Associations between anticholinergic medication exposure and adverse health outcomes in older people with frailty: A systematic review and meta-analysis

Drugs – Real World Outcomes

Supplementary information file: Appendices

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Appendix 1: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 (+Appendix 2 in supplementary info file)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6 (+Figure 1)
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-7 (+Table 1)
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	11
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-11 (+Table 3 and 4)
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Appendix 6 in supplementary info file
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

Appendix 2: Search strategy for each database

MEDLINE (EBSCO)

Rows combined with "OR" and columns combined with "AND"

Elderly/frailty domain	**Anticholinergic domain**	**Epidemiological filters domain**
(MH "Aged+")	(MH "Muscarinic Antagonists")	(MH "Epidemiologic Studies")
late* life	(MH "Anticholinergic Syndrome")	(MH "Case-Control Studies+")
(MH "Age Factors+")	(MH "Cholinergic Antagonists+")	(MH "Cohort Studies+")
older adult*	anti#choliner*	case control
elderly	anti#muscarinic*	cohort stud*
(MH "Geriatrics")	(anti#choliner*) N5 (drug* or medic* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	cohort analy*
geriatric*	cholinergic block*	cohort N5 (study or studies)
senior*	(cholinergic blocking* or anti#muscarinic* or muscarinic antagonist* or parasympatholytic* or atropinic*) N5 (drug* or medic* or agent* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	follow N5 (study or studies)
pensioner*	muscarinic antagonist*	observation* N5 (study or studies)
oap*	anticholinergic syndrome*	longitudinal
(MH "Retirement")	cholinergic antagonist*	retrospective
retired	parasympatholytic*	cross sectional
retiree*	muscarinic receptor block*	cross sectional N5 (study or studies)
oldest old	atropin*	survey
deep old age	(anti#choliner* or anti#muscarinic*) N5 (burden* or risk* or assess* or scale* or tool* or quantif* or measure* or rating* or load* or accumulat* or capacit*)	(MH "Epidemiologic Studies+")
polypathologic*	anti#cholinergic cognit* burden	
(MH "Geriatric Assessment")	acb	
geriatric assessment	drug burden index	
retirement	anticholinergic risk scale	
aged	ars	
comprehensive geriatric assessment	anticholinergic drug scale*	
(MH "Frailty")	ads	
frail*	Sedative N1 (load or burden or accumulat*)	
(MH "Geriatric Psychiatry")		

geriatric psychiatry		
geriatric psychology		
geriatric psychopharmacology		
pre-frail*		
robust		
mild* frail*		
moderat* frail*		
severe* frail*		
extreme* frail*		
frail* stat*		
cognitiv* frail*		
physic* frail*		
geriatric syndrome*		
function* status		
(MH "Sarcopenia")		
sarcop#eni*		
cumulative deficit*		
phenotype model*		
(edmonton or fried) N5 (index* or indicator* or score* or scale* or tool* or test* or model* or phenotype* or criteri* or marker* or method* or instrument* or assess* or exam* or evaluat* or measure* or screen* or diagnos* or detect* or identif*)		
(MH "Walking Speed")		
gait speed*		
grip strength		
(MH "Hand Strength+")		
time* up and go		
time* up and go test*		
tugt		
gug		
get up and go test*		
get up and go		
(MH "Activities of Daily Living+")		
physical N3 function*		
multi-morbid*		
advanced age*		
multi-disease*		
(multidisease* or multi-disease* or (multiple N1 (ill* or disease# or condition* or syndrome* or disorder*)))		

Symbols:

MH = Exact subject heading.

(*) = Replaces one or more letters

(#) = Matches one optional character.

Near operator (N): **N5** finds the words if they are a maximum of five words apart from one another, regardless of the order in which they appear.

(+) = Explode

CINAHL (EBSCO)

Rows combined with "OR" and columns combined with "AND"

Elderly/frailty domain	**Anticholinergic domain**	**Epidemiological filters domain**
(MH "Aged+")	(MH "Muscarinic Antagonists")	(MH "Epidemiological Research")
late* life	anticholinergic syndrome	(MH "Case-Control Studies+")
(MH "Age Factors")	(MH "Cholinergic Antagonists+")	(MH "Prospective studies+")
older adult*	anti#choliner*	case control
elderly	anti#muscarinic*	cohort stud*
(MH "Geriatrics")	(anti#choliner*) N5 (drug* or medic* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	cohort analy*
geriatric*	cholinergic block*	cohort N5 (study or studies)
senior*	(cholinergic blocking* or anti#muscarinic* or muscarinic antagonist* or parasympatholytic* or atropinic*) N5 (drug* or medic* or agent* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	follow N5 (study or studies)
pensioner*	muscarinic antagonist*	observation* N5 (study or studies)
oap*	anticholinergic syndrome*	longitudinal
(MH "Retirement")	cholinergic antagonist*	retrospective
retired	parasympatholytic*	cross sectional
retiree*	muscarinic receptor block*	cross sectional N5 (study or studies)
oldest old	atropin*	survey
deep old age	(anti#choliner* or anti#muscarinic*) N5 (burden* or risk* or assess* or scale* or tool* or quantif* or measure* or rating* or load* or accumulat* or capacit*)	(MH "Epidemiological Research+")
polypathologic*	anti#cholinergic cognit* burden	epidemiological study
(MH "Geriatric Assessment")	acb	

geriatric assessment	drug burden index	
retirement	anticholinergic risk scale	
aged	ars	
comprehensive geriatric assessment	anticholinergic drug scale*	
(MH "Frailty Syndrome")	ads	
frail*	Sedative N1 (load or burden or accumulat*)	
(MH "Geriatric Psychiatry")		
geriatric psychiatry		
geriatric psychology		
geriatric psychopharmacology		
pre-frail*		
robust		
mild* frail*		
moderat* frail*		
severe* frail*		
extreme* frail*		
frail* stat*		
cognitiv* frail*		
physic* frail*		
geriatric syndrome*		
function* status		
(MH "Sarcopenia")		
sarcop#eni*		
cumulative deficit*		
phenotype model*		
(edmonton or fried) N5 (index* or indicator* or score* or scale* or tool* or test* or model* or phenotype* or criteri* or marker* or method* or instrument* or assess* or exam* or evaluat* or		

measure* or screen* or diagnos* or detect* or identif*)		
(MH "Walking Speed")		
gait speed*		
grip strength		
(MH "Grip Strength")		
time* up and go		
time* up and go test*		
tugt		
gug		
get up and go test*		
get up and go		
(MH "Activities of Daily Living+")		
physical N3 function*		
multi-morbid*		
advanced age*		
multi-disease*		
(multidisease* or multi-disease* or (multiple N1 (ill* or disease# or condition* or syndrome* or disorder*)))		

Symbols:

MH = Exact subject heading.

(*) = Matches multiple characters.

(#) = Matches one optional character.

Near operator (N): **N5** finds the words if they are a maximum of five words apart from one another, regardless of the order in which they appear.

(+) = Explode

EMBASE

Each term in each domain will be searched with OR, and then the three domains will be searched with AND.

Elderly/frailty domain (searched with OR)

	26,463
#58 multidisease* OR 'multi disease*' OR (multiple NEAR/1 (ill* OR disease* OR condition* OR syndrome* OR disorder*))	
	181
#57 'multi disease*'	
	23,591
#56 'advanced age*'	
	1,104
#55 'multi morbid*'	
	61,968
#54 physical NEAR/3 function*	
	83,129
#53 'daily life activity'/exp OR 'daily life activity'	
	575
#52 'get up and go'	
	358
#51 'get up and go test*'	
	480
#50 gug	
	218
#49 tugt	
	4,340
#48 'time* up and go test*'	
	6,245
#47 'time* up and go'	
	23,453
#46 'hand strength'/exp OR 'hand strength'	
	23,489
#45 'grip strength'	
	6,382
#44 'gait speed*'	
	13,037
#43 'walking speed'/de	
	4,664

#42 (edmonton OR fried) NEAR/5 (index* OR indicator* OR score* OR scale* OR tool* OR test* OR model* OR phenotype* OR criteri* OR marker* OR method* OR instrument* OR assess* OR exam* OR evaluat* OR measure* OR screen* OR diagnos* OR detect* OR identif*)	212
#41 'phenotype model*'	161
#40 'cumulative deficit*'	13,564
#39 sarcop?ni*	7,824
#38 'sarcopenia'/de	67,295
#37 'function* status'	2,147
#36 'geriatric syndrome*'	925
#35 'physic* frail*'	164
#34 'cognitiv* frail*'	1,112
#33 'frail* stat*'	36
#32 'extreme* frail*'	247
#31 'severe* frail*'	103
#30 'moderat* frail*'	81
#29 'mild* frail*'	222,566
#28 robust	933
#27 'pre frail*'	
#25 'geriatric psychopharmacology'	189
#24 'geriatric psychology'	24
#23 'geriatric psychiatry'	15,897

	7,419
#22 'gerontopsychiatry'/de	
	35,672
#21 frail*	
	6,933
#20 'frailty'/de	
	3,388
#19 'comprehensive geriatric assessment'	
	21,529
#18 retirement	
	17,002
#17 'geriatric assessment'	
	14,862
#16 'geriatric assessment'/de	
	122
#15 polypathologic*	
	1
#14 'deep old age'	
	2,966
#13 'oldest old'	
	1,776
#12 retiree*	
	10,138
#11 retired	
	14,588
#10 'retirement'/de	
	1,086
#9 oap*	
	2,573
#8 pensioner*	
	69,188
#7 senior*	
	290,034
#6 geriatric*	
	44,730
#5 'geriatrics'/de	
	508,098
#4 elderly	
	88,963
#3 'older adult*'	

	21,564
#2 'late* life'	
	4,261,046

Anticholinergic domain (searched with OR)

	119
#80 'anticholinergic drug scale'/exp OR 'anticholinergic drug scale'	
	55,932
#79 ars	
	122
#78 'anticholinergic risk scale'	
	122
#77 'anticholinergic risk scale'/exp OR 'anticholinergic risk scale'	
	163
#76 'drug burden index'/exp OR 'drug burden index'	
	5,476
#75 acb	
	153
#74 'anticholinergic cognit* burden'	
	1,381
#73 (anti$choliner* OR anti$muscarinic*) NEAR/5 (burden* OR risk* OR assess* OR scale* OR tool* OR quantif* OR measure* OR rating* OR load* OR accumulat* OR capacit*)	
	81,931
#72 atropin*	
	9,085
#71 'muscarinic receptor block*'	
	1,363
#70 parasympatholytic*	
	1,230
#69 'cholinergic antagonist*'	
	1,011
#68 'anticholinergic syndrome*'	
	4,408
#67 'muscarinic antagonist*'	
	9,836
#66 'cholinergic blocking*' OR 'antimuscarinic*' OR 'muscarinic antagonist*' OR 'parasympatholytic*' OR ('atropinic*' NEAR/5 (drug* OR medic* OR agent* OR therap* OR regime* OR treatment* OR preparation* OR remed* OR pill* OR tablet* OR prescri* OR dose* OR dosing*))	

#65 'cholinergic block*'	967
#64 anti$choliner* NEAR/5 (drug* OR medic* OR therap* OR regime* OR treatment* OR preparation* OR remed* OR pill* OR tablet* OR prescri* OR dose* OR dosing*)	10,336
#63 anti$muscarinic*	4,075
#62 anti$choliner*	20,743
#61 'cholinergic receptor blocking agent'/de OR 'cholinergic receptor blocking agent'	30,433
#60 'anticholinergic syndrome'/de OR 'anticholinergic syndrome'	1,006
#59 'muscarinic receptor blocking agent'/de	8,754

Epidemiological filters domain

#96 'questionnaire'/de	633,427
#95 'cross sectional' NEAR/5 (study OR studies)	380,229
#94 'cross sectional'	484,584
#93 retrospective	1,097,928
#92 longitudinal	335,504
#91 observation* NEAR/5 (study OR studies)	286,957
#90 follow NEAR/5 (study OR studies)	229,526
#89 cohort NEAR/5 (study OR studies)	417,579
#88 'cohort analy*'	478,475
#87 'cohort stud*'	265,450

	213,795
#86 'case control'	
	477,978
#85 'cohort analysis'/exp OR 'cohort analysis'	
	187,495
#84 'case control study'/exp OR 'case control study'	
	216,014
#83 'epidemiology'/de	

The final search comprises of:

Elderly/frailty domain AND anticholinergic domain AND epidemiological filter domain

Symbols

(/de) = Emtree term

(*) = Matches multiple characters.

($) = Replaces one or no letters

(?) = Single letter truncation

Near operator (N): **NEAR/5** finds the words if they are a maximum of five words apart from one another, regardless of the order in which they appear.

The Cochrane Database of Systematic Reviews

Elderly/frailty domain (searched with OR)

ID	Search	Hits
#1	MeSH descriptor: [Aged] explode all trees	1236
#2	"late* life"	33
#3	MeSH descriptor: [Age Factors] explode all trees	9860
#4	"older adult*"	759
#5	elderly	47287
#6	MeSH descriptor: [Geriatrics] this term only	198
#7	geriatric*	14275
#8	senior*	4396
#9	pensioner*	72
#10	oap*	67
#11	MeSH descriptor: [Retirement] this term only	49
#12	retired	477
#13	retiree*	89
#14	"oldest old*"	93
#15	"deep old age"	0
#16	polypathologic*	8
#17	MeSH descriptor: [Geriatric Assessment] this term only	1412
#18	"geriatric assessment"	1957
#19	retirement	455
#20	aged	475124
#21	"comprehensive geriatric assessment"	306
#22	MeSH descriptor: [Frailty] this term only	31
#23	frail*	3193
#24	MeSH descriptor: [Geriatric Psychiatry] this term only	39
#25	"geriatric psychiatry"	1502
#26	"geriatric psychology"	3
#27	"geriatric psychopharmacology"	54
#29	"pre-frail*"	130
#30	robust	10458
#31	"mild frailty"	2

#32	"moderate frailty"	3
#33	"severe frailty"	6
#34	"extreme frailty"	1
#35	"frailty status"	104
#36	"cognitive frailty"	9
#37	"physical frailty"	92
#38	"geriatric syndrome*"	53
#39	"function* status"	113
#40	MeSH descriptor: [Sarcopenia] this term only	312
#41	sarcop?ni*	1143
#42	"cumulative deficit*"	6
#43	"phenotype model*"	8
#44	("edmonton" or "fried") NEAR/5 (index* or indicator* or score* or scale* or tool* or test* or model* or phenotype* or criteri* or marker* or method* or instrument* or assess* or exam* or evaluat* or measure* or screen* or diagnos* or detect* or identif*)	353
#45	MeSH descriptor: [Walking Speed] this term only	80
#46	"gait speed*"	1331
#47	"grip strength"	3631
#48	MeSH descriptor: [Hand Strength] explode all trees	1311
#49	"time* up and go"	176
#50	"time* up and go test*"	104
#51	tugt	78
#52	gug	7
#53	"get up and go test*"	135
#54	"get up and go"	187
#55	MeSH descriptor: [Activities of Daily Living] explode all trees	8760
#56	physical NEAR/3 function*	11690
#57	multi-morbid*	415
#58	"advanced age*"	901
#59	multi-disease*	21

#60 (multidisease* or multidisease* or (multiple NEAR/1 (ill* or disease# or condition* or syndrome* or disorder*)))

1251

#61 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60

521408

Anticholinergic domain (searched with OR)

#62 MeSH descriptor: [Muscarinic Antagonists] this term only 850

#63 MeSH descriptor: [Anticholinergic Syndrome] this term only 1

#64 MeSH descriptor: [Cholinergic Antagonists] explode all trees 1220

#65 anti?choliner* 3509

#66 anti?muscarinic* 761

#67 (anti?choliner*) NEAR/5 (drug* or medic* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*) 1737

#68 "cholinergic block*" 0

#69 ("cholinergic blocking*" or anti?muscarinic* or "muscarinic antagonist*" or parasympatholytic* or atropinic*) NEAR/5 (drug* or medic* or agent* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)
1046

#70 "muscarinic antagonist*" 590

#71 "anticholinergic syndrome*" 31

#72 "cholinergic antagonist*" 49

#73 parasympatholytic* 821

#74 "muscarinic receptor block*" 0

#75 atropin* 3498

#76 (anti?choliner* or anti?muscarinic*) NEAR/5 (burden* or risk* or assess* or scale* or tool* or quantif* or measure* or rating* or load* or accumulat* or capacit*)
241

#77 "anticholinergic cognitive burden" 6

#78 acb 563

#79 "drug burden index" 21

#80 "anticholinergic risk scale" 5

#81 ars 674

#82 "anticholinergic drug scale*" 10

#83	ads	625
#84	Sedative NEAR/1 (load or burden or accumulat*)	4
#85	#62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84	10727

Epidemiological filters domain (searched with OR)

#86	MeSH descriptor: [Epidemiologic Studies] this term only	40
#87	MeSH descriptor: [Case-Control Studies] explode all trees	12803
#88	MeSH descriptor: [Cohort Studies] explode all trees	142437
#89	"case control"	11344
#90	"cohort study"	10664
#91	"cohort analysis*"	16749
#92	cohort NEAR/5 (study or studies)	28214
#93	follow NEAR/5 (study or studies)	99954
#94	observation* NEAR/5 (study or studies)	21125
#95	longitudinal	19596
#96	retrospective	30177
#97	"cross sectional"	16162
#98	"cross sectional" NEAR/5 (study or studies)	11914
#99	survey	28935
#100	MeSH descriptor: [Epidemiologic Studies] explode all trees	148834
#101	#86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100	277398

Final search of all three domains (searched with AND)

#102	#61 AND #85 AND #101	1258
After only including Cochrane reviews		275

Symbols

MeSH = Exact subject heading.

(*) = One or more characters

(?) = Zero or one characters

Near operator (NEAR/x): **NEAR/5** finds the words if they are a maximum of five words apart from one another, regardless of the order in which they appear.

Web of Science

Rows combined with "OR" and columns combined with "AND"

All terms were searched in "ALL FIELDS" unless stated otherwise.

The search was conducted in the Core Collection

Elderly/frailty domain	**Anticholinergic domain**	**Epidemiological filters domain**
Aged	"Muscarinic Antagonists"	"Epidemiologic Studies"
"late* life"	"Anticholinergic Syndrome"	"Case-Control Studies"
"Age Factors"	"Cholinergic Antagonists"	"Cohort Studies"
"older adult*"	anticholiner*	"case control"
elderly	antimuscarinic*	"cohort stud*"
geriatric*	TOPIC: (anticholiner*) NEAR/5 (drug* or medic* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	"cohort analy*"
senior*	"cholinergic block*"	TOPIC: cohort NEAR/5 (study or studies)
pensioner*	TOPIC: ("cholinergic blocking*" or antimuscarinic* or "muscarinic antagonist*" or parasympatholytic* or atropinic*) NEAR/5 (drug* or medic* or agent* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	TOPIC: follow NEAR/5 (study or studies)
oap*	"muscarinic antagonist*"	TOPIC: observation* NEAR/5 (study or studies)
Retirement	"anticholinergic syndrome*"	longitudinal
retired	"cholinergic antagonist*"	retrospective
retiree*	parasympatholytic*	"cross sectional"
"oldest old"	"muscarinic receptor block*"	TOPIC: "cross sectional" NEAR/5 (study or studies)
"deep old age"	atropin*	survey
polypathologic*	TOPIC: (anticholiner* or antimuscarinic*) NEAR/5 (burden* or risk* or assess* or scale* or tool* or quantif* or measure* or rating* or load* or accumulat* or capacit*)	

“Geriatric Assessment"	“anticholinergic cognit* burden”	
“comprehensive geriatric assessment”	acb	
Frailty"	“drug burden index”	
frail*	“anticholinergic risk scale”	
"Geriatric Psychiatry"	ars	
“geriatric psychology”	“anticholinergic drug scale*”	
“geriatric psychopharmacology”	ads	
old*	TOPIC: Sedative NEAR/1 (load or burden or accumulat*)	
“pre-frail*”		
robust		
“mild* frail*”		
“moderat* frail*”		
“severe* frail*”		
“extreme* frail*”		
“frail* stat*”		
“cognitiv* frail*”		
“physic* frail*”		
“geriatric syndrome*”		
“function* status”		
Sarcopenia		
Sarcop?ni*		
“cumulative deficit*”		
“phenotype model*”		
TOPIC: (edmonton or fried) NEAR/5 (index* or indicator* or score* or scale* or tool* or test* or model* or phenotype* or criteri* or marker* or method* or instrument* or assess* or exam* or evaluat* or measure* or screen* or diagnos* or detect* or identif*)		

“Walking Speed"		
“gait speed*”		
“grip strength”		
"Hand Strength"		
“time* up and go”		
“time* up and go test*”		
tugt		
gug		
“get up and go test*”		
“get up and go”		
"Activities of Daily Living"		
TOPIC: physical NEAR/3 function*		
“multi-morbid*”		
“advanced age*”		
“multi-disease*”		
TOPIC: (multidisease* or multi-disease* or (multiple NEAR/1 (ill* or disease or condition* or syndrome* or disorder*)))		

Symbols:

(*) = Matches multiple characters.

(?) = Single letter truncation

Near operator (NEAR/): **NEAR/5** finds the words if they are a maximum of five words apart from one another, regardless of the order in which they appear.

PsycINFO (EBSCO)

Rows combined with "OR" and columns combined with "AND"

Elderly/frailty domain	**Anticholinergic domain**	**Epidemiological filters domain**
Aged	"Muscarinic Antagonists"	(DE "Epidemiology")
"late* life"	"Anticholinergic Syndrome"	"epidemiologic studies"
"Age Factors"	"Cholinergic Antagonistss="	"case-control studies"
"older adult*"	anti#choliner*	(DE "Cohort Analysis")
elderly	anti#muscarinic*	case control
(DE "Geriatrics")	(anti#choliner*) N5 (drug* or medic* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	cohort stud*
geriatric*	"cholinergic block*"	cohort analy*
senior*	(cholinergic blocking* or anti#muscarinic* or muscarinic antagonist* or parasympatholytic* or atropinic*) N5 (drug* or medic* or agent* or therap* or regime* or treatment* or preparation* or remed* or pill* or tablet* or prescri* or dose* or dosing*)	cohort N5 (study or studies)
pensioner*	"muscarinic antagonist*"	follow N5 (study or studies)
oap*	"anticholinergic syndrome*"	observation* N5 (study or studies)
(DE "Retirement")	"cholinergic antagonist*"	longitudinal
retired	parasympatholytic*	retrospective
retiree*	"muscarinic receptor block*"	"cross sectional"
"oldest old"	atropin*	"cross sectional" N5 (study or studies)
"deep old age"	(anti#choliner* or anti#muscarinic*) N5 (burden* or risk* or assess* or scale* or tool* or quantif* or measure* or rating* or load* or accumulat* or capacit*)	survey
polypathologic*	"anti#cholinergic cognit* burden"	
(DE "Geriatric Assessment")	acb	
"geriatric assessment"	"drug burden index"	

retirement	“anticholinergic risk scale”	
“comprehensive geriatric assessment”	ars	
Frailty	“anticholinergic drug scale*”	
frail*	ads	
(DE "Geriatric Psychiatry")	Sedative N1 (load or burden or accumulat*)	
(DE "Geropsychology")		
“geriatric psychology”		
“geriatric psychopharmacology”		
“pre-frail*”		
robust		
“mild* frail*”		
“moderat* frail*”		
“severe* frail*”		
“extreme* frail*”		
“frail* stat*”		
“cognitiv* frail*”		
“physic* frail*”		
“geriatric syndrome*”		
(DE "Functional Status")		
Sarcopenia		
sarcop#eni*		
“cumulative deficit*”		
“phenotype model*”		
(edmonton or fried) N5 (index* or indicator* or score* or scale* or tool* or test* or model* or phenotype* or criteri* or marker* or method* or instrument* or assess* or exam* or evaluat* or		

measure* or screen* or diagnos* or detect* or identif*)		
“Walking Speed"		
“gait speed*”		
“grip strength”		
“Hand Strength”		
“time* up and go”		
“time* up and go test*”		
tugt		
gug		
“get up and go test*”		
“get up and go”		
(DE "Activities of Daily Living")		
physical N3 function*		
“multi-morbid*”		
“advanced age*”		
“multi-disease*”		
(multidisease* or multi-disease* or (multiple N1 (ill* or disease# or condition* or syndrome* or disorder*)))		

Symbols:

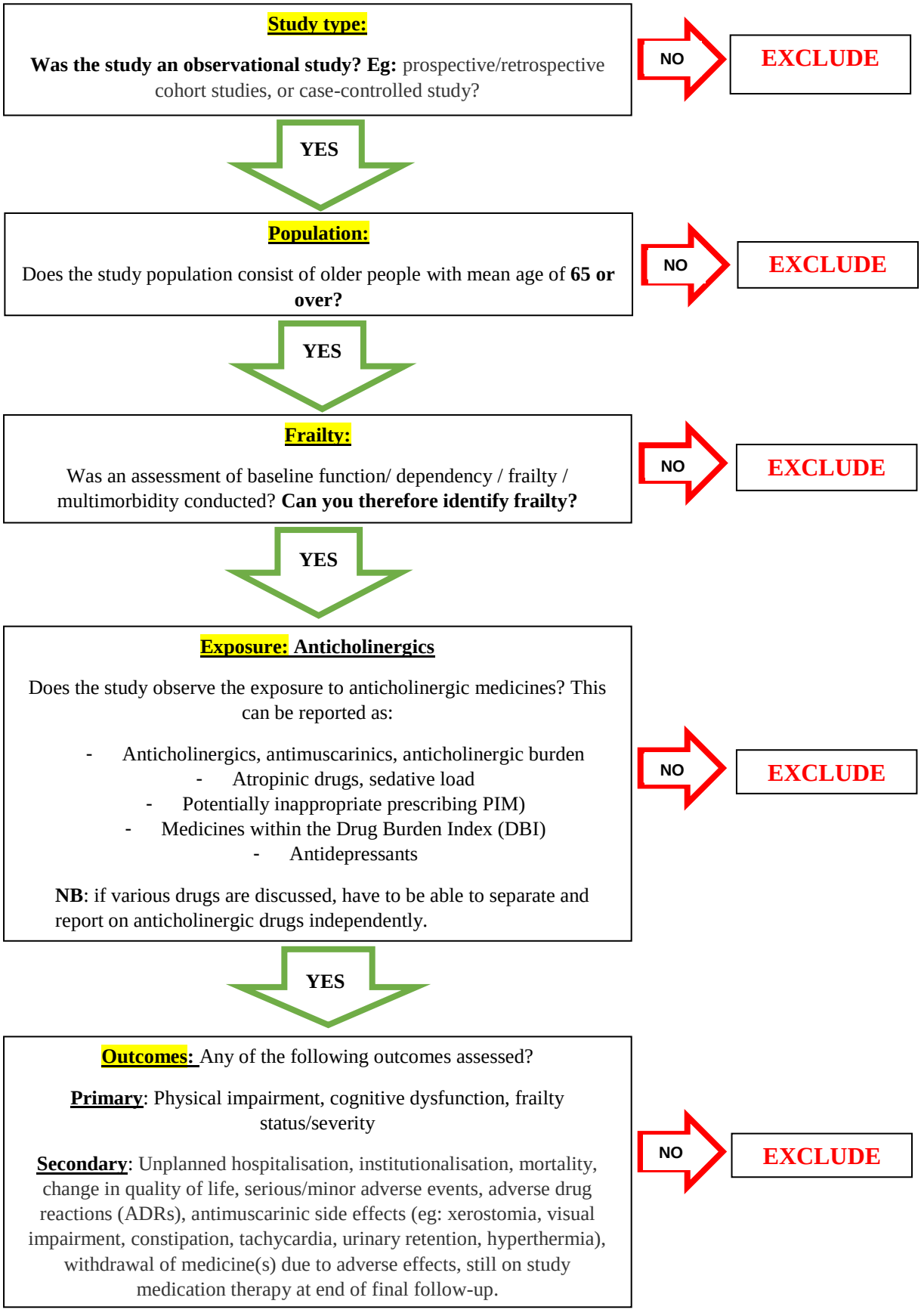
DE = Subjects [exact].

(*) = Replaces one or more letters

(#) = Matches one optional character.

Near operator (N): **N5** finds the words if they are a maximum of five words apart from one another, regardless of the order in which they appear.

Appendix 3: Screening flowchart for title/abstracts and full-texts



Appendix 4: Reaching judgement of overall risk of bias using the ROBINS-I tool

Response Option	Criteria
Low risk of bias (the study is comparable to a well-performed randomized trial);	The study is judged to be at **low risk of bias for all domains.**
Moderate risk of bias (the study appears to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial);	The study is judged to be at **low or moderate risk of bias for all domains.**
Serious risk of bias (the study has some important problems);	The study is judged to be at **serious risk of bias** in at least one domain, but not at critical risk of bias in any domain.
Critical risk of bias (the study is too problematic to provide any useful evidence and should not be included in any synthesis);	The study is judged to be at **critical risk of bias in at least one domain.**
No information on which to base a judgement about risk of bias.	There is no clear indication that the study is at serious or critical risk of bias *and* there is a lack of information in one or more key domains of bias *(a judgement is required for this).*

Appendix 5: Summary of reasons for excluding studies at full-text review stage

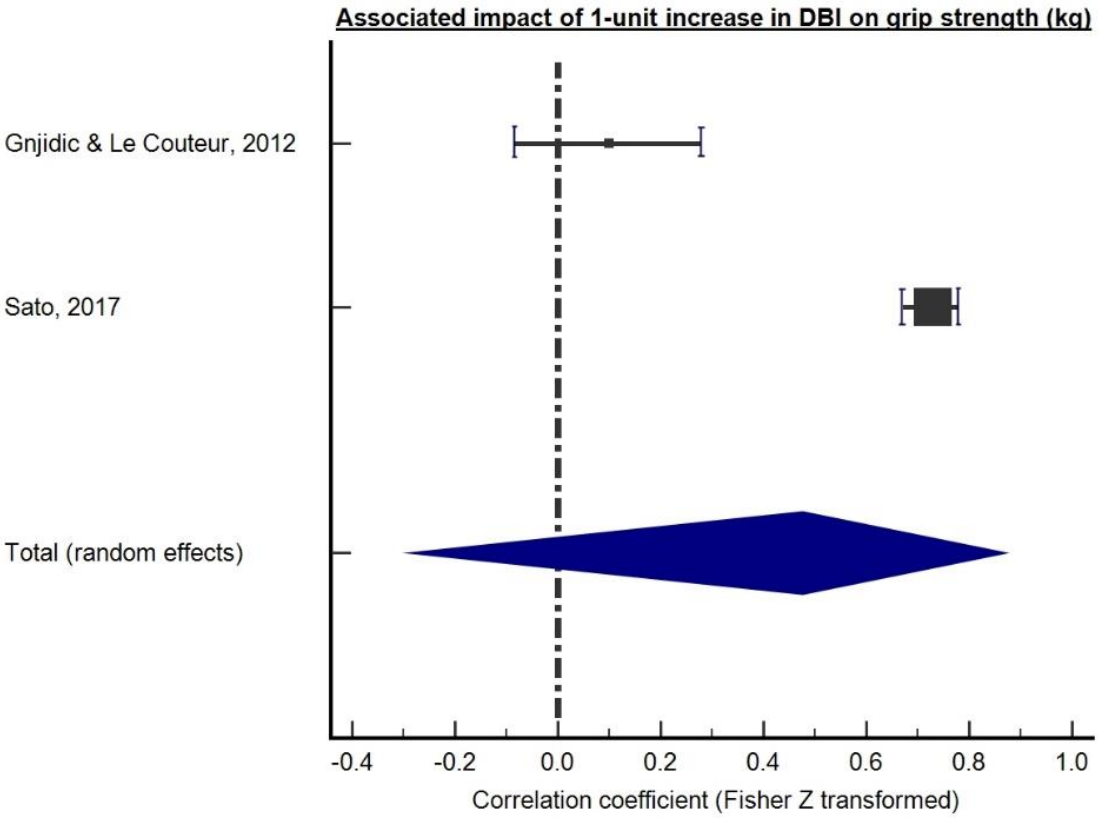
Study first author (year)	Study title	Reason for exclusion
Aizenburg, (2002) [1]	Anticholinergic Burden and the Risk of Falls Among Elderly Psychiatric Inpatients: A 4-Year Case-Control Study	No validated measure of frailty.
Ancelin, (2006) [2]	Non-degenerative mild cognitive impairment in elderly people and use of anticholinergic drugs: longitudinal cohort study	No validated measure of frailty.
Andre, (2019) [3]	Anticholinergic exposure and cognitive decline in older adults: effect of anticholinergic exposure definitions in a 3-year analysis of the multidomain Alzheimer preventive trial (MAPT) study	Frailty reported, however outcomes stratified by frailty not reported.
Ball, (2015) [4]	Anticholinergic Burden Assessed using General Practice Electronic records	No validated measure of frailty.
Berdot, (2009) [5]	Inappropriate medication use and risk of falls – A prospective study in a large community-dwelling elderly cohort	No validated measure of frailty.
Bostock, (2013) [6]	Associations between different measures of anticholinergic drug exposure and Barthel Index in older hospitalized patients	No validated measure of frailty.
Bottiggi, (2006) [7]	Long-Term Cognitive Impact of Anticholinergic Medications in Older Adults	No validated measure of frailty.
Byrne, (2019) [8]	Impact of drug burden index on adverse health outcomes in Irish community-dwelling older people: a cohort study	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Campbell, (2011) [9]	Association Between Prescribing of Anticholinergic Medications and Incident Delirium: A Cohort Study	No validated measure of frailty.
Cancelli, (2010) [10]	Anticholinergic drugs increase the risk of cognitive decline and dementia in older people	No validated measure of frailty.
Chatterjee, (2017) [11]	Risk of Mortality Associated with Anticholinergic Use in Elderly Nursing Home Residents with Depression	No validated measure of frailty.
Esin, (2015) [12]	Influence of antimuscarinic therapy on cognitive functions and quality of life in geriatric patients treated for overactive bladder	No validated measure of frailty.
George, (2017) [13]	Polypharmacy and Gait Performance in Community–dwelling Older Adults	Unable to isolate anticholinergics from the exposure variable.
Giron, (2001) [14]	The appropriateness of drug use in older nondemented and demented population	No validated measure of frailty.
Gnjidic, (2009) [15]	Drug Burden Index and physical function in older Australian men	No evidence of a pre-frail/frail sample.

Gnjidic, (2014) [16]	Sedative load and functional outcomes in community-dwelling older Australian men: the CHAMP study	No evidence of a pre-frail/frail sample.
Gnjidic, (2012) [17]	High-Risk Prescribing and Incidence of Frailty among Older community-Dwelling Men	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Han, (2008) [18]	Cumulative Anticholinergic Exposure Is Associated with Poor Memory and Executive Function in Older Men	No validated measure of frailty.
Hassan, (2018) [19]	Associations between Drug Burden Index, medication appropriateness and patient-reported outcomes in the community pharmacy setting in Malaysia	Frailty reported, however outcomes stratified by frailty not reported.
Herr (2017) [20]	Frailty, polypharmacy, and potentially inappropriate medications in old people: findings in a representative sample of the French population	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Hilmer (2009) [21]	Drug Burden Index Score and Functional Decline in Older People	No evidence of a pre-frail/frail sample.
Huang (2012) [22]	Relationship between Potentially Inappropriate Anticholinergic Drugs (PIADs) and Adverse Outcomes among Elderly Patients in Taiwan	No validated measure of frailty.
Inkeri, (2019) [23]	Anticholinergic drug use and its association with self-reported symptoms among older persons with and without diabetes	No validated measure of frailty.
Jamsen, (2017) [24]	Drug Burden Index and change in cognition over time in community-dwelling older men: the CHAMP study	No validated measure of frailty.
Kersten, (2015) [25]	Clinical impact of potentially inappropriate medications during hospitalization of acutely ill older patients with multimorbidity	Unable to isolate anticholinergics from the exposure variable. (Unable to contact corresponding author to request this data)
Khan, (2013) [26]	Clinical Decision Support System and Incidence of Delirium in Cognitively Impaired Older Adults Transferred to Intensive Care	No validated measure of frailty.
Koyama, (2014) [27]	Long-term Cognitive and Functional Effects of Potentially Inappropriate Medications in Older Women	No validated measure of frailty.
Kroger, (2019) [28]	Is the Drug Burden Index Related to Declining Functional Status at Follow-up in Community-Dwelling Seniors Consulting for Minor Injuries? Results from the Canadian Emergency Team Initiative Cohort Study	Unable to isolate anticholinergics from the exposure variable. (Unable to contact corresponding author to request this data)
Lampela, (2013) [29]	Anticholinergic Drug Use, Serum Anticholinergic Activity, and Adverse Drug Events Among Older People: A Population-Based Study	No validated measure of frailty.
Lampela, (2016) [30]	Association Between Anticholinergic Load and Frailty in Community-dwelling Older People	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Landi, (2014) [31]	Anticholinergic Drug Use and Negative Outcomes Among the Frail Elderly Population Living in a Nursing Home	No validated measure of frailty.

Lowry, (2011) [32]	Associations Between the Anticholinergic Risk Scale Score and Physical Function: Potential Implications for Adverse Outcomes in Older Hospitalized Patients	No validated measure of frailty.
MacLagan, (2017) [33]	Frailty and Potentially Inappropriate Medication Use at Nursing Home Transition	No reporting of clinical outcomes.
Merchant, (2009) [34]	Use of drugs with anticholinergic effects and cognitive impairment in community-living older persons	No validated measure of frailty.
Moulis, (2015) [35]	Exposure to Atropinic Drugs and Frailty Status	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Movig, (2001) [36]	Association Between Oxybutynin and Neuropsychiatric Adverse Effects Not Confirmed In Daily Practice	No validated measure of frailty.
Myint, (2015) [37]	Total anticholinergic burden and risk of mortality and cardiovascular disease over 10 years in 21,636 middle-aged and older men and women of EPIC-Norfolk prospective population study	No validated measure of frailty.
O'Connell, (2018) [38]	Drug burden index to define the burden of medicines in older adults with intellectual disabilities: An observational cross-sectional study	No validated measure of frailty.
O'Connell, (2019) [39]	Association of Drug Burden Index with grip strength, timed up and go and Barthel index activities of daily living in older adults with intellectual disabilities: an observational cross-sectional study	Inappropriate population.
Oken, (2006) [40]	Cognition and fatigue in multiple sclerosis: Potential effects of medications with central nervous system activity	No validated measure of frailty.
Pasina, (2013) [41]	Association of Anticholinergic Burden with Cognitive and Functional Status in a Cohort of Hospitalized Elderly: Comparison of the Anticholinergic Cognitive Burden Scale and Anticholinergic Risk Scale	No validated measure of frailty.
Peklar, (2015) [42]	Sedative Load and Frailty Among Community-Dwelling Population Aged 65 Years	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Petrov, (2014) [43]	Benzodiazepine (BZD) use in community-dwelling older adults: Longitudinal associations with mobility, functioning, and pain	No validated measure of frailty.
Risacher, (2016) [44]	Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults	No validated measure of frailty.
Salahudeen, (2015) [45]	Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review	Inappropriate study design.

Salahudeen, (2015) [46]	Comparison of Anticholinergic Risk Scales and Associations with Adverse Health Outcomes in Older People	No validated measure of frailty.
Sanders, (2017) [47]	Relationship between drug burden and physical and cognitive functions in a sample of nursing home patients with dementia	No evidence of a pre-frail/frail sample. (Unable to contact corresponding author to request further)
Sargent, (2018) [48]	Anticholinergic Drug Induced Cognitive and Physical Impairment: Results from the InCHIANTI Study	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Seifert, (1983) [49]	Use of anticholinergics in the nursing home: an empirical study and review	Unable to obtain full text.
Shapiro (2017) [50]	Medication Use Leading to Hospital Readmission in Frail Elders	No validated measure of frailty.
Sharma, (2018) [51]	Predictors of Falls and Fractures Leading to Hospitalization in People with Dementia: A Representative Cohort Study	No validated measure of frailty.
Sura, (2015) [52]	Anticholinergic drugs and health-related quality of life in older adults with dementia	No validated measure of frailty.
Taipale, (2011) [53]	Muscle Strength and Sedative Load in Community- Dwelling People Aged 75 Years and Older: A Population- Based Study	Unable to isolate anticholinergics from the exposure variable.
Teramura-Grönblad, (2011) [54]	Use of Anticholinergic Drugs and Cholinesterase Inhibitors and Their Association with Psychological Well-Being Among Frail Older Adults in Residential Care Facilities	No validated measure of frailty.
Uusvaara, (2013) [55]	Detailed Cognitive Function and Use of Drugs with Anticholinergic Properties in Older People	No validated measure of frailty.
Villalba-Moreno, (2018) [56]	Association Between Drug Burden Index and Functional and Cognitive Function in Patients with Multimorbidity	No validated measure of frailty.
Wauters, (2016) [57]	Polypharmacy in a Belgian cohort of community- dwelling oldest old (80+)	No validated measure of frailty.
Wouters, (2017) [58]	Quantification of anticholinergic and sedative drug load with the Drug Burden Index: a review of outcomes and methodological quality of studies	Inappropriate study design.
Wouters, (2019) [59]	Long-Term Exposure to Anticholinergic and Sedative Medications and Cognitive and Physical Function in Later Life	No evidence of a pre-frail/frail sample.
Wu, (2017) [60]	Association between using medications with anticholinergic properties and short-term cognitive decline among older men: A retrospective cohort study in Taiwan	Frailty reported as an outcome, but unable to identify whether there is a change in frailty state associated with the exposure.
Yalya, (2015) [61]	Drugs with anticholinergic side-effects in primary care	Very few participants in the study exposed to anticholinergic medicines.

Appendix 6: Results of the meta-analysis



Study	Sample size	Correlation coefficient	95% CI	z	P	Weight (%)	
						Fixed	Random
Gnjidic, Le Couteur, 2012	115	0.100	-0.0847 to 0.278			26.99	49.59
Sato, 2017	306	0.730	0.673 to 0.778			73.01	50.41
Total (fixed effects)	421	0.608	0.543 to 0.665	14.365	<0.001	100.00	100.00
Total (random effects)	421	0.476	-0.286 to 0.869	1.250	0.211	100.00	100.00

Q	56.1157
DF	1
Significance level	P < 0.0001
I^2 (inconsistency)	98.22%
95% CI for I^2	95.94 to 99.22

A forest plot reporting standardised pooled estimates of the change in grip strength (kg) with a one-unit increase in Drug Burden Index (DBI) score. Random effects modelling was adopted as the I^2 value was ≥ 50%.

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