Inclusion of Individuals with Multiple Chronic Conditions in Randomized Controlled Trials of Behavioral Interventions

PI: Graham Colditz, MD, DrPH

Study Director: Carrie Stoll, MPH, MSW

Department of Surgery
Division of Public Health Sciences

Paige Green, PhD, MPH

Jerry Suls, PhD
National Cancer Institute

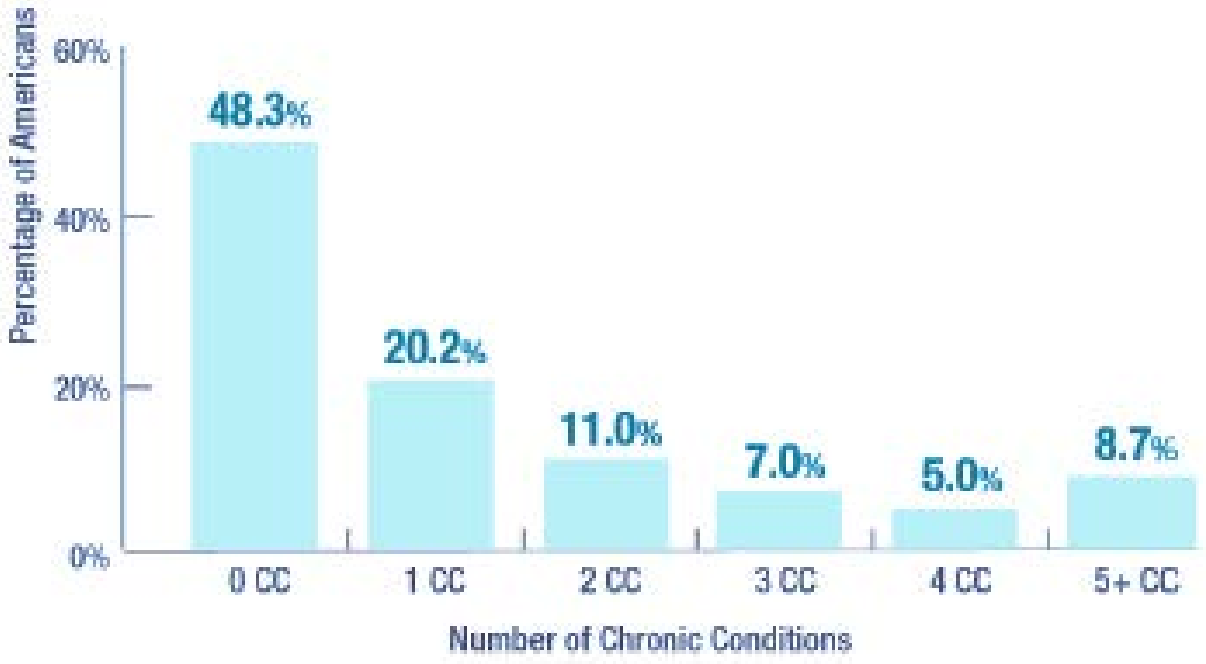
Washington University in St. Louis
School of Medicine

Disclosures

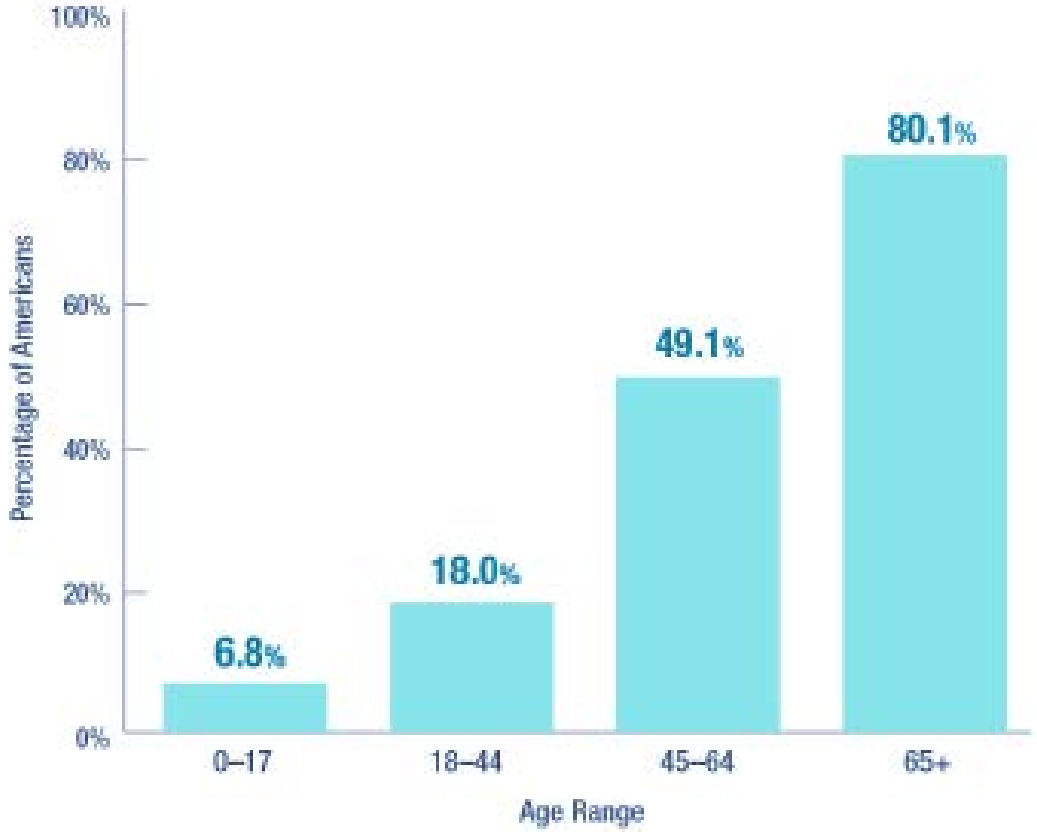
- This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views or polices of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations to imply endorsement by the U.S. Government.

- This work was supported in part by the Foundation for Barnes-Jewish Hospital.

Percentage of All Americans with Chronic Conditions, by Number of Chronic Conditions – 2010

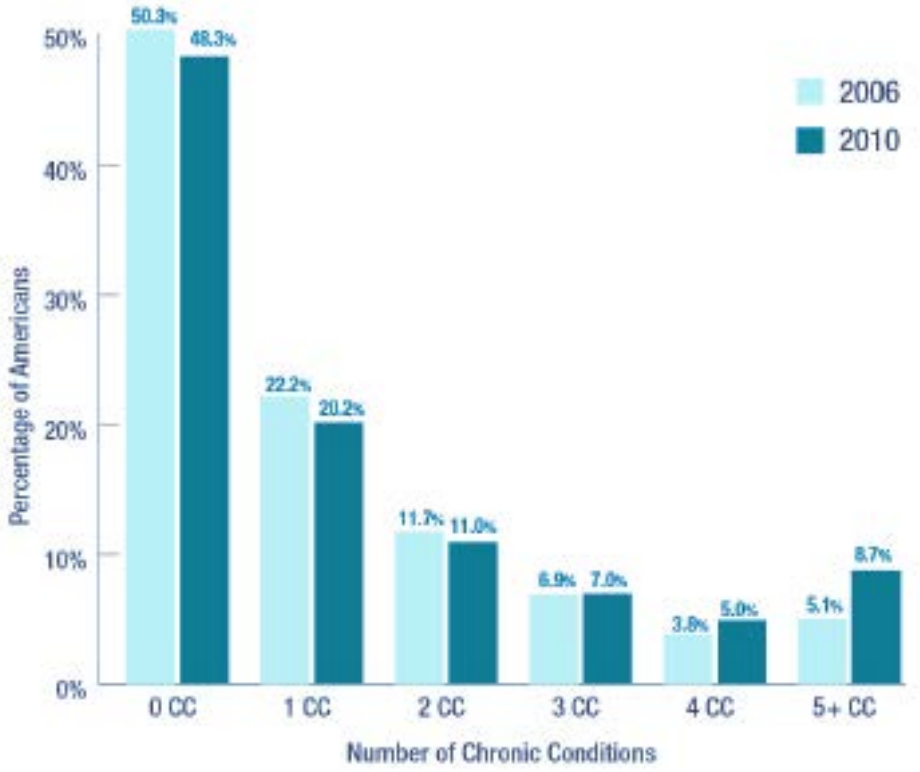


Percent of All Americans with Multiple Chronic Conditions, by Age Group – 2010

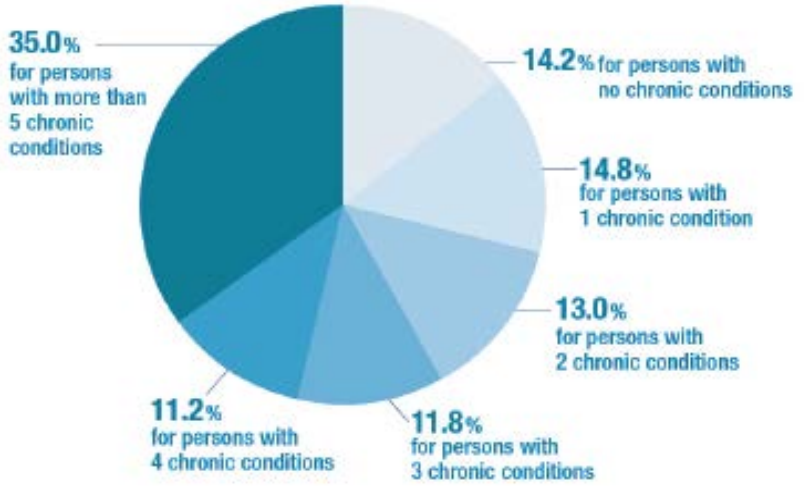


Gerteis J, Izrael D, Deitz D, LeRoy L, Ricciardi R, Miller T, Basu J. Multiple Chronic Conditions Chartbook. AHRQ Publications No, Q14-0038. Rockville, MD: Agency for Healthcare Research and Quality. April 2014

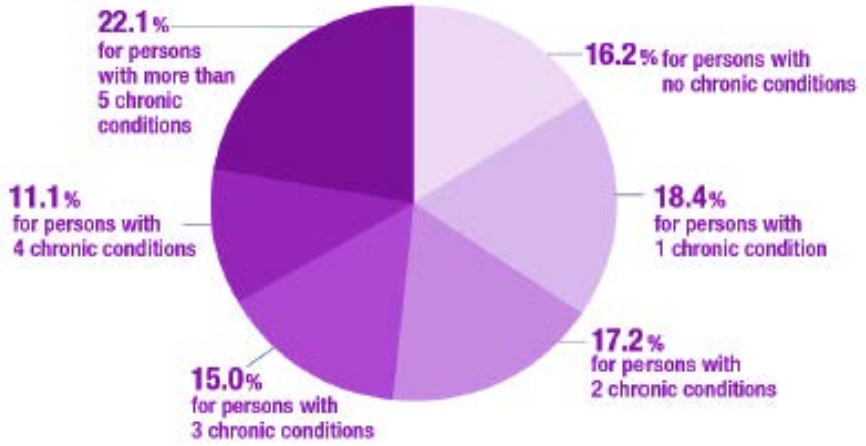
Percent of All Americans with Chronic Conditions, by Number of Chronic Conditions – 2006 and 2010



Total U.S. Healthcare Spending by Number of Chronic Conditions in 2010



Total U.S. Healthcare Spending by Number of Chronic Conditions in 2006



Gerteis J, Izrael D, Deitz D, LeRoy L, Ricciardi R, Miller T, Basu J. Multiple Chronic Conditions Chartbook. AHRQ Publications No, Q14-0038. Rockville, MD: Agency for Healthcare Research and Quality. April 2014

Previous assessments of inclusion of MCC in RCTs

Jadad 2011

- Reviewed 284 RCTs published from 1995 to 2010, did not limit by type of intervention
- Found MCC excluded in 63% of trial reports, with no significant difference in exclusion over time

Additional reviews (Van Spall 2007, Zulman 2011, Boyd 2012, Schmidt 2014)

- Eligibility criteria is often vague or hard to replicate
- People with common comorbidities of the index condition are frequently excluded
- Upper age limits are common and may limit generalizability
- Additional eligibility criteria may disproportionately impact complex, older adults
- Use of comorbidities in subgroup analyses is rare

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.; 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. PMC3411714:; 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.; Zulman DM, Sussman JB, Chen X, Cigolle CT, Blaum CS, Hayward RA. Examining the evidence: a systematic review of the inclusion and analysis of older adults in randomized controlled trials. *Journal of general internal medicine.* 2011;26(7):783-790.; Schmidt AF, Groenwold RH, van Delden JJ, et al. Justification of exclusion criteria was underreported in a review of cardiovascular trials. *Journal of clinical epidemiology.* Jun 2014;67(6):635-644.

Goals of the current review

In partnership with the Behavioral Research Program we performed a review with 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

Contributions of this review

- Focuses solely on RCTs of behavioral and/or psychosocial interventions
- Considers previously defined list of 20 chronic conditions
  - Chronicity, prevalence, and potential to be modifiable by public health and/or clinical interventions
- Reviews a large representative subset of the literature across 15 years (2000-2014)
- Evaluates a wide range of variables
  - Trial design, trial quality, eligibility criteria, participant selection, and consideration of comorbidities in analysis
- Uses best practices for systematic reviews
  - Review of search results and selection of included studies
  - Extraction of data by two independent readers

Methods- Eligibility criteria

- RCTs testing behavioral or psychosocial interventions
  - Defined as any intervention that is non-pharmacological and non-surgical and includes at least one behavior change technique (Michie 2013)
- Target at least 1 of 20 conditions, or target chronic conditions generally
  - 20 conditions taken from a list compiled by the Office of the Assistant Secretary of Health. Conditions meet the definition for chronicity, are prevalent, and have potential to be modifiable by public health and/or clinical interventions (Goodman 2013)
- Primary report of the trial
- Limited to adults (18+)
- Patients enrolled at the individual level
- Published in English

Chronic Conditions (OASH)
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)

Michie S, Richardson M, Johnston M, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine.* Aug 2013;46(1):81-95.; Goodman RA, Posner SF, Huang ES, Parekh AK, Koh HK. Defining and Measuring Chronic Conditions: Imperatives for Research, Policy, Program, and Practice. *Preventing Chronic Disease.* 2013;10:E66.

Methods- Searching and sampling strategy

Literature search

- Search designed by a medical librarian with expertise in systematic reviews
- RCTs in adults regarding chronic illness in PubMed Medline and Embase from 2000-2014

Sampling strategy

- Three separate literature searches using identical keywords performed within 3 time periods (2000-2004, 2005-2009, 2010-2014)
- Within each time period, search results randomly ordered and eligibility criteria applied in order until 200 studies meeting selection criteria were identified per time period
  - Total of 600 studies

Study selection

- Search results screened independently by two reviewers
- At each level of screening, excluded article and reason for exclusion were documented
- Disagreement resolved by discussion

Methods- Data collection and analysis

Data extraction and management

- REDCap electronic data capture tools
- Each article extracted independently by two trained reviewers & differences resolved by a third party

Variables extracted and assessment of risk of bias

- Variables designed to assess inclusion and reporting of MCC in all phases of a trial
  - Basic study characteristics
  - Intervention details
  - Eligibility information
  - Participant selection details
  - Study outcomes
  - Risk of bias assessment (Cochrane)

Analysis

- Basic study characteristics summarized and exploratory data analysis using summary statistics performed

Higgins J. Green S. Cochrane handbook for systematic reviews of interventions version 5.1. 0. 2008.

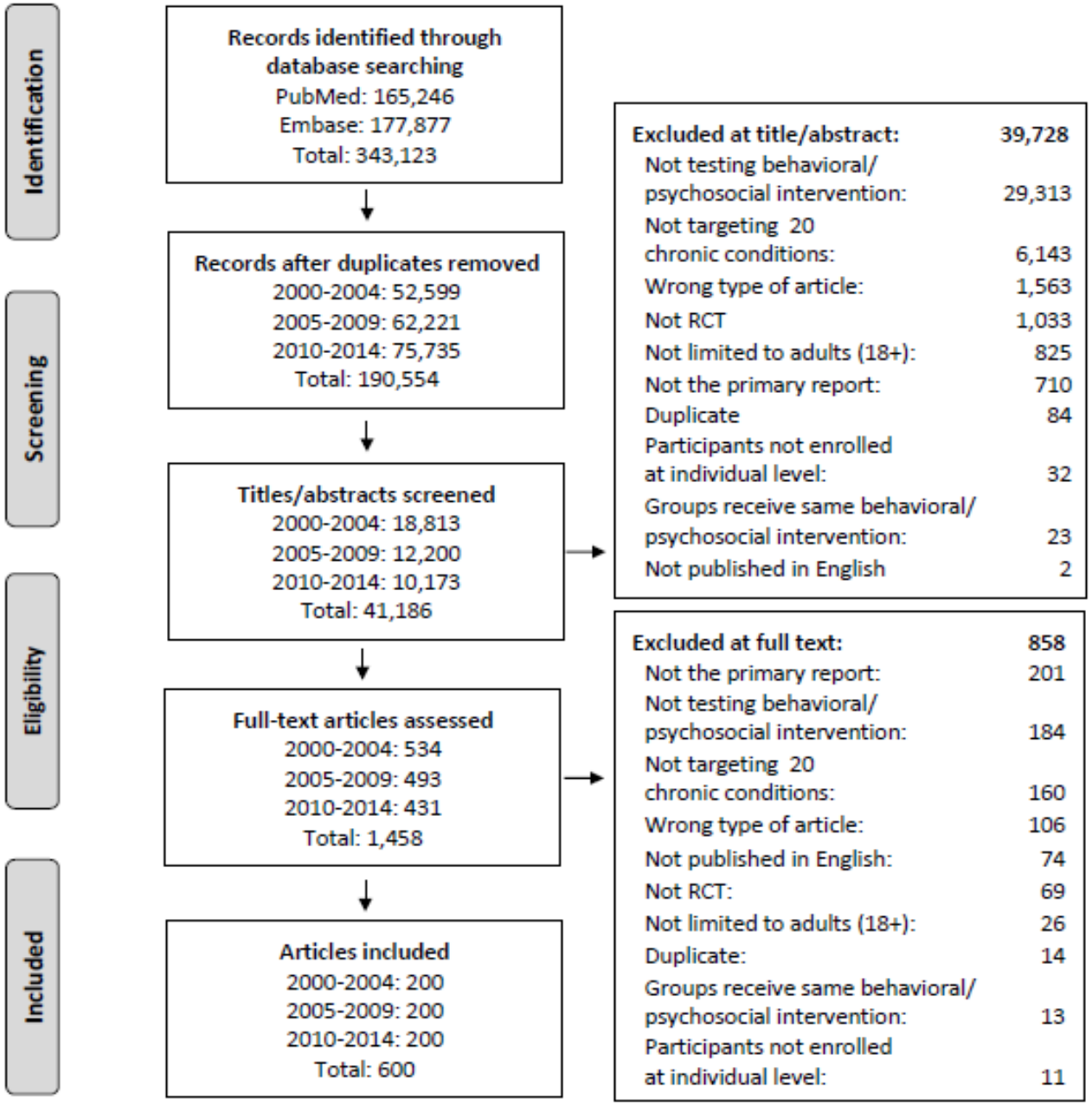
Are participants with MCC represented in an RCT?

- For each trial we must answer:
  - 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 MCC?
  - What is the prevalence of MCC among participants?
  - Are MCC considered in analysis?

Results (n=600)

- Study selection
- Study characteristics and quality
- Eligibility
  - Inclusion criteria
  - Exclusion criteria
    - Chronic conditions
    - Age
    - Behavioral risk factors
    - Stratified by targeted condition
  - Participant screening
- Participant characteristics
- Analysis

Results- Study selection



Study Characteristics

	2000-2004 (N=200)	2005-2009 (N=200)	2010-2014 (N=200)	Total (N=600)
Journal Type				
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				
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)
Other	79 (39.5)	99 (49.5)	113 (56.5)	291 (48.5)
Registered				
Yes (clinicaltrials.gov or other)	0 (0.0)	26 (13.0)	71 (35.5)	97 (16.2)
No	200 (100.0)	174 (87.0)	129 (64.5)	503 (83.8)
Sample size (N=596) median (range)	112 (8 – 2957)	110 (14 – 3522)	96.5 (10 – 8517)	104.5 (8 – 8517)

Study Characteristics

Intervention focus	2000-2004 (N=200)	2005-2009 (N=200)	2010-2014 (N=200)	Total (N=600)
Psychological well-being	82 (42.0)	66 (33.0)	63 (31.5)	213 (35.5)
Weight management/diet/physical activity	49 (24.5)	57 (28.5)	59 (29.5)	165 (27.5)
Adherence to disease management	45 (22.5)	52 (26.0)	41 (20.5)	138 (23.0)
Other	18 (9.0)	22 (11.0)	32 (16.0)	72 (12.0)
Tobacco habits	4 (2.0)	3 (1.5)	5 (2.5)	12 (2.0)

Study Characteristics - Quality

Based on Cochrane Risk of Bias Tool

	2000-2014 (n=600)
Random sequence generation (selection bias)	
Low risk of bias	286 (47.7)
High risk of bias	29 (4.8)
Unclear risk of bias	285 (47.5)
Allocation sequence concealment (selection bias)	
Low risk of bias	197 (32.8)
High risk of bias	20 (3.3)
Unclear risk of bias	383 (63.8)
Blinding of participants and personnel (performance bias)	
Low risk of bias	84 (14.0)
High risk of bias	109 (18.2)
Unclear risk of bias	407 (67.8)
Blinding of outcome assessment (detection bias)	
Low risk of bias	295 (49.2)
High risk of bias	50 (8.3)
Unclear risk of bias	255 (42.5)
Risk of bias score*	-2.6 (1.7)

*p<.001 over time

Risk of bias score calculated by summing low risk = -1, unclear risk = 0, high risk = 1

Eligibility- Inclusion Criteria

Which specific conditions do they target?

Do studies target MCC?

	2000-2014
No (target only 1 condition)	574 (95.7)
Yes	26 (4.3)

Which conditions are targeted?

	2000-2004	2005-2009	2010-2014	Total
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)
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)

Eligibility- Exclusion Criteria (Conditions)

Does the trial exclude MCC?

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

Eligibility- Exclusion Criteria (Conditions)

Do trials exclude MCC?

Exclusion of MCC	2000-2004	2005-2009	2010-2014	Total
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)

*NS over time, p=0.87

Eligibility- Exclusion Criteria (Conditions)

Which specific conditions are excluded most often?

	Specific exclusions for condition (2000-2014)
Substance Abuse Disorders	47 (19.0)
Dementia	42 (16.9)
Schizophrenia	35 (14.1)
Stroke	21 (8.5)
Congestive Heart Failure	20 (8.1)
Chronic Kidney Disease	18 (7.3)
Cancer	16 (6.5)
COPD	13 (5.2)
All conditions	**255 (42.5)**

Eligibility- Exclusion Criteria (Age, Risk factors)

Does the trial exclude people over a certain age?

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

*NS over time, p=0.15

Does the trial use risk factors for MCC in exclusion criteria?

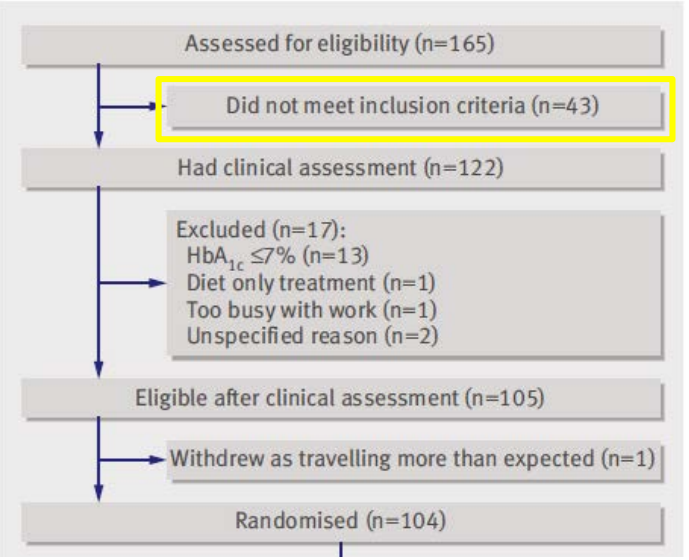
	Total
	N (%)
Any behavioral factor	86 (14.3)
Physical activity	36 (6.0)
Smoking or tobacco use	24 (4.0)
Weight	23 (3.8)
Other substance abuse	17 (2.9)
Alcohol use	10 (1.7)
Diet	2 (0.3)

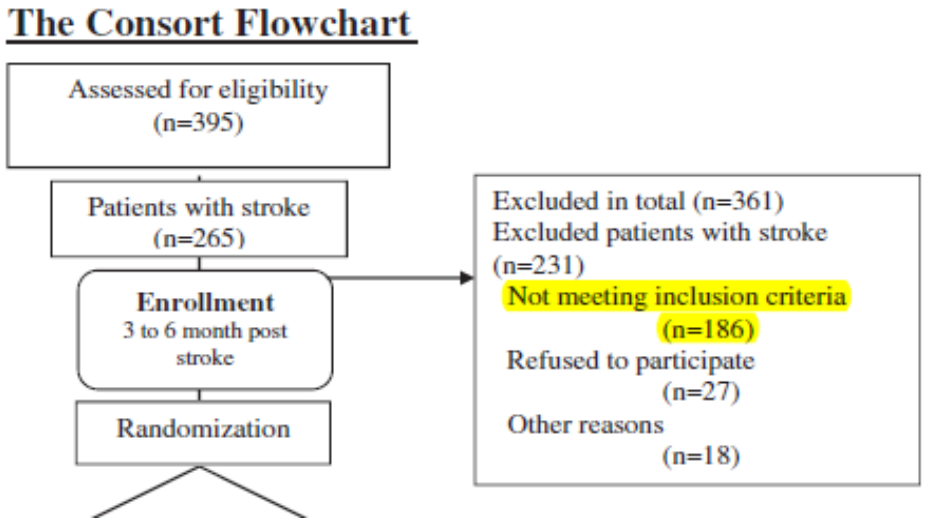
Examples: “smoked more than 10 packs a year,” “BMI of less than 25 or greater than 40”

Participant Screening

If potential participants are excluded for having MCC, is the number of people excluded for this reason reported?

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

Do trials describe presence of MCC (specific conditions or general measure) among participants?

	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)

*NS over time, p=0.07

General measures can include percentage with comorbidity, mean number of comorbidities per patient, or mean Charlson Comorbidity Index, or can just mean that it is mentioned somehow that any number of participants have MCC

When MCC are reported, is the prevalence reported?

	Yes	No
Condition specific description	111 (64.5)	61 (35.5)
General description	65 (95.6)	3 (4.4)
Specific OR general description*	128 (59.5)	87 (40.5)

Participant Characteristics

How many additional specific conditions are reported?

Report specific conditions (N=172)	
Number of additional conditions reported	
Mean	2.1
Median	2
Range	0 - 7

Which general measures of MCC are used?

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

Analysis

Are comorbidities considered in analysis in any way?

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)

Limitations

- Only included trials targeting a chronic condition
- Focusing on specific list of conditions may have prevented consideration of information
- Limited in analyses due to variation in amount and format of relevant information in trials

Conclusions

Study characteristics and quality

- The sample is comprised of RCTs across 2000-2014. Most are from specialty journals (84%), from North America (52%), funded by non-industry sources (77%), and not registered (84%).
- Over time, the percentage of trials with low risk of bias across bias categories has increased, and fewer studies have an unclear risk of bias, suggesting that reporting of trial details has improved.

Eligibility

Inclusion criteria

- Studies target patients with cancer (17%), diabetes (13%), depression (12%), and substance abuse disorders (12%). Less than 5% of studies target participants with MCC.

Conclusions

Eligibility (continued)

Exclusion criteria

- MCC are excluded directly, through specific (43%) or general exclusions (7%), or indirectly through exclusions based on age (28%) or risk factors (14%).
- Vague exclusions that may impact MCC are common in trials (48%).

Participant screening

- Although MCC are often excluded, the number of potential participants excluded for these reasons is rarely reported (16%).

Conclusions

Participant characteristics

- Trials are more likely to report individual specific conditions among participants (29%) over a general measure of comorbidities (11%).
- Trials that explicitly include MCC do not always report prevalence of MCC (41%). When reporting additional specific conditions, trials report details on an average of 2 comorbidities.

Results

- Considering comorbidities in analyses is rare (5%).

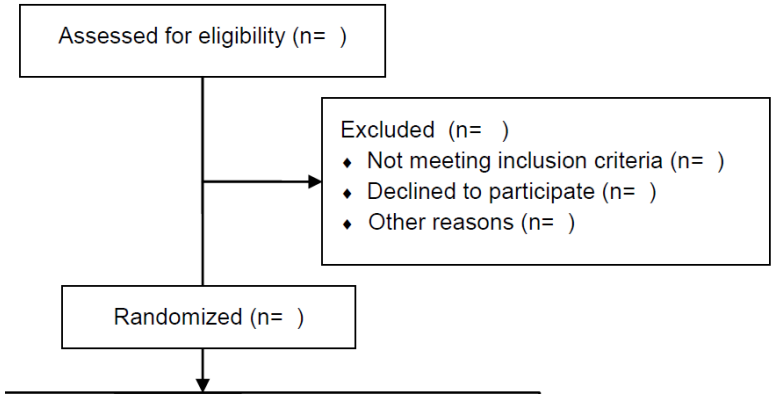
Are participants with MCC represented in an RCT?

Poor reporting reduces our ability to answer this question.

- Does the RCT explicitly exclude MCC?
  - Trial reports often use vague or general terms that are not clearly defined and make it difficult to determine if MCC are excluded
- Is the RCT likely to have excluded MCC due to exclusion criteria regarding other factors?
  - Exclusion criteria based on age or risk factors may result in indirect exclusion of MCC
- To what extent are participants excluded for MCC?
  - Details on screening are often not reported, making it difficult to judge how prevalent exclusions for MCC were
- Does the RCT select MCC?
  - Trials often do not report if participants have MCC, which comorbidities exist, and how prevalent these conditions are in the trial population

Is CONSORT the solution?

- CONSORT asks for “a comprehensive description of the eligibility criteria used to select the trial participants”
- Journals may require submission of the CONSORT checklist, but this only indicates if information is present
- CONSORT Extension for pragmatic trials may get closer to requiring more explicit eligibility criteria



Participants	4a	Eligibility criteria for participants
	4b	Settings and locations where the data were collected

Eligibility criteria for participants and the settings and the locations where the data were collected

Extension for pragmatic trials: Eligibility criteria should be explicitly framed to show the degree to which they include typical participants and, where applicable, typical providers (eg, nurses), institutions (eg, hospitals), communities (or localities eg, towns) and settings of care (eg, different healthcare financing systems).

Is trial registration the solution?

- Protocols do not always match publication (Blümle 2011)
  - Accessed trial protocols approved during one year by the research ethics committee of a university in Germany and identified matching publications (n=52)
  - Considered 7 categories of eligibility criteria including comorbidity
  - Classified eligibility criteria as matching, missing from, modified, or added in a publication
  - For each missing, modified, or added criterion, considered whether the difference between protocol and publication would broaden or narrow the study population assumed by a reader of the publication

Table 4 | Eligibility criteria classified by content category and type of discrepancy of protocol and subsequent publications

Content category	No of trials	Total No (%) of eligibility criteria	No (%) of eligibility criteria			
			Matching	Missing in publication	Modified in publication	Added in publication
Comorbidity	52	546 (42)	212 (39)	227 (41)	80 (15)	27 (5)
Treatment	49	258 (20)	107 (41)	105 (41)	34 (13)	12 (5)
Type or severity of illness	51	223 (17)	139 (62)	46 (21)	34 (15)	4 (2)
Pregnancy related criteria	43	73 (6)	35 (48)	34 (46)	2 (3)	2 (3)
Personal criteria	51	67 (5)	44 (66)	17 (25)	5 (7)	1 (2)
Diagnostic procedures	13	30 (2)	12 (40)	15 (50)	3 (10)	0
Other	47	102 (8)	57 (56)	35 (34)	5 (5)	5 (5)
Total		1299 (100)	606 (46)	479 (37)	163 (13)	51 (4)

Blümle, Anette, et al. "Reporting of eligibility criteria of randomised trials: cohort study comparing trial protocols with subsequent articles." *BMJ* 342 (2011).

Examples from our dataset

Clinicaltrials.gov

Criteria

Inclusion Criteria:

- African American
- Uncontrolled Hypertension
- at least 3 practice visits in the past 2 years
- One lipid panel since 2005

Exclusion Criteria:

- No recent lipid panel
- Kept less than 60% of primary care visits in the prior 2 years

Criteria

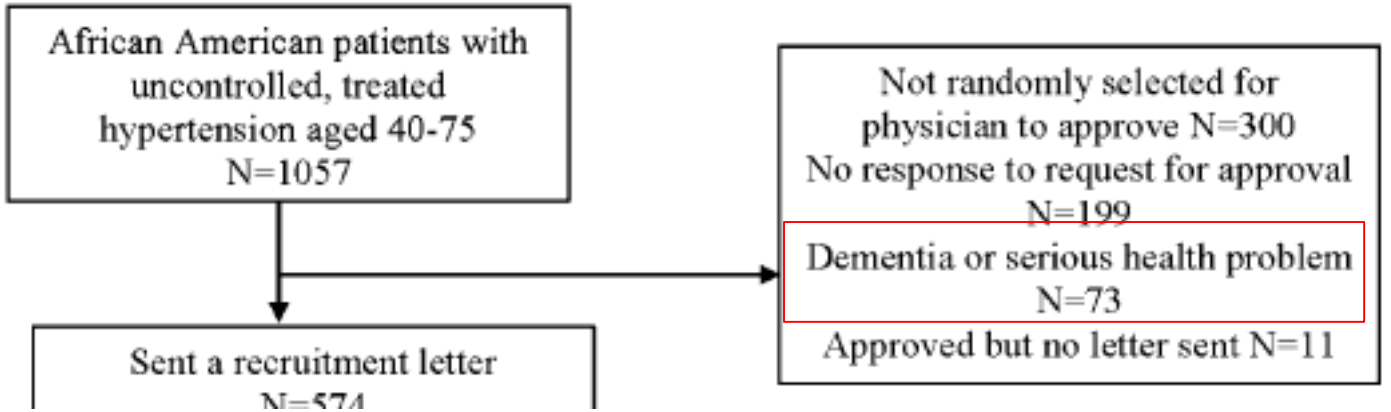
Inclusion Criteria:

- 55 years of age or older
- stroke diagnosis 3-6 months prior to inclusion
- ability to walk 10 meter with or without assistive device
- ability to understand simple instructions

Exclusion Criteria:

- TIA
- independent in walking outdoors
- serious visual impairment
- serious hearing impairment
- long distance to intervention station

Publication



comply with instructions in Swedish. Individuals were excluded if they had the ability to walk outdoors independently (i.e. without assistance or walking device), severe aphasia, severe vision or hearing impairment, any medical condition that a physician determined was inconsistent with study participation, and living too far away (>100 km) from the training facilities.

Is trial registration the solution?

- Does not require necessary detail
  - When the problem is that the criteria is vague, access to the protocol or registration does not necessarily solve this

Eligibility Criteria * FDAAA

Definition: Summary criteria for participant selection. The preferred format includes lists of inclusion and exclusion criteria a

- Although required by many journals, registration is still not common

	2000-2004 (N=200)	2005-2009 (N=200)	2010-2014 (N=200)	Total (N=600)
Registered				
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)

How do we get to a solution?

Implications for further research

- Goal: Any clinician can read a trial and determine if the findings are applicable to their population
- Must develop recommendations for reporting MCC and other relevant characteristics in the literature
- Effects of MCC clustering
- Inclusion of MCC in trials not targeting a condition
- Relationship between efficacy/effectiveness of interventions and inclusion of MCC
- Consideration of pragmatic-explanatory trials and MCC
- Assessing general reporting of RCTs with CONSORT
- Specific aims of trials compared to trial report

For more information:

- www.mccsystematicreview.wustl.edu
- Access to database, data dictionary, codebook, and other project materials.

- Contact us:

Graham Colditz colditzg@wudosis.wustl.edu

Carrie Stoll stollc@wudosis.wustl.edu

Study Team

- Graham Colditz, MD, DrPH[1]
- Carrie Stoll, MPH, MSW[1]
- Sonya Izadi, BA[1]
- Sydney Philpott, BS[1]
- Susan Fowler, MLIS[2]
- Ratna Pakpahan, MHA[1]
- Paige Green, PhD, MPH[3]
- Jerry Suls, PhD[3]
- Alwiya Ahmed[1]
- Joyce Dieterly[1]
- Nageen Mir[1]
- Jeff Viox[1]
- Eva Williams[1]
- Daoxin Yin[1]
- Jingsong Zhao[1]
- Aimee James, PhD, MPH[1]
- Kate Wolin, ScD, FACSM[4]
- Amy McQueen, PhD[5]
- Wendy Demark-Wahnefried, PhD, RD[6]
- Gary Bennett, PhD[7]

[1]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine in St. Louis
[2]Becker Medical Library, Washington University School of Medicine in St. Louis
[3]Behavioral Research Program, National Cancer Institute
[4]Coeus Health
[5]Division of Health Behavior Research, Department of Medicine, Washington University School of Medicine in St. Louis
[6]UAB Comprehensive Cancer Center
[7]Duke University