	mcc_infer_10 Show the field ONLY if: [mcc_reported_cond(10)]="1"	Is the total number of participants with Dementia reported?	dropdown 0 No 1 Yes
99	mcc_infer_11 Show the field ONLY if: [mcc_reported_cond(11)]="1"	Is the total number of participants with Depression reported?	dropdown 0 No 1 Yes
100	mcc_infer_12 Show the field ONLY if: [mcc_reported_cond(12)]="1"	Is the total number of participants with Diabetes reported?	dropdown 0 No 1 Yes
101	mcc_infer_13 Show the field ONLY if: [mcc_reported_cond(13)]="1"	Is the total number of participants with Hepatitis reported?	dropdown 0 No 1 Yes
102	mcc_infer_14 Show the field ONLY if: [mcc_reported_cond(14)]="1"	Is the total number of participants with HIV reported?	dropdown 0 No 1 Yes
103	mcc_infer_15 Show the field ONLY if: [mcc_reported_cond(15)]="1"	Is the total number of participants with Hyperlipidemia reported?	dropdown 0 No 1 Yes
104	mcc_infer_16	Is the total number of	dropdown 0 No

	Show the field ONLY if: [mcc_reported_cond(16)]="1"	participants with Hypertension reported?	1 Yes
105	mcc_infer_17 Show the field ONLY if: [mcc_reported_cond(17)]="1"	Is the total number of participants with Osteoporosis reported?	dropdown 0 No 1 Yes
106	mcc_infer_18 Show the field ONLY if: [mcc_reported_cond(18)]="1"	Is the total number of participants with Schizophrenia reported?	dropdown 0 No 1 Yes
107	mcc_infer_19 Show the field ONLY if: [mcc_reported_cond(19)]="1"	Is the total number of participants with Stroke reported?	dropdown 0 No 1 Yes
108	mcc_infer_20 Show the field ONLY if: [mcc_reported_cond(20)]="1"	Is the total number of participants with Substance Abuse Disorders reported?	dropdown 0 No 1 Yes
109	mcc_report_cond_total	What is the total number of chronic conditions (aside from index condition) reported in the trial (explicit or inferred)?	text (integer, Min: 0, Max: 20)
110	mcc_reported_number Show the field ONLY if: [mcc_reported_spec(0)] = 1	Are any of the following statistics regarding participants	checkbox 0 mcc_reported_number___0 Number 1 mcc_reported_number___1 Percentage 2 mcc_reported_number___2 Mean 3 mcc_reported_number___3 Charlson comorbidity index

		with MCC reported?	4 | mcc_reported_number___4 | Not reported
111	patient_selection_complete	Complete?	dropdown 0 | Incomplete 1 | Unverified 2 | Complete
Instrument:**Quality Assessment**			
112	bias_rand_seq	Random sequence generation (selection bias)	dropdown 0 | Low Risk 1 | High Risk 2 | Unclear Risk
113	bias_alloc	Allocation concealment (selection bias)	dropdown 0 | Low Risk 1 | High Risk 2 | Unclear Risk
114	bias_performance	Blinding of participants and personnel (performance bias)	dropdown 0 | Low Risk 1 | High Risk 2 | Unclear Risk
115	bias_detection	Blinding of outcome assessment (detection bias)	dropdown 0 | Low Risk 1 | High Risk 2 | Unclear Risk
116	bias_attrition	Incomplete outcome data (attrition bias)	dropdown 0 | Low Risk 1 | High Risk 2 | Unclear Risk
117	bias_report	Selective outcome reporting (reporting bias)	dropdown 0 | Low Risk 1 | High Risk 2 | Unclear Risk
118	quality_score	Quality Score	calc Calculation: sum((if([bias_rand_seq]>1,0,if([bias_rand_seq]<1,-1,[bias_rand_seq])) ,(if([bias_alloc]>1,0,if([bias_alloc]<1,-1,[bias_alloc])) ,(if([bias_performance]>1,0,if([bias_performance]<1,-1,[bias_performance])) ,(if([bias_detection]>1,0,if([bias_detection]<1,-1,[bias_detection])) ,(

			if([bias_attrition]>1,0,if([bias_attrition]<1,-1,[bias_attrition]))) ,(if([bias_report]>1,0,if([bias_report]<1,-1,[bias_report]))))
119	quality_assessment_complete	Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete
Instrument: **Outcomes**			
120	sub_analysis_comorbid	Were comorbidities used in a subgroup analysis?	dropdown 0, No 1, Yes
121	outcomes_complete	Complete?	dropdown 0, Incomplete 1, Unverified 2, Complete

6. Included studies

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7. Key informant information

Key informants contacted

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Summary of comments

GENERAL COMMENTS

- Consider commenting on exclusion of behavioral trials that don't assess/report MCC (e.g. the number excluded, how excluded trials may have affected results)
    - Could include a flow chart diagraming screening process used and exclusions w/ reasons at each stage
- Note the varied ways comorbidity is measured → use broad inclusion of chronic conditions
- Consider how to capture exclusion of MCC based on safety issue for participation
- Does the inclusion/exclusion of MCC vary by PI experience? (e.g. clinicians more likely to include)
- Consider how MCC are reported (self-report, med record extracted/confirmed)

SPECIFIC COMMENTS

- Included Studies
    - Overall study characteristics
        - Diet = 5/day fruits & veggies
        - Adherence to disease management = medication adherence, glucose monitoring, etc
        - Include: cancer screening; vaccinations (non-cancer – flu, pneumonia, child)
        - Include: sample characteristics (i.e. if the study was amply powered); the duration of the trial; delivery of intervention (e.g. face-to-face, other, etc)
        - Consider how to handle intervention components directed a multiple behaviors
    - Summary stats
        - Detail & categorize: standard measures (y/n), scale vs. single item(s), objective vs. self-report, single vs. repeated assessment
    - Study quality summary
        - Classify studies
- Patient Eligibility and Selection
    - Exclusion criteria
        - Consider studies that exclude people with a "narrowed" version of targeted condition (e.g. cancer screening studies excluding people with history of cancer)
        - Consider effect of how specific conditions are identified/confirmed (e.g. self-report MCC)
        - Include cognitive limitations in mental illness category

        - Make clear what trials are excluding specified "behavioral factors" (e.g. diabetes trial excluding smokers, not smoking cessation trial requiring everyone to be smokers)
        - Include age upper bound in analysis & consider range and mean/mode of upper bound
    - Participant screening
        - Consider that flow chart info etc may only be included in methods paper of studies
        - Organize presence of flow chart, specific # MCC exclusion, specific condition exclusion **by time**
- Study Participants
    - Consider self-report MCC in prevalence of reporting & be aware of studies using "count" system (e.g. 1 CC, 2 CC)
    - Of those reporting prevalence, consider recruitment approach
- Outcomes
    - Include: % including comorbidity in analysis at all & & reporting and effect of comorbidity on outcomes (sig, not sig)
    - Sub-group analysis include when comorbidities "controlled" in model
- Additional Variables for Stratification
    - Stratification in general → consider setting?
    - Behavioral component of intervention → more specific criteria?
    - Funding source → add government & foundation; for non-industry differentiate b/w peer reviewed and non-peer reviewed
    - Quality of study
        - Analyze each of 6 bias variables independently and the aggregate score
        - Blinding of outcome assessment includes objective data

Individual Comments
AMY MCQUEEN

- General Comments
    - Many behavioral trials that don't assess/report MCC → comment on how excluded trials may have affected results, the # excluded
        - Potential flow chart to include:
            - Number of articles reporting on an eligible RTC of a behavioral or psychosocial intervention
            - Number of those in #1 that include any assessment of co/multimorbidity
                a. Number of those in #2 that report measuring it but don't report using it in analyses, and provide no data on it
                b. Number of those in #2 that assess it and exclude anyone with co/multimorbidity
                c. Number of those in #2 that assess it and report it in descriptive results only (either for sample as a whole or by group)
                d. Number of those in #2 that assess it and report its association with the intervention effect
    - Comorbidity measured in variety of ways → use broad inclusion of chronic conditions to get a multimorbidity & note differences between measures and definitions used in studies

- Specific Comments (re: preliminary results)
    - Included Studies
        - Overall study characteristics → diet = 5/day fruits & veggies; adherence = medication adherence, glucose monitoring, etc; include: cancer screening, vaccination (non-cancer – flu, pneumonia, child)
        - Summary stats → detail & categorize: standard measures (y/n), scale vs. single item(s), objective vs. self-report, single vs. repeated assessment
        - Study quality summary → classify studies
    - Patient Eligibility and Selection
        - Exclusion criteria
            - Narrow condition consider those that are cancer studies that exclude people with history of cancer & consider self-reporting MCC effect
            - Age exclusion → include range and mean/mode of the upper bound (consider upper bound age in guidelines when interpreting results)
    - Study Participants
        - Consider self-report MCC in prevalence of reporting
        - For prevalence → describe recruitment approach (non-random, random selection from list/registry; non-random, random selection from community; other)
    - Outcomes
        - Add % that include comorbidity info in analysis at all & % that report any effect of comorbidity on outcomes (summarize the effect: sig or not sig)
    - Additional Variables for Stratification
        - Behavioral component of intervention → Susan Michie's taxonomy work
        - Funding source → add government & foundation
        - Quality of study → analyze each of 6 bias variables & aggregate score

KATE WOLIN

- General Comments
    - Some trials use "standard tool" (e.g. Physical Activity Readiness questionnaire) to establish eligibility → exclude MCC b/c safety issue [how to capture this idea]
        - PI expertise make a difference in inclusion/exclusion of MCC? (Clinician = more likely?)
    - Consider how MCC are reported (self-report, medical record extracted/confirmed)

WENDY DEMARK-WAHNEFRIED

- Specific Comments (re: preliminary results)
    - Included Studies
        - Overall study characteristics → include: sample characteristics (i.e. if the study was amply powered); the duration of the trial; delivery of intervention (e.g. face-to-face, other, etc)
    - Patient Eligibility and Selection
        - Participant screening → consider the fact that flow chart info etc missing from primary outcomes paper, so may need to check methods paper to find it
    - Additional Variables for Stratification

        - Quality of study → blinding of outcome data can also include objective data (e.g. accelerometer data)

AIMEE JAMES

- Specific Comments (re: preliminary results)
    - Patient Eligibility and Selection
        - Exclusion criteria
            - Include cognitive limitations in mental illness?
            - Make it clear what trials are excluding for "behavioral factors" (e.g. diabetes trial that excludes smokers, not a smoking cessation trial the requires everyone to be smokers)
            - Recommend keeping analysis of trials using upper bound of age as exclusion criteria
        - Participant screening → organize presence of flow chart, specific # MCC exclusion, specific condition exclusion **by time**
    - Outcomes
        - Subgroup analysis → does this include if they "control" for it in the model?
    - Additional Variables for Stratification
        - Funding source → non-industry: differentiate between peer-reviewed (e.g. NIH, foundation) and not peer-reviewed (e.g. internal funding)

GARY BENNETT

- Specific Comments (re: preliminary results)
    - Included Studies
        - Overall study characteristics → consider trials that are strictly behavioral w/o attention to condition & consider how to handle trials that include intervention components directed to multiple behaviors (e.g. trials where complementary behaviors are mentioned, but they aren't the focus)
    - Patient Eligibility and Selection
        - Exclusion criteria → consideration of how specific conditions are identified
            - Consideration of how specific conditions are identified (confirmed)
            - Other conditions: pregnancy, nursing, intentions to become pregnant
    - Study Participants
        - % of trials reporting MCC details → addressing metabolic syndrome?
        - MCC prevalence → some studies may use "count" system instead of naming conditions (e.g. 1 CC, 2 CC)
    - Additional Variables for Stratification
        - Stratification → what about setting? Including feeding trials?