

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

The prevalence of frailty in diabetes mellitus and association with clinical outcomes: A systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037476
Article Type:	Protocol
Date Submitted by the Author:	04-Feb-2020
Complete List of Authors:	Hanlon, Peter; University of Glasgow Institute of Health and Wellbeing, ; Fauré, Isabella ; University of Glasgow Institute of Health and Wellbeing Corcoran, Neave ; University of Glasgow Institute of Health and Wellbeing Butterly, Elaine; University of Glasgow Institute of Health and Wellbeing McAllister, David; University of Glasgow Institute of Health and Wellbeing Mair, Frances; University of Glasgow Institute of Health and Wellbeing
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, EPIDEMIOLOGY, GERIATRIC MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The prevalence of frailty in diabetes mellitus and association with clinical outcomes: A systematic review protocol

Authors:

Dr Peter Hanlon¹
Ms Isabella Fauré¹
Dr Neave Corcoran¹
Dr Elaine Butterly²
Dr David McAllister²
Professor Frances S Mair¹

Affiliations:

1. General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
2. Public Health, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

Corresponding author:

Dr Peter Hanlon
General Practice and Primary Care
Institute of Health and Wellbeing
University of Glasgow
1 Horselethill Road
Glasgow, G12 9LX

Peter.hanlon@glasgow.ac.uk

+44 141 330 8383

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

25 Word count: 2311

26 **Keywords:** Frailty, Diabetes Mellitus, Systematic review, Protocol

For peer review only

27 **Abstract**

28 **Introduction:**

29 Diabetes mellitus is common and growing in prevalence, and an increasing proportion of people with
30 diabetes are living to older age. Frailty is therefore becoming an important concept in diabetes.
31 Frailty is associated with older age and describes a state of increased susceptibility to
32 decompensation in response to physiological stress. A range of measures have been used to quantify
33 frailty. This systematic review aims to identify measures used to quantify frailty in people with
34 diabetes (type 1, type 2, or unspecified); to summarize the prevalence of frailty in diabetes; and to
35 describe the relationship between frailty and adverse clinical outcomes in people with diabetes.

36 **Methods and analysis:**

37 Three electronic databases (Medline, Embase and Web of Science) will be searched from 2000 to
38 November 2019 and supplemented by citation searching of relevant articles and hand-searching of
39 reference lists. Two reviewers will independently review titles, abstracts and full texts. Inclusion
40 criteria include: (1) Adults with diabetes mellitus (type 1, type 2, or unspecified); (2) Quantify frailty
41 using any validated frailty measure; (3) Report the prevalence of frailty and/or the association
42 between frailty and clinical outcomes in people with diabetes; (4) Studies that assess generic (e.g.
43 mortality, hospital admission, falls) or diabetes specific outcomes (e.g. hypoglycaemic episodes,
44 cardiovascular events, diabetic nephropathy, diabetic retinopathy); (5) Cross-sectional and
45 longitudinal observational studies. Study quality will be assessed using the Newcastle-Ottawa scale
46 for observational studies. Clinical and methodological heterogeneity will be assessed, and a random
47 effects meta-analysis performed if appropriate. Otherwise, a narrative synthesis will be performed.

48 Ethics and dissemination:

49 This study will summarise current knowledge about measurement, prevalence and implications of
50 frailty in diabetes. This will inform future research and clinical guidelines to assess the balance of
51 risks and treatment priorities in the growing number of people living with frailty and diabetes.

52 Registration number:

53 PROSPERO CRD42020163109.

54

55 Strengths and Limitations

56 This systematic review will provide a comprehensive overview of the prevalence and implications of
57 frailty in people with diabetes.

58 We will include a broad range of frailty definitions and clinical outcomes relevant to diabetes.

59 There is likely to be significant heterogeneity between population characteristics and frailty
60 definitions in included studies.

61 Introduction

62 The prevalence of diabetes mellitus is increasing across the world. Population demographics are also
63 shifting towards an ageing population. Among people above the age of 65, the prevalence of
64 diabetes can be as high as 30%.⁽¹⁾ Diabetes in older people is therefore a growing clinical and public
65 health priority. One factor with important implications for disease management in older age is
66 frailty.

67 Frailty is a state characterised by reduced functional reserve across multiple physiological
68 systems.⁽²⁾ People living with frailty have impaired resolution of homeostasis following physiological
69 stressors. Frailty therefore carries an increased risk of a range of adverse health outcomes, such as
70 falls, cognitive decline, hospital admission and mortality.⁽³⁾ Frailty is widely recognised to be a
71 multidimensional and dynamic state, associated with older age and with a range of non-

72 communicable diseases.⁽³⁾ However, there is no single universally accepted operational definition of
73 frailty. Rather, a wide range of definitions have been utilized in both research and clinical practice.⁽⁴⁾

74 The two dominant paradigms in the frailty literature are the frailty phenotype and the frailty index.

75 The frailty phenotype, described by *Fried et al* in 2001, defines frailty as the presence of three or
76 more out of five features: low hand-grip strength, unintentional weight loss, low physical activity,
77 exhaustion, and slow walking pace.⁽⁵⁾ The presence of one or two of these features is classified as a
78 pre-frail state. The frailty index, described by Rockwood and Mitnitski in 2007, is based on a

79 cumulative-deficit model of frailty whereby frailty is identified by counting the number of health
80 'deficits' present in an individual.⁽⁶⁾ At least 30 deficits are required to construct a frailty index, all of
81 which must increase in prevalence with age, be associated with poor health, and not saturate too
82 early (i.e. be universally present among older people).⁽⁷⁾ Both the frailty phenotype and frailty index
83 have been associated with adverse health outcomes in a range of older populations, however the
84 populations identified as frail by each are different. Since their original description, a wide range of

1
2
3 85 other frailty instruments, as well as adaptations of the frailty index and phenotype, have been
4
5 86 developed for both epidemiological studies and for clinical practice.(3, 4)
6
7
8 87 The relationship between diabetes mellitus and frailty is complex. Diabetes is associated with a
9
10 88 higher prevalence of frailty.(8-11) Both type 1 and type 2 diabetes lead to microvascular and
11
12 89 macrovascular complications which have important physical, cognitive and functional consequences,
13
14 90 that may contribute to the development of frailty. Hyperglycaemia is also recognized to directly
15
16 91 impact muscle mass and quality, exacerbating age-related sarcopenia and, in turn, physical
17
18 92 function.(12) However, the association between frailty and poor functional outcomes in people with
19
20 93 diabetes is only partially explained by direct complications of diabetes.(10, 13)
21
22
23
24 94 The importance of frailty in the context of diabetes is increasingly recognised in clinical guidelines.
25
26 95 Specifically, higher HbA1c targets are recommended in the context of frailty, in part due to the
27
28 96 increased risks associated with hypoglycaemia.(14) Despite this, up to 40% of older people with
29
30 97 diabetes may be over-treated (with HbA1c <7%).(15, 16) Conversely, poor glycaemic control and
31
32 98 associated vascular complications risk causing, or accelerating the progression of, frailty.(17)
33
34
35
36 99 One recent meta-analysis demonstrated a consistent relationship between frailty and mortality,
37
38 100 hospitalisation, and cardiovascular events in the context of diabetes.(18) We are not aware of any
39
40 101 systematic review to assess the prevalence of frailty in diabetes, or to consider a broader range of
41
42 102 outcomes relevant to the management of diabetes. Given the risks of both over- and under-
43
44 103 treatment of diabetes in the context of frailty, understanding the range of potential associations is
45
46 104 required to inform clinical decisions and to underpin future research.
47
48
49
50 105 To enhance understanding of the implications and management of diabetes within an ageing
51
52 106 population, it is important to fully describe the association between diabetes and frailty. Given the
53
54 107 risks of both over- and under-treatment of diabetes in the context of frailty, it is important to
55
56 108 understand the associations between frailty and a range of potential outcomes in diabetes. This
57
58 109 includes generic outcomes such as mortality and hospitalisation and disability and disease specific
59
60

1
2
3 110 outcomes such as retinopathy, neuropathy, and hypoglycaemic events. An understanding of the
4
5 111 range and complexity of these associations is required to inform clinical decisions around treatment
6
7 112 priorities and to underpin future research. This includes quantifying the prevalence of frailty in
8
9 113 people with diabetes, and the impact that different frailty definitions might have on this prevalence.
10
11
12 114 This manuscript describes the protocol of a systematic review aiming to synthesise existing evidence
13
14 115 relating to these questions.
15
16

17 116 Aims

18
19
20
21 117 The systematic review will aim to:

- 22
23
24 118 • Identify which frailty measures have been used to assess frailty in people with diabetes
25
26 119 mellitus (type1, type 2, or mixed/unspecified)
- 27
28
29 120 • Quantify the prevalence of frailty among people with diabetes
- 30
31 121 • Describe the association between frailty and both generic (e.g. mortality) and disease
32
33 122 specific (e.g. hypoglycaemia) clinical outcomes in the context of diabetes
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

123 Methods and analysis

124 This protocol is registered with PROSPERO (CRD42020163109). The review will be conducted and
 125 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 126 (PRISMA) statement.(19)

127 Eligibility criteria for inclusion

128 The eligibility criteria for this review are summarized in table 1 and explained in more detail below.

PICOS component	Description
Population	Adults (≥ 18 years old) Diabetes mellitus (type 1, type 2, or unspecified)
Exposure	Frailty as assessed by a validated frailty measure
Comparator	People with diabetes not classified as frail
Outcomes	Generic: <ul style="list-style-type: none"> • Mortality • Major Adverse Cardiovascular Events • Hospital admission • Admission to long-term care facility • Falls • Number of clinic attendances • Quality of life • Disability/functional status Diabetes specific: <ul style="list-style-type: none"> • HbA1c (cross sectional association, or longitudinal)

	<ul style="list-style-type: none"> • Glycaemic variability • Hypoglycaemic episodes • Diabetic retinopathy (cross sectional association, or longitudinal) • Diabetic nephropathy (cross sectional association, or longitudinal) <ul style="list-style-type: none"> ○ Include development of end-stage renal disease • Diabetic foot complications (cross sectional association, or longitudinal) • Treatment burden (e.g. Diabetic Treatment Burden Questionnaire)
Settings	Community (including care home/nursing home) Outpatient clinic Inpatient
Study design	Cross sectional or longitudinal Cohort
Other exclusions	Conference abstracts, letters, review articles, intervention studies

129 Population

130 We will include studies analysing data from people with any form of diabetes mellitus.

131 From an initial scoping of the literature, it is likely that many studies describing frailty in older

132 populations measure unspecified 'diabetes' rather than explicitly type 1 or type 2 diabetes. We will

133 therefore include any study which includes people with type 1, type 2 diabetes, or people with

134 unspecified diabetes. Given that frailty is a state associated with older age, and that type 2 diabetes

135 is both more prevalent than type 1 diabetes and becomes more prevalent with age, it is likely that

136 most (but not all) people with diabetes in the relevant populations will have type 2 diabetes. Studies

1
2
3 137 of type 1 diabetes, type 2 diabetes and those of unspecified diabetes will be considered separately in
4
5 138 any subsequent analysis.
6
7

8 139 We will include studies focusing purely on people with diabetes, or population-based studies that
9
10 140 report results for people with diabetes separately.
11
12

13 14 141 **Exposure**

15
16
17 142 The 'exposure' of interest is frailty. Many epidemiological measures and clinical tools have been
18
19 143 developed to identify frailty for research or clinical practice.(4)
20
21

22 144 To be eligible for inclusion, a study must use a measure which explicitly seeks to quantify frailty. We
23
24 145 will include measures developed primarily as epidemiological tools (e.g. the frailty phenotype frailty
25
26 146 index).(5, 6) We will also include measures designed primarily for clinical practice (e.g. the Clinical
27
28 147 Frailty Scale).(20)
29
30

31
32 148 Studies focusing solely on comorbidity (i.e. no additional measures to identify 'frailty') will be
33
34 149 excluded unless these are explicitly operationalised as a 'frailty index'. In this case studies would
35
36 150 generally be expected to include additional deficits (such as symptoms, functional limitations,
37
38 151 laboratory measures etc.). Studies which use a single parameter as a proxy for frailty (e.g. grip
39
40 152 strength alone, self-rated health) will be excluded.
41
42

43 44 153 **Comparator**

45
46
47 154 Studies that report the prevalence of frailty will be eligible for inclusion if they report the prevalence
48
49 155 of frailty in diabetes only. Studies should report the number or proportion of participants with and
50
51 156 without frailty (or with varying degrees of frailty, depending on the measure used).
52
53

54
55 157 For assessing the association between frailty and clinical outcomes in the context of diabetes,
56
57 158 studies should report the association with the outcome in the presence of absence of frailty (if a
58
59 159 binary or categorical measure is used) or by degree of frailty.
60

160 Outcomes

161 Outcomes of interest are summarized in table 1. We will include studies assessing any of these
 162 outcomes as long as the association is specifically quantified in people with diabetes and frailty.

163 Setting

164 We will include studies of community-dwelling patients, outpatient populations or hospital
 165 inpatients.

166 For the purposes of this review, given the focus on frailty, people living in long-term care facilities
 167 (e.g. care-homes, nursing-homes) will be considered to be 'community-dwelling'. Therefore, any
 168 study including, or specifically recruiting, nursing home residents will be eligible for inclusion.

169 Identification of studies

170 Electronic searches

171 Medline, Embase, and Web of Science (Core collection) databases will be search using a combination
 172 of Medical Subject Headings (MeSH) and keyword searches. The terms used for the medline search
 173 are shown in table 2. These terms will be adapted for the other databases. Searches will be from
 174 2000 to November 2019. The year 2000 was chosen as the start date as the first seminal paper
 175 operationalising the concept of frailty in an epidemiological study was published in 2001. Articles
 176 published prior to this date are therefore unlikely to be relevant. No language restriction will be
 177 applied to the search, but only English language articles will be included at the screening level.

Table 2: Medline Search

- | |
|-----------------------|
| 1. Exp Frailty/ |
| 2. Exp Frail Elderly/ |

3. Frail*.tw
4. 1 or 2 or 3
5. Exp Diabetes Mellitus
6. Diabet*.tw
7. (IDDM or NIDDM or MODY or T1DM, or T2DM or T1D or T2D).tw
8. (non insulin* depend* or non insulin depend* or non insulin?depend* or non insulin ?depend).tw
9. (insulin* depend* or insulin ?depend*).tw
10. 5 or 6 or 7 or 8 or 9
11. Exp Diabetes Insipidus/
12. Diabet* insipidus.tw
13. 11 or 12
14. 10 not 13
15. 4 and 14

178 Identifying additional articles

179 Electronic searches will be supplemented by hand searching reference lists of relevant articles. A
180 citation search of all relevant articles will also be carried out using the Web of Science citation search
181 tool.

182 Data collection and analysis

183 Selection of studies

184 Two reviewers, working independently, will screen all titles and abstracts of records identified in the
185 database searches. PICOS criteria outlined above will be used to determine eligibility. Where there is
186 disagreement, studies will be retained for full-text screening.

187 Full texts of all potentially eligible studies will be screened independently by two reviewers.

188 Disagreements about eligibility will be resolved by consensus, involving a third reviewer where
189 necessary.

190 Data extraction

191 A standard data extraction form will be designed and piloted before being applied to each of the
192 included studies. Extracted data will include:

193 Study details

- 194 • Author
- 195 • Year
- 196 • Location
- 197 • Setting (community, outpatient, residential care)
- 198 • Method of recruitment (e.g. random sample, postal invitation, consecutive patients)
- 199 • Method of assessment (face-to-face, survey, linkage to healthcare records)

200 Population

- 201 • Age
- 202 • Sex
- 203 • Ethnicity

- 1
2
3 204 • Socioeconomic status
4
5 205 • Comorbidities
6
7
8 206 • Medications
9
10 207 • Social circumstances (e.g. living independently, requiring carers, family support etc)
11
12 208 • Smoking status
13
14
15 209 • Physical activity
16
17 210 Diabetes details
18
19
20 211 • Type of diabetes (type 1, type 2 or unspecified)
21
22
23 212 • Method of confirmation (self-report, medical records, clinical assessment)
24
25 213 • Measure of control (e.g. HbA1c)
26
27 214 • Medication (e.g. proportion taking insulin, oral antidiabetics etc.)
28
29 215 • Presence and severity of complications (e.g. retinopathy, nephropathy, neuropathy,
30
31 ulceration, Charcot arthropathy)
32 216
33
34 217 Frailty definition
35
36
37 218 • Frailty measure used
38
39 219 • Definitions for each component of the frailty measure (e.g. cut-points used for continuous
40
41 measures, method of assessment (questionnaire, interview etc.))
42 220
43
44 221 Frailty prevalence
45
46
47 222 Outcomes (generic):
48
49
50 223 • Mortality
51
52 224 • Major Adverse Cardiovascular Events
53
54 225 • Hospital admission
55
56 226 • Admission to long-term care facility
57
58 227 • Falls
59
60

228 • Number of clinic attendances

229 • Quality of life

230 • Disability/functional status

231 Outcomes (diabetes specific):

232 • HbA1c (cross sectional association, or longitudinal)

233 • Glycaemic variability

234 • Hypoglycaemic episodes

235 • Diabetic retinopathy (cross sectional association, or longitudinal)

236 • Diabetic nephropathy (cross sectional association, or longitudinal)

237 • Diabetic foot complications (cross sectional association, or longitudinal)

238 • Treatment burden (e.g. Diabetic Treatment Burden Questionnaire)

239 For each outcome reported we will record

240 • The association between frailty and the outcome (e.g. prevalence, odds ratio, hazard ratio
241 etc.)

242 • Adjustment for any potential confounders

243 • Length of follow-up over which the outcome was assessed

244 • Method of analysis of competing risks when assessing each outcome

245 Assessment of methodological quality

246 The Newcastle-Ottawa scale will be used to assess the risk of bias for each study.(21) This scale is
247 widely used for the assessment of observational studies. Where studies are purely cross-sectional,
248 an adapted version of the Newcastle-Ottawa scale will be applied to assess risk of bias in selection,
249 comparability, and exposure. In assessing the comparability of frail/non-frail groups, age will be
250 taken as the most important factor for which studies should account.

251 Data synthesis

252 The appropriate method of data synthesis will be determined after assessment of the heterogeneity
253 of the included studies, in terms of population selection and demographics, frailty definition, and
254 method of outcome assessment.

255 If appropriate, we will combine these in a random effects meta-analysis (anticipating heterogeneity
256 in the true association). As well as a pooled estimate and 95% confidence intervals, we will also
257 calculate the prediction interval to assess the range of plausible estimates from the observed data.
258 Heterogeneity will be quantified using the I^2 statistic. Where heterogeneity is present, we will
259 attempt to explore potential sources of heterogeneity using subgroup analyses (e.g. by method of
260 determining frailty, age of sample population, method of outcome assessment). By doing so, we
261 propose to explore factors that may influence the estimates reported in observational studies in the
262 presence of heterogeneity, rather than provide a definitive single estimate.(22)

263 Only those studies that are judged to be sufficiently comparable will be included in meta-analyses.
264 For outcomes where there are too few studies, or the included studies are too heterogenous to
265 permit a meaningful meta-analysis (for example, in terms of outcome definition or method of
266 assessing frailty), we will perform a narrative synthesis of the study findings. This will report the
267 methods used to identify frailty along with the prevalence and association with outcomes, to explore
268 the impact of the method of assessment on the observed relationship. This will be reported
269 alongside detail of the recruitment strategy, age profile, and characteristics of each sample included.

270 Ethics and dissemination

271 This systematic review will provide an overview of the prevalence of frailty in diabetes, and the
272 relationship between frailty and adverse health outcomes in people with diabetes.

273 As the prevalence of both frailty and diabetes increase, it will become increasingly important for
274 clinical guidelines for the treatment of diabetes to explicitly consider the needs of people living with
275 frailty. Quantifying the prevalence of frailty in diabetes will allow the scale of this challenge to be
276 better appreciated. By including any reported definition of frailty within our inclusion criteria, this
277 review will demonstrate which of the wide range of frailty instruments and measures have been
278 used to study frailty in diabetes. It will also be possible to compare if and how prevalence and
279 association with outcomes differs depending on the frailty definition used.

280 Given the likely heterogeneity in frailty definitions, as well as inherent differences in the populations
281 studied, it may not be possible to undertake a meta-analysis of the findings of this review. If this is
282 the case, we propose to conduct a detailed narrative synthesis, systematically describing and
283 synthesizing details of the populations under study as well as the details of frailty definitions used.

284 We also propose to search for and extract data for a wide range of clinical outcomes. Given the
285 multidimensional nature of frailty, and the vulnerability to decompensation that is inherent to any
286 frailty definition, it is likely that frailty will be associated with a range of adverse outcomes. The
287 challenge in translating these associations into meaningful recommendations is understanding the
288 balance of these risks, and how they might inform clinical decisions and recommendations. The
289 balance of risks in diabetes, and treatment priorities, may differ depending on the degree of frailty
290 experienced by an individual. The associations may also differ in their nature or magnitude
291 depending on the method used to identify frailty. This review will aim to provide an overview of
292 what is known about the relationship between frailty and both generic and disease specific

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

293 outcomes. This is likely to inform priorities for future research into the consequences of frailty in
294 diabetes.
295 As this project is a systematic review, ethical approval is not required. Patients or the public were
296 not involved in the development of this protocol.

For peer review only

297 **Author contributions**

298 All authors (PH, IF, NC, DM and FM) contributed to the conception and design of the proposed study.
299 PH, DM and FM developed the data sources and search strategy. PH, IF, NC, DM and FM refined the
300 inclusion criteria. PH, IF, NC, DM and FM developed the data extraction template which was piloted
301 by PH, IF and NC. PH and IF wrote the first draft. All authors critically reviewed this and subsequent
302 drafts. All authors approved the final version of the manuscript for submission. FM is the guarantor
303 of the review. All authors accept accountability for the accuracy of the protocol.

304 **Funding statement**

305 Dr Peter Hanlon was funded by a Medical Research Council Clinical Research Training Fellowship
306 (Grant reference MR/S021949/1) entitled "Understanding prevalence and impact of frailty in chronic
307 disease and implications for clinical management. The funder had no role in protocol development.

308 **Competing interests statement**

309 The authors declare no competing interests.

310

311 **References**

- 312 1. Sinclair AJ, Rodriguez-Mañas L. Diabetes and Frailty: Two Converging Conditions? *Canadian*
313 *Journal of Diabetes*. 2016;40(1):77-83.
- 314 2. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The Lancet*.
315 2013;381(9868):752-62.
- 316 3. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for
317 clinical practice and public health. *The Lancet*. 2019;394(10206):1365-75.
- 318 4. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, Singh-Manoux A, et al. Measures of
319 frailty in population-based studies: an overview. *BMC Geriatrics*. 2013;13(1):64.
- 320 5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older
321 Adults: Evidence for a Phenotype. *The Journals of Gerontology: Series A*. 2001;56(3):M146-M57.
- 322 6. Rockwood K, Mitnitski A. Frailty in Relation to the Accumulation of Deficits. *The Journals of*
323 *Gerontology: Series A*. 2007;62(7):722-7.
- 324 7. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating
325 a frailty index. *BMC Geriatrics*. 2008;8(1):24.
- 326 8. Kotsani M, Chatziadamidou T, Economides D, Benetos A. Higher prevalence and earlier
327 appearance of geriatric phenotypes in old adults with type 2 diabetes mellitus. *Diabetes Research*
328 *and Clinical Practice*. 2018;135:206-17.
- 329 9. Thein FS, Li Y, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Physical frailty and cognitive impairment is
330 associated with diabetes and adversely impact functional status and mortality. *Postgraduate*
331 *Medicine*. 2018;130(6):561-7.
- 332 10. Castro-Rodríguez M, Carnicero JA, Garcia-Garcia FJ, Walter S, Morley JE, Rodríguez-Artalejo
333 F, et al. Frailty as a Major Factor in the Increased Risk of Death and Disability in Older People With
334 Diabetes. *Journal of the American Medical Directors Association*. 2016;17(10):949-55.
- 335 11. Hanlon P, Hannigan L, Fischbacher C, Welton N, Dias S, Mair F, et al. Representation of
336 people with comorbidity and multimorbidity in clinical trials of novel drug therapies; an individual-
337 level participant data analysis. *BMC Medicine* (in press). 2019.
- 338 12. Yoon JW, Ha Y-C, Kim KM, Moon JH, Choi SH, Lim S, et al. Hyperglycemia Is Associated with
339 Impaired Muscle Quality in Older Men with Diabetes: The Korean Longitudinal Study on Health and
340 Aging. *Diabetes Metab J*. 2016;40(2):140-6.
- 341 13. Maggi S, Noale M, Gallina P, Marzari C, Bianchi D, Limongi F, et al. Physical disability among
342 older Italians with diabetes. The ILSA Study. *Diabetologia*. 2004;47(11):1957-62.
- 343 14. Scherthaner G, Scherthaner-Reiter MH. Diabetes in the older patient: heterogeneity
344 requires individualisation of therapeutic strategies. *Diabetologia*. 2018;61(7):1503-16.
- 345 15. Formiga F, Franch-Nadal J, Rodriguez L, Ávila L, Fuster E. Inadequate glycaemic control and
346 therapeutic management of adults over 65 years old with type 2 diabetes mellitus in Spain. *The*
347 *journal of nutrition, health & aging*. 2017;21(10):1365-70.
- 348 16. Braun AK, Kubiak T, Kuntsche J, Meier-Höfig M, Müller UA, Feucht I, et al. SGS: a structured
349 treatment and teaching programme for older patients with diabetes mellitus—a prospective
350 randomised controlled multi-centre trial. *Age and ageing*. 2009;38(4):390-6.
- 351 17. Quartuccio M, Buta B, Kalyani RR. Comparative effectiveness for glycemic control in older
352 adults with diabetes. *Current geriatrics reports*. 2017;6(3):175-86.
- 353 18. Ida S, Kaneko R, Imataka K, Murata K. Relationship between frailty and mortality,
354 hospitalization, and cardiovascular diseases in diabetes: a systematic review and meta-analysis.
355 *Cardiovascular Diabetology*. 2019;18(1):81.
- 356 19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews
357 and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.

- 1
2
3 358 20. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical
4 359 measure of fitness and frailty in elderly people. Canadian Medical Association Journal.
5 360 2005;173(5):489.
6 361 21. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality
7 362 of nonrandomized studies in meta-analyses. European Journal of Epidemiology. 2010;25(9):603-5.
8 363 22. Mueller M, D'Addario M, Egger M, Cevallos M, Dekkers O, Mugglin C, et al. Methods to
9 364 systematically review and meta-analyse observational studies: a systematic scoping review of
10 365 recommendations. BMC Medical Research Methodology. 2018;18(1):44.

11
12
13 366
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

1 **Registration**
2
3

4 [#2](#) If registered, provide the name of the registry (such as 3
5
6 PROSPERO) and registration number
7
8

9
10 **Authors**
11

12
13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all 1
14
15 protocol authors; provide physical mailing address of
16
17 corresponding author
18

19
20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the 18
21
22 guarantor of the review
23
24

25
26 **Amendments**
27

28
29 [#4](#) If the protocol represents an amendment of a previously n/a
30
31 completed or published protocol, identify as such and list
32
33 changes; otherwise, state plan for documenting important
34
35 protocol amendments
36
37

38
39 **Support**
40

41
42 **Sources** [#5a](#) Indicate sources of financial or other support for the review 18
43
44

45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor 18
46
47

48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or 18
49
50 funder
51 institution(s), if any, in developing the protocol
52

53 **Introduction**
54
55
56
57
58
59
60

1	Rationale	#6	Describe the rationale for the review in the context of what is	4,5
2			already known	
3				
4				
5				
6	Objectives	#7	Provide an explicit statement of the question(s) the review	6
7			will address with reference to participants, interventions,	
8			comparators, and outcomes (PICO)	
9				
10				
11				
12				
13				
14	Methods			
15				
16				
17	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	7-10
18			design, setting, time frame) and report characteristics (such	
19			as years considered, language, publication status) to be	
20			used as criteria for eligibility for the review	
21				
22				
23				
24				
25				
26				
27	Information	#9	Describe all intended information sources (such as	10
28			electronic databases, contact with study authors, trial	
29	sources		registers or other grey literature sources) with planned dates	
30			of coverage	
31				
32				
33				
34				
35				
36				
37	Search strategy	#10	Present draft of search strategy to be used for at least one	10-11
38			electronic database, including planned limits, such that it	
39			could be repeated	
40				
41				
42				
43				
44				
45	Study records -	#11a	Describe the mechanism(s) that will be used to manage	11
46	data management		records and data throughout the review	
47				
48				
49				
50	Study records -	#11b	State the process that will be used for selecting studies	11-12
51	selection process		(such as two independent reviewers) through each phase of	
52			the review (that is, screening, eligibility and inclusion in	
53			meta-analysis)	
54				
55				
56				
57				
58				
59				
60				

1	Study records -	#11c	Describe planned method of extracting data from reports	12-13
2				
3	data collection		(such as piloting forms, done independently, in duplicate),	
4				
5	process		any processes for obtaining and confirming data from	
6				
7			investigators	
8				
9				
10				
11	Data items	#12	List and define all variables for which data will be sought	12-13
12				
13			(such as PICO items, funding sources), any pre-planned	
14				
15			data assumptions and simplifications	
16				
17				
18				
19	Outcomes and	#13	List and define all outcomes for which data will be sought,	13-14
20				
21	prioritization		including prioritization of main and additional outcomes, with	
22				
23			rationale	
24				
25				
26	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	14
27				
28	individual studies		individual studies, including whether this will be done at the	
29				
30			outcome or study level, or both; state how this information	
31				
32			will be used in data synthesis	
33				
34				
35				
36	Data synthesis	#15a	Describe criteria under which study data will be	14-15
37				
38			quantitatively synthesised	
39				
40				
41				
42	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	14-15
43				
44			planned summary measures, methods of handling data and	
45				
46			methods of combining data from studies, including any	
47				
48			planned exploration of consistency (such as I ² , Kendall's τ)	
49				
50				
51	Data synthesis	#15c	Describe any proposed additional analyses (such as	n/a
52				
53			sensitivity or subgroup analyses, meta-regression)	
54				
55				
56				
57				
58				
59				
60				

1	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	15
2			of summary planned	
3				
4				
5				
6	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	n/a
7			publication bias across studies, selective reporting within	
8			studies)	
9				
10				
11				
12				
13				
14	Confidence in	#17	Describe how the strength of the body of evidence will be	n/a
15	cumulative		assessed (such as GRADE)	
16	evidence			
17				
18				
19				
20				
21				

22 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
23 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool
24 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

The identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: A systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037476.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Apr-2020
Complete List of Authors:	Hanlon, Peter; University of Glasgow Institute of Health and Wellbeing, ; Fauré, Isabella ; University of Glasgow Institute of Health and Wellbeing Corcoran, Neave ; University of Glasgow Institute of Health and Wellbeing Butterly, Elaine; University of Glasgow Institute of Health and Wellbeing Lewsey, Jim; University of Glasgow Institute of Health and Wellbeing McAllister, David; University of Glasgow Institute of Health and Wellbeing Mair, Frances; University of Glasgow Institute of Health and Wellbeing
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	General practice / Family practice, Geriatric medicine
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, EPIDEMIOLOGY, GERIATRIC MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: A systematic review protocol

Authors:

Dr Peter Hanlon¹
Ms Isabella Fauré¹
Dr Neave Corcoran¹
Dr Elaine Butterly²
Professor Jim Lewsey³
Dr David McAllister^{2*}
Professor Frances S Mair^{1*}

*Joint senior author

Affiliations:

1. General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
2. Public Health, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
3. Health Economics and Health Technology Assessment, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

Corresponding author:

Dr Peter Hanlon
General Practice and Primary Care
Institute of Health and Wellbeing
University of Glasgow
1 Horselethill Road
Glasgow, G12 9LX

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

28 Peter.hanlon@glasgow.ac.uk

29 +44 141 330 8383

30 Word count: 2311

31 **Keywords:** Frailty, Diabetes Mellitus, Systematic review, Protocol

For peer review only

32 Abstract

33 Introduction:

34 Diabetes mellitus is common and growing in prevalence, and an increasing proportion of people with
35 diabetes are living to older age. Frailty is therefore becoming an important concept in diabetes.
36 Frailty is associated with older age and describes a state of increased susceptibility to
37 decompensation in response to physiological stress. A range of measures have been used to quantify
38 frailty. This systematic review aims to identify measures used to quantify frailty in people with
39 diabetes (type 1, type 2, or unspecified); to summarize the prevalence of frailty in diabetes; and to
40 describe the relationship between frailty and adverse clinical outcomes in people with diabetes.

41 Methods and analysis:

42 Three electronic databases (Medline, Embase and Web of Science) will be searched from 2000 to
43 November 2019 and supplemented by citation searching of relevant articles and hand-searching of
44 reference lists. Two reviewers will independently review titles, abstracts and full texts. Inclusion
45 criteria include: (1) Adults with diabetes mellitus (type 1, type 2, or unspecified); (2) Quantify frailty
46 using any validated frailty measure; (3) Report the prevalence of frailty and/or the association
47 between frailty and clinical outcomes in people with diabetes; (4) Studies that assess generic (e.g.
48 mortality, hospital admission, falls) or diabetes specific outcomes (e.g. hypoglycaemic episodes,
49 cardiovascular events, diabetic nephropathy, diabetic retinopathy); (5) Cross-sectional and
50 longitudinal observational studies. Study quality will be assessed using the Newcastle-Ottawa scale
51 for observational studies. Clinical and methodological heterogeneity will be assessed, and a random
52 effects meta-analysis performed if appropriate. Otherwise, a narrative synthesis will be performed.

53 Ethics and dissemination:

54 This study will summarise current knowledge about measurement, prevalence and clinical
55 implications of frailty in diabetes. This will inform future research and clinical guidelines to assess the
56 balance of risks and treatment priorities in the growing number of people living with frailty and
57 diabetes.

58 Registration number:

59 PROSPERO CRD42020163109.

60

61 Strengths and Limitations

62 This systematic review will provide a comprehensive overview of the prevalence and implications of
63 frailty in people with diabetes.

64 We will include a broad range of frailty definitions and clinical outcomes relevant to diabetes.

65 There is likely to be significant heterogeneity between population characteristics and frailty
66 definitions in included studies.

67 By including only English language articles, there is a chance of language bias in the results of the
68 review.

69 We exclude Grey literature, which may lead to publication bias.

70 Introduction

71 Diabetes mellitus (hereafter “diabetes”) describes a collection of metabolic disorders, with distinct
72 pathological processes, that are characterised by elevated blood glucose.(1) The most common are
73 type 1 diabetes and type 2 diabetes. Type 1 diabetes is caused by insulin deficiency resulting from
74 destruction of pancreatic beta cells, usually by an autoimmune process.(2) Type 2 diabetes describes
75 a relative insulin deficiency caused by beta-cell dysfunction and insulin resistance of target
76 organs.(2) Both are associated with a range of complications including macrovascular disease,
77 retinopathy, nephropathy and neuropathy.(3) The prevalence of diabetes is increasing across the
78 world.(4) Population demographics are also shifting towards an ageing population.(5) Among people
79 above the age of 65, the prevalence of diabetes can be as high as 30%.(6) Diabetes in older people is
80 therefore a growing clinical and public health priority. One factor with important implications for
81 disease management in older age is frailty.(7)

82 Frailty is a state characterised by reduced functional reserve across multiple physiological
83 systems.(8) People living with frailty have impaired resolution of homeostasis following physiological
84 stressors.(8) Frailty therefore carries an increased risk of a range of adverse health outcomes, such
85 as falls, cognitive decline, hospital admission and mortality.(9) Frailty is widely recognised to be a
86 multidimensional and dynamic state, associated with older age and with a range of non-
87 communicable diseases.(9) However, there is no single universally accepted operational definition of
88 frailty. Rather, a wide range of definitions have been utilized in both research and clinical
89 practice.(10)

90 The two dominant paradigms in the frailty literature are the frailty phenotype and the frailty index.
91 The frailty phenotype, described by *Fried et al* in 2001, defines frailty as the presence of three or
92 more out of five features: low hand-grip strength, unintentional weight loss, low physical activity,
93 exhaustion, and slow walking pace.(11) The presence of one or two of these features is classified as

1
2
3 94 a pre-frail state. The frailty index, described by Rockwood and Mitnitski in 2007, is based on a
4
5 95 cumulative-deficit model of frailty whereby frailty is identified by counting the number of health
6
7 96 'deficits' present in an individual.(12) At least 30 deficits are required to construct a frailty index, all
8
9
10 97 of which must increase in prevalence with age, be associated with poor health, and not saturate too
11
12 98 early (i.e. be universally present among older people).(13) Both the frailty phenotype and frailty
13
14 99 index have been associated with adverse health outcomes in a range of older populations, however
15
16 100 the populations identified as frail by each are different.(14) Since their original description, a wide
17
18 101 range of other frailty instruments, as well as adaptations of the frailty index and phenotype, have
19
20 102 been developed for both epidemiological studies and for clinical practice.(9, 10)
21
22

23
24 103 The relationship between diabetes and frailty is complex. Diabetes is associated with a higher
25
26 104 prevalence of frailty.(15-18) Both type 1 and type 2 diabetes lead to microvascular and
27
28 105 macrovascular complications which have important physical, cognitive and functional consequences,
29
30 106 that may contribute to the development of frailty.(6) Hyperglycaemia is also recognized to directly
31
32 107 impact muscle mass and quality, exacerbating age-related sarcopenia and, in turn, physical
33
34 108 function.(19) However, the association between frailty and poor functional outcomes in people with
35
36 109 diabetes is only partially explained by direct complications of diabetes.(17, 20)
37
38
39

40 110 The importance of frailty in the context of diabetes is increasingly recognised in clinical guidelines.(7)
41
42 111 Specifically, higher HbA1c targets are recommended in the context of frailty, in part due to the
43
44 112 increased risks associated with hypoglycaemia.(21) Despite this, up to 40% of older people with
45
46 113 diabetes may be over-treated (with HbA1c <7%).(22, 23) Conversely, poor glycaemic control and
47
48 114 associated vascular complications risk causing, or accelerating the progression of, frailty.(24)
49
50

51
52 115 One recent meta-analysis demonstrated a consistent relationship between frailty and mortality,
53
54 116 hospitalisation, and cardiovascular events in the context of diabetes.(25) We are not aware of any
55
56 117 systematic review to assess the prevalence of frailty in diabetes, or to consider a broader range of
57
58 118 outcomes relevant to the management of diabetes. Given the risks of both over- and under-
59
60

1
2
3 119 treatment of diabetes in the context of frailty, understanding the range of potential associations is
4
5 120 required to inform clinical decisions and to underpin future research.
6
7
8 121 To enhance understanding of the implications and management of diabetes within an ageing
9
10 122 population, it is important to fully describe the association between diabetes and frailty. Given the
11
12 123 risks of both over- and under-treatment of diabetes in the context of frailty, it is important to
13
14 124 understand the associations between frailty and a range of potential outcomes in diabetes. This
15
16 125 includes generic outcomes such as mortality and hospitalisation and disability and disease specific
17
18 126 outcomes such as retinopathy, neuropathy, and hypoglycaemic events. An understanding of the
19
20 127 range and complexity of these associations is required to inform clinical decisions around treatment
21
22 128 priorities and to underpin future research. This includes quantifying the prevalence of frailty in
23
24 129 people with diabetes, and the impact that different frailty definitions might have on this prevalence.
25
26 130 This manuscript describes the protocol of a systematic review aiming to synthesise existing evidence
27
28 131 relating to these questions.
29
30
31
32
33

34 132 Aims

35
36
37 133 The systematic review will aim to:

- 38
39
40 134 • Identify which frailty measures have been used to assess frailty in people with diabetes
41
42 (type1, type 2, or mixed/unspecified)
 - 43 135 • Quantify the prevalence of frailty among people with diabetes
 - 44
45 136 • Describe the association between frailty and both generic (e.g. mortality) and disease
46
47 137 specific (e.g. hypoglycaemia) clinical outcomes in the context of diabetes
48
49 138
- 50
51
52
53
54
55
56
57
58
59
60

139 **Methods and analysis**

140 This protocol is registered with PROSPERO (CRD42020163109). The review will be conducted and
 141 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 142 (PRISMA) statement.⁽²⁶⁾ Where a meta-analysis is undertaken, we will report findings according to
 143 the Meta-analyses Of Observational Studies in Epidemiology checklist.

144 **Eligibility criteria for inclusion**

145 The eligibility criteria for this review are summarized in table 1 and explained in more detail below.

Table 1. Inclusion Criteria	
PECOS component	Description
Population	Adults (≥ 18 years old) Diabetes (type 1, type 2, or unspecified)
Exposure	Frailty as assessed by any frailty measure
Comparator	People with diabetes not classified as frail
Outcomes	Generic: <ul style="list-style-type: none"> • Mortality • Major Adverse Cardiovascular Events • Hospital admission • Admission to long-term care facility • Falls • Number of clinic attendances • Quality of life • Disability/functional status Diabetes specific:

	<ul style="list-style-type: none"> • HbA1c (cross sectional association, or longitudinal) • Glycaemic variability • Hypoglycaemic episodes • Diabetic retinopathy (cross sectional association, or longitudinal) • Diabetic nephropathy (cross sectional association, or longitudinal) <ul style="list-style-type: none"> ○ Include development of end-stage renal disease • Diabetic foot complications (cross sectional association, or longitudinal) • Treatment burden (e.g. Diabetic Treatment Burden Questionnaire)
Settings	Community (including care home/nursing home) Outpatient clinic Inpatient
Study design	Cross sectional or longitudinal Cohort
Other exclusions	Conference abstracts, letters, review articles, intervention studies, Grey literature

146 Population

147 We will include studies analysing data from people with any form of diabetes.

148 While frailty is a state associated with increasing age, there is evidence that frailty is identifiable in
149 relatively younger people, particularly in certain contexts such as multimorbidity (2 or more co-
150 existing long-term conditions) or in areas of high socioeconomic deprivation. We will therefore
151 include studies of adults of any age (≥ 18 years). However, we anticipate that most studies will focus
152 predominantly on 'older' populations.

1
2
3 153 From an initial scoping of the literature, it is likely that many studies describing frailty in population-
4
5 154 based studies measure unspecified 'diabetes' rather than explicitly type 1 or type 2 diabetes. We will
6
7 155 therefore include any study which includes people with type 1, type 2 diabetes, or people with
8
9 156 unspecified diabetes. Given that frailty is a state associated with older age, and that type 2 diabetes
10
11 157 is both more prevalent than type 1 diabetes and becomes more prevalent with age, it is likely that
12
13 158 most (but not all) people with diabetes in the relevant populations will have type 2 diabetes. Studies
14
15 159 of type 1 diabetes, type 2 diabetes and those of unspecified diabetes will be considered separately in
16
17 160 any subsequent analysis.

18
19
20
21 161 We will include studies focusing purely on people with diabetes, or population-based studies that
22
23 162 report results for people with diabetes separately.

24 25 26 27 163 Exposure

28
29
30 164 The 'exposure' of interest is frailty. Many epidemiological measures and clinical tools have been
31
32 165 developed to identify frailty for research or clinical practice.(10)

33
34
35 166 To be eligible for inclusion, a study must use a measure which explicitly seeks to quantify frailty. We
36
37 167 will include measures developed primarily as epidemiological tools (e.g. the frailty phenotype frailty
38
39 168 index).(11, 12) We will also include measures designed primarily for clinical practice (e.g. the Clinical
40
41 169 Frailty Scale).(27)

42
43
44
45 170 Studies focusing solely on comorbidity (i.e. no additional measures to identify 'frailty') will be
46
47 171 excluded unless these are explicitly operationalised as a 'frailty index'. In this case studies would
48
49 172 generally be expected to include additional deficits (such as symptoms, functional limitations,
50
51 173 laboratory measures etc.). Studies which use a single parameter as a proxy for frailty (e.g. grip
52
53 174 strength alone, self-rated health) will be excluded.

175 **Comparator**

176 Studies that report the prevalence of frailty will be eligible for inclusion if they report the prevalence
177 of frailty in diabetes only. Studies should report the number or proportion of participants with and
178 without frailty (or with varying degrees of frailty, depending on the measure used).

179 For assessing the association between frailty and clinical outcomes in the context of diabetes,
180 studies should report the association between frailty and the outcome of interest. This may be
181 reported either as the association with the presence or absence of frailty (in the case of a binary or
182 categorical measure) or the association between the degree of frailty and the outcome (in the case
183 of a continuous or ordinal measure of frailty).

184 **Outcomes**

185 Outcomes of interest are summarized in table 1. We will include studies assessing any of these
186 outcomes as long as the association is specifically quantified in people with diabetes and frailty.

187 **Setting**

188 We will include studies of community-dwelling patients, outpatient populations or hospital
189 inpatients.

190 For the purposes of this review, given the focus on frailty, people living in long-term care facilities
191 (e.g. care-homes, nursing-homes) will be considered to be 'community-dwelling'. Therefore, any
192 study including, or specifically recruiting, nursing home residents will be eligible for inclusion.

1
2
3
4 193 Identification of studies
5
6
7

8 194 Electronic searches
9

10
11 195 Medline, Embase, and Web of Science (Core collection) databases will be search using a combination
12
13 196 of Medical Subject Headings (MeSH) and keyword searches (Supplementary file 1). The terms used
14
15 197 for the medline search are shown in table 2. These terms will be adapted for the other databases.
16
17 198 Searches will be from 2000 to November 2019. The year 2000 was chosen as the start date as the
18
19 199 first seminal paper operationalising the concept of frailty in an epidemiological study was published
20
21 200 in 2001. Articles published prior to this date are therefore unlikely to be relevant. No language
22
23 201 restriction will be applied to the search, but only English language articles will be included at the
24
25 202 screening level. This language restriction is a pragmatic decision, however we acknowledge that this
26
27 203 may lead to a language bias in the results, potentially excluding relevant studies published in other
28
29 204 languages.
30
31
32
33

34 Table 2: Medline Search
35

- | |
|--|
| <p>36 1. Exp Frailty/
37
38 2. Exp Frail Elderly/
39
40 3. Frail*.tw
41
42 4. 1 or 2 or 3
43
44 5. Exp Diabetes Mellitus
45
46 6. Diabet*.tw
47
48 7. (IDDM or NIDDM or MODY or T1DM, or T2DM or T1D or T2D).tw
49
50 8. (non insulin* depend* or non insulin depend* or non insulin?depend* or non
51
52 insulin ?depend).tw
53
54 9. (insulin* depend* or insulin ?depend*).tw
55
56 10. 5 or 6 or 7 or 8 or 9
57
58
59
60</p> |
|--|

1
2
3 11. Exp Diabetes Insipidus/
4

5 12. Diabet* insipidus.tw
6

7 13. 11 or 12
8

9 14. 10 not 13
10

11 15. 4 and 14
12
13
14
15
16

17 205 Identifying additional articles

18
19
20 206 Electronic searches will be supplemented by hand searching reference lists of relevant articles. A
21
22
23 207 citation search of all relevant articles will also be carried out using the Web of Science citation search
24
25 208 tool.
26
27

28 209 Data collection and analysis

29 210 Selection of studies

30
31
32
33
34
35
36 211 Two reviewers, working independently, will screen all titles and abstracts of records identified in the
37
38 212 database searches. PECOS criteria outlined above will be used to determine eligibility. Where there
39
40 213 is disagreement, studies will be retained for full-text screening.
41
42

43 214 Full texts of all potentially eligible studies will be screened independently by two reviewers.

44
45 215 Disagreements about eligibility will be resolved by consensus, involving a third reviewer where
46
47 216 necessary.
48
49

50 217 Data extraction

51
52
53
54 218 A standard data extraction form will be designed and piloted before being applied to each of the
55
56 219 included studies. Extracted data will include:

57
58
59 220 Study details
60

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

- 221 • Author
- 222 • Year
- 223 • Location
- 224 • Setting (community, outpatient, residential care)
- 225 • Method of recruitment (e.g. random sample, postal invitation, consecutive patients)
- 226 • Method of assessment (face-to-face, survey, linkage to healthcare records)
- 227 Population
- 228 • Age
- 229 • Sex
- 230 • Ethnicity
- 231 • Socioeconomic status
- 232 • Comorbidities
- 233 • Medications
- 234 • Social circumstances (e.g. living independently, requiring carers, family support etc)
- 235 • Smoking status
- 236 • Physical activity
- 237 Diabetes details
- 238 • Type of diabetes (type 1, type 2 or unspecified)
- 239 • Method of confirmation (self-report, medical records, clinical assessment)
- 240 • Measure of control (e.g. HbA1c)
- 241 • Medication (e.g. proportion taking insulin, oral antidiabetics etc.)
- 242 • Presence and severity of complications (e.g. retinopathy, nephropathy, neuropathy,
243 ulceration, Charcot arthropathy)
- 244 Frailty definition

- 1
2
3 245 • Frailty measure used
4
5 246 • Definitions for each component of the frailty measure (e.g. cut-points used for continuous
6
7 247 measures, method of assessment (questionnaire, interview etc.))
8
9

10 248 Frailty prevalence
11
12

13 249 Outcomes (generic):
14
15

- 16 250 • Mortality
17
18 251 • Major Adverse Cardiovascular Events
19
20 252 • Hospital admission
21
22 253 • Admission to long-term care facility
23
24 254 • Falls
25
26 255 • Number of clinic attendances
27
28 256 • Quality of life
29
30 257 • Disability/functional status
31
32
33

34 258 Outcomes (diabetes specific):
35
36

- 37 259 • HbA1c (cross sectional association, or longitudinal)
38
39 260 • Glycaemic variability
40
41 261 • Hypoglycaemic episodes
42
43 262 • Diabetic retinopathy (cross sectional association, or longitudinal)
44
45 263 • Diabetic nephropathy (cross sectional association, or longitudinal)
46
47 264 • Diabetic foot complications (cross sectional association, or longitudinal)
48
49 265 • Treatment burden (e.g. Diabetic Treatment Burden Questionnaire)
50
51
52
53

54 266 As we include a wide range of outcomes, it is likely that the way outcomes are assessed will vary
55
56 267 depending on the outcome in question. Studies may also assess similar outcomes (e.g. hospital
57
58 268 admission) in different ways (e.g. number of admissions over specified follow-up, time to first
59
60

1
2
3 269 admission, presence of absence of admission during follow-up). For the outcomes listed above, we
4
5 270 will extract data regardless of the method of assessment. Heterogeneity in the way outcome data
6
7 271 were collected will be used to inform the approach to data synthesis (i.e. meta-analysis versus
8
9
10 272 narrative synthesis). For each outcome reported we will record

- 11
12
13 273 • The method of outcome assessment (e.g. linkage to healthcare records, face-to-face
14
15 274 assessment, questionnaire etc.)
16
17 275 • Method of analysis (e.g. time-to-event, mean difference etc.)
18
19 276 • The association between frailty and the outcome (e.g. prevalence, odds ratio, hazard ratio
20
21 277 etc.)
22
23
24 278 • Adjustment for any potential confounders
25
26 279 • Length of follow-up over which the outcome was assessed
27
28
29 280 • Method of analysis of competing risks when assessing each outcome.

30
31 281 Where available, we will also extract data on both relative (e.g. hazard ratios) and absolute (e.g.
32
33 282 events per 1000 people) associations with outcomes.

34 35 36 37 283 **Assessment of methodological quality**

38
39
40 284 The Newcastle-Ottawa scale will be used to assess the risk of bias for each study (Supplementary file
41
42 285 2).(28) This scale is widely used for the assessment of observational studies, and has frequently been
43
44 286 adapted to the context of specific systematic reviews. We have adapted the criteria in order to be
45
46 287 explicit about how the 'exposure assessment' related to frailty: specifically, awarding one point for
47
48 288 the use of a validated frailty assessment measure. For cross-sectional studies, only the first 5
49
50 289 elements of the scale were relevant to quality assessment (the remainder concerning the
51
52 290 longitudinal assessment of outcomes). We will use this subsection of the Newcastle-Ottawa scale to
53
54 291 assess the quality of cross-sectional studies to allow direct comparability with the baseline
55
56 292 assessments of longitudinal studies (from which we will also extract data on frailty prevalence). In
57
58
59
60

1
2
3 293 assessing the comparability of frail/non-frail groups, age will be taken as the most important factor
4
5 294 for which studies should account.
6
7
8

9 295 Data synthesis

10
11
12 296 The appropriate method of data synthesis will be determined after assessment of the heterogeneity
13
14 297 of the included studies, in terms of population selection and demographics, frailty definition, and
15
16 298 method of outcome assessment.
17
18

19
20 299 With regards to the prevalence of frailty, different frailty measures will be considered separately (i.e.
21
22 300 we will not perform a meta-analysis of frailty prevalence measured using different scales). We will
23
24 301 also consider community studies separately from studies focussing on outpatient clinic populations
25
26 302 (as these may represent people with more severe diabetes), inpatients or people living in residential
27
28 303 care. We will also assess the inclusion criteria and demographics of the sample population, with
29
30 304 particular attention to age (as frailty is strongly associated with age) and sex (as women tend to have
31
32 305 a higher prevalence of frailty than men) to determine the most appropriate method of synthesis.
33
34

35 306 Where samples have been drawn from populations with a markedly different age/sex structure, a
36
37 307 pooled estimate of the mean prevalence of frailty across these studies is unlikely to be a meaningful
38
39 308 summary. Similarly, other inclusion criteria used by the individual studies (such as excluding
40
41 309 'institutionalised' people, people with cognitive impairment, of people with impaired mobility
42
43 310 unable to attend an assessment) may disproportionately impact on the estimation of frailty
44
45 311 prevalence. The appropriateness, or otherwise, of a meta-analysis of frailty prevalence will be
46
47 312 judged only after examination of these aspects of the included studies.
48
49

50
51 313 For the assessment of outcomes, the approach to synthesis will also be judged based on
52
53 314 heterogeneity of the method of outcome assessment and the analytic approach. As above, different
54
55 315 frailty measures will be considered separately.
56
57
58
59
60

1
2
3 316 If appropriate, we will combine these in a random effects meta-analysis (anticipating heterogeneity
4
5 317 in the true association). As well as a pooled estimate and 95% confidence intervals, we will also
6
7 318 calculate the prediction interval to assess the range of plausible estimates from the observed data.
8
9
10 319 Heterogeneity will be quantified using the I^2 statistic. Where heterogeneity is present, we will
11
12 320 attempt to explore potential sources of heterogeneity using subgroup analyses (e.g. by method of
13
14 321 determining frailty, age of sample population, method of outcome assessment). By doing so, we
15
16 322 propose to explore factors that may influence the estimates reported in observational studies in the
17
18 323 presence of heterogeneity, rather than provide a definitive single estimate.(29) We will use funnel
19
20 324 plots to assess for potential publication bias.
21
22
23
24 325 Only those studies that are judged to be sufficiently comparable will be included in meta-analyses.
25
26 326 For outcomes where there are too few studies, or the included studies are too heterogenous to
27
28 327 permit a meaningful meta-analysis (for example, in terms of outcome definition or method of
29
30 328 assessing frailty), we will perform a narrative synthesis of the study findings. This will report the
31
32 329 methods used to identify frailty along with the prevalence and association with outcomes, to explore
33
34 330 the impact of the method of assessment on the observed relationship. This will be reported
35
36 331 alongside detail of the recruitment strategy, age profile, and characteristics of each sample included.
37
38
39

40 332 Patient and public involvement

41
42
43
44 333 No patients were involved in the development of this review.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

334 Ethics and dissemination

335 This systematic review will provide an overview of the prevalence of frailty in diabetes, and the
336 relationship between frailty and adverse health outcomes in people with diabetes.

337 As the prevalence of both frailty and diabetes increase, it will become increasingly important for
338 clinical guidelines for the treatment of diabetes to explicitly consider the needs of people living with
339 frailty.(7) Quantifying the prevalence of frailty in diabetes will allow the scale of this challenge to be
340 better appreciated. By including any reported definition of frailty within our inclusion criteria, this
341 review will demonstrate which of the wide range of frailty instruments and measures have been
342 used to study frailty in diabetes. It will also be possible to compare if and how prevalence and
343 association with outcomes differs depending on the frailty definition used.

344 Given the likely heterogeneity in frailty definitions, as well as inherent differences in the populations
345 studied, it may not be possible to undertake a meta-analysis of the findings of this review. If this is
346 the case, we propose to conduct a detailed narrative synthesis, systematically describing and
347 synthesizing details of the populations under study as well as the details of frailty definitions used.

348 We also propose to search for and extract data for a wide range of clinical outcomes. Given the
349 multidimensional nature of frailty,(8) and the vulnerability to decompensation that is inherent to any
350 frailty definition,(9) it is likely that frailty will be associated with a range of adverse outcomes. The
351 challenge in translating these associations into meaningful recommendations is understanding the
352 balance of these risks, and how they might inform clinical decisions and recommendations. The
353 balance of risks in diabetes, and treatment priorities, may differ depending on the degree of frailty
354 experienced by an individual. The associations may also differ in their nature or magnitude
355 depending on the method used to identify frailty. This review will aim to provide an overview of
356 what is known about the relationship between frailty and both generic and disease specific

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

357 outcomes. This is likely to inform priorities for future research into the consequences of frailty in
358 diabetes.
359 As this project is a systematic review, ethical approval is not required. Patients or the public were
360 not involved in the development of this protocol.

For peer review only

361 **Author contributions**

362 All authors (PH, IF, NC, EB, JL, DM and FM) contributed to the conception and design of the proposed
363 study. PH, DM and FM developed the data sources and search strategy. PH, IF, NC, DM and FM
364 refined the inclusion criteria. PH, IF, NC, DM and FM developed the data extraction template which
365 was piloted by PH, IF and NC. PH and IF wrote the first draft. All authors critically reviewed this and
366 subsequent drafts. All authors approved the final version of the manuscript for submission. FM is the
367 guarantor of the review. All authors accept accountability for the accuracy of the protocol.

368 **Funding statement**

369 Dr Peter Hanlon was funded by a Medical Research Council Clinical Research Training Fellowship
370 (Grant reference MR/S021949/1) entitled "Understanding prevalence and impact of frailty in chronic
371 disease and implications for clinical management. The funder had no role in protocol development.

372 **Competing interests statement**

373 The authors declare no competing interests.

374

375 **References**

- 376 1. Moini J. *Epidemiology of Diabetes*: Elsevier; 2019.
- 377 2. Ozougwu J, Obimba K, Belonwu C, Unakalamba C. The pathogenesis and pathophysiology of
378 type 1 and type 2 diabetes mellitus. *Journal of physiology and pathophysiology*. 2013;4(4):46-57.
- 379 3. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history
380 of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study
381 experience. *Diabetes*. 2006;55(5):1463-9.
- 382 4. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and
383 2030. *Diabetes research and clinical practice*. 2010;87(1):4-14.
- 384 5. United Nations. *World Population Ageing [Report] 2015* [Available from:
385 [https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.](https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf)
386 [pdf](https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf)].
- 387 6. Sinclair AJ, Rodriguez-Manas L. Diabetes and Frailty: Two Converging Conditions? *Canadian*
388 *journal of diabetes*. 2016;40(1):77-83.
- 389 7. Sinclair AJ, Abdelhafiz A, Dunning T, Izquierdo M, Manas LR, Bourdel-Marchasson I, et al. An
390 international position statement on the management of frailty in diabetes mellitus: summary of
391 recommendations 2017. *The Journal of frailty & aging*. 2018;7(1):10-20.
- 392 8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The Lancet*.
393 2013;381(9868):752-62.
- 394 9. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for
395 clinical practice and public health. *The Lancet*. 2019;394(10206):1365-75.
- 396 10. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, Singh-Manoux A, et al. Measures of
397 frailty in population-based studies: an overview. *BMC Geriatrics*. 2013;13(1):64.
- 398 11. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older
399 Adults: Evidence for a Phenotype. *The Journals of Gerontology: Series A*. 2001;56(3):M146-M57.
- 400 12. Rockwood K, Mitnitski A. Frailty in Relation to the Accumulation of Deficits. *The Journals of*
401 *Gerontology: Series A*. 2007;62(7):722-7.
- 402 13. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating
403 a frailty index. *BMC Geriatrics*. 2008;8(1):24.
- 404 14. Santos-Eggimann B, Sirven N. Screening for frailty: older populations and older individuals.
405 *Public health reviews*. 2016;37(1):7.
- 406 15. Kotsani M, Chatziadamidou T, Economides D, Benetos A. Higher prevalence and earlier
407 appearance of geriatric phenotypes in old adults with type 2 diabetes mellitus. *Diabetes Research*
408 *and Clinical Practice*. 2018;135:206-17.
- 409 16. Thein FS, Li Y, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Physical frailty and cognitive impairment is
410 associated with diabetes and adversely impact functional status and mortality. *Postgraduate*
411 *medicine*. 2018;130(6):561-7.
- 412 17. Castro-Rodriguez M, Carnicero JA, Garcia-Garcia FJ, Walter S, Morley JE, Rodriguez-Artalejo
413 F, et al. Frailty as a Major Factor in the Increased Risk of Death and Disability in Older People With
414 Diabetes. *Journal of the American Medical Directors Association*. 2016;17(10):949-55.
- 415 18. Hanlon P, Hannigan L, Fischbacher C, Welton N, Dias S, Mair F, et al. Representation of
416 people with comorbidity and multimorbidity in clinical trials of novel drug therapies; an individual-
417 level participant data analysis. *BMC Medicine* (in press). 2019.
- 418 19. Yoon JW, Ha Y-C, Kim KM, Moon JH, Choi SH, Lim S, et al. Hyperglycemia Is Associated with
419 Impaired Muscle Quality in Older Men with Diabetes: The Korean Longitudinal Study on Health and
420 Aging. *Diabetes Metab J*. 2016;40(2):140-6.
- 421 20. Maggi S, Noale M, Gallina P, Marzari C, Bianchi D, Limongi F, et al. Physical disability among
422 older Italians with diabetes. *The ILSA Study*. *Diabetologia*. 2004;47(11):1957-62.

- 1
2
3 423 21. Scherthner G, Scherthner-Reiter MH. Diabetes in the older patient: heterogeneity
4 424 requires individualisation of therapeutic strategies. *Diabetologia*. 2018;61(7):1503-16.
5 425 22. Formiga F, Franch-Nadal J, Rodriguez L, Ávila L, Fuster E. Inadequate glycaemic control and
6 426 therapeutic management of adults over 65 years old with type 2 diabetes mellitus in Spain. *The*
7 427 *journal of nutrition, health & aging*. 2017;21(10):1365-70.
8 428 23. Braun AK, Kubiak T, Kuntsche J, Meier-Höfig M, Müller UA, Feucht I, et al. SGS: a structured
9 429 treatment and teaching programme for older patients with diabetes mellitus—a prospective
10 430 randomised controlled multi-centre trial. *Age and ageing*. 2009;38(4):390-6.
11 431 24. Quartuccio M, Buta B, Kalyani RR. Comparative effectiveness for glycemic control in older
12 432 adults with diabetes. *Current geriatrics reports*. 2017;6(3):175-86.
13 433 25. Ida S, Kaneko R, Imataka K, Murata K. Relationship between frailty and mortality,
14 434 hospitalization, and cardiovascular diseases in diabetes: a systematic review and meta-analysis.
15 435 *Cardiovascular Diabetology*. 2019;18(1):81.
16 436 26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews
17 437 and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
18 438 27. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical
19 439 measure of fitness and frailty in elderly people. *Canadian Medical Association Journal*.
20 440 2005;173(5):489.
21 441 28. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality
22 442 of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*. 2010;25(9):603-5.
23 443 29. Mueller M, D'Addario M, Egger M, Cevallos M, Dekkers O, Mugglin C, et al. Methods to
24 444 systematically review and meta-analyse observational studies: a systematic scoping review of
25 445 recommendations. *BMC Medical Research Methodology*. 2018;18(1):44.
26
27
28
29
30 446
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Medline Search Strategy

Search Terms

1. Exp Frailty/
2. Exp Frail Elderly/
3. Frail*.tw
4. 1 or 2 or 3
5. Exp Diabetes Mellitus
6. Diabet*.tw
7. (IDDM or NIDDM or MODY or T1DM, or T2DM or T1D or T2D).tw
8. (non insulin* depend* or non insulin depend* or non insulin?depend* or non insulin ?depend).tw
9. (insulin* depend* or insulin ?depend*).tw
10. 5 or 6 or 7 or 8 or 9
11. Exp Diabetes Insipidus/
12. Diabet* insipidus.tw
13. 11 or 12
14. 10 not 13
15. 4 and 14

Language restriction

None applied to search (non-English language studies excluded at screening stage)

Years searched

2001-November 2019

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

For peer review only

The Newcastle-Ottawa Scale

Adaptation for studies assessing the prevalence and impact of frailty in diabetes

1 – Representativeness of the exposed (i.e. frail) cohort

- a) Truly representative (one star)
- b) Somewhat representative (one star)
- c) Selected group
- d) No description of the derivation of the cohort

2 – Selection of the non-exposed (i.e. non-frail) cohort

- a) Drawn from the same community as the exposed cohort (one star)
- b) Drawn from a different source
- c) No description of the derivation of the non-exposed cohort

3 – Ascertainment of exposure

- a) Validated measurement tool for frailty (two stars)
- b) Non-validated measurement tool, but the tool is available or described (one star)
- c) No description of measurement tool

4 – Non-respondents

- a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory (one star)
- b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory
- c) No description of the response rate of the characteristics of the responders and non-responders

5 – Demonstration that outcome of interest was not present at the start of the study

- a) Yes (one star)
- b) No

Comparability:

1 – Comparability of the cohorts on the basis of the design or analysis being controlled for confounders

- a) The study controls for age and sex (one star)
- b) The study controls for other factors (one star)

1
2 c) Cohorts are not comparable on the basis of the design or analysis controlled for
3 confounders
4

5
6 **Outcomes:**
7

8 **1 – Assessment of outcomes**
9

10 a) Independent assessment (one star)

11
12 b) Record linkage (one star)

13
14 c) Self-report

15
16 d) No description

17
18 e) Other
19
20

21
22 **2 – Follow-up long enough for outcomes to occur**
23

24 a) Yes (one star)

25
26 b) No
27

28 **3 – Adequacy of follow-up of cohorts**
29

30 a) Complete follow-up: all subjects accounted for (one star)

31
32 b) Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to
33 20% or description of those lost suggested no different from those followed (one star)
34

35
36 c) Follow-up rate less than 80% and no description of those lost

37
38 d) No statement
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

1 **Registration**
2
3

4 [#2](#) If registered, provide the name of the registry (such as 3
5
6 PROSPERO) and registration number
7
8
9

10 **Authors**
11

12
13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all 1
14
15 protocol authors; provide physical mailing address of
16
17 corresponding author
18
19

20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the 18
21
22 guarantor of the review
23
24

25 **Amendments**
26
27

28
29 [#4](#) If the protocol represents an amendment of a previously n/a
30
31 completed or published protocol, identify as such and list
32
33 changes; otherwise, state plan for documenting important
34
35 protocol amendments
36
37
38

39 **Support**
40

41
42 **Sources** [#5a](#) Indicate sources of financial or other support for the review 18
43
44

45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor 18
46
47

48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or 18
49
50 funder
51 institution(s), if any, in developing the protocol
52

53 **Introduction**
54
55
56
57
58
59
60

1	Rationale	#6	Describe the rationale for the review in the context of what is	4,5
2			already known	
3				
4				
5				
6	Objectives	#7	Provide an explicit statement of the question(s) the review	6
7			will address with reference to participants, interventions,	
8			comparators, and outcomes (PICO)	
9				
10				
11				
12				
13				
14	Methods			
15				
16				
17	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	7-10
18			design, setting, time frame) and report characteristics (such	
19			as years considered, language, publication status) to be	
20			used as criteria for eligibility for the review	
21				
22				
23				
24				
25				
26				
27	Information	#9	Describe all intended information sources (such as	10
28			electronic databases, contact with study authors, trial	
29	sources		registers or other grey literature sources) with planned dates	
30			of coverage	
31				
32				
33				
34				
35				
36				
37	Search strategy	#10	Present draft of search strategy to be used for at least one	10-11
38			electronic database, including planned limits, such that it	
39			could be repeated	
40				
41				
42				
43				
44				
45	Study records -	#11a	Describe the mechanism(s) that will be used to manage	11
46	data management		records and data throughout the review	
47				
48				
49				
50	Study records -	#11b	State the process that will be used for selecting studies	11-12
51	selection process		(such as two independent reviewers) through each phase of	
52			the review (that is, screening, eligibility and inclusion in	
53			meta-analysis)	
54				
55				
56				
57				
58				
59				
60				

1	Study records -	#11c	Describe planned method of extracting data from reports	12-13
2				
3	data collection		(such as piloting forms, done independently, in duplicate),	
4				
5	process		any processes for obtaining and confirming data from	
6				
7			investigators	
8				
9				
10				
11	Data items	#12	List and define all variables for which data will be sought	12-13
12				
13			(such as PICO items, funding sources), any pre-planned	
14				
15			data assumptions and simplifications	
16				
17				
18				
19	Outcomes and	#13	List and define all outcomes for which data will be sought,	13-14
20				
21	prioritization		including prioritization of main and additional outcomes, with	
22				
23			rationale	
24				
25				
26	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	14
27				
28	individual studies		individual studies, including whether this will be done at the	
29				
30			outcome or study level, or both; state how this information	
31				
32			will be used in data synthesis	
33				
34				
35				
36	Data synthesis	#15a	Describe criteria under which study data will be	14-15
37				
38			quantitatively synthesised	
39				
40				
41				
42	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	14-15
43				
44			planned summary measures, methods of handling data and	
45				
46			methods of combining data from studies, including any	
47				
48			planned exploration of consistency (such as I ² , Kendall's τ)	
49				
50				
51	Data synthesis	#15c	Describe any proposed additional analyses (such as	n/a
52				
53			sensitivity or subgroup analyses, meta-regression)	
54				
55				
56				
57				
58				
59				
60				

1	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	15
2			of summary planned	
3				
4				
5				
6	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	n/a
7			publication bias across studies, selective reporting within	
8			studies)	
9				
10				
11				
12				
13				
14	Confidence in	#17	Describe how the strength of the body of evidence will be	n/a
15	cumulative		assessed (such as GRADE)	
16				
17	evidence			
18				
19				
20				
21				

22 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
23 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool
24 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

BMJ Open

The identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: A systematic review protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2020-037476.R2
Article Type:	Protocol
Date Submitted by the Author:	23-Jul-2020
Complete List of Authors:	Hanlon, Peter; University of Glasgow Institute of Health and Wellbeing, ; Fauré, Isabella ; University of Glasgow Institute of Health and Wellbeing Corcoran, Neave ; University of Glasgow Institute of Health and Wellbeing Butterly, Elaine; University of Glasgow Institute of Health and Wellbeing Lewsey, Jim; University of Glasgow Institute of Health and Wellbeing McAllister, David; University of Glasgow Institute of Health and Wellbeing Mair, Frances; University of Glasgow Institute of Health and Wellbeing
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	General practice / Family practice, Geriatric medicine
Keywords:	Diabetes & endocrinology < INTERNAL MEDICINE, EPIDEMIOLOGY, GERIATRIC MEDICINE

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

The identification and prevalence of frailty in diabetes mellitus and association with clinical outcomes: A systematic review protocol

Authors:

Dr Peter Hanlon¹
Ms Isabella Fauré¹
Dr Neave Corcoran¹
Dr Elaine Butterly²
Professor Jim Lewsey³
Dr David McAllister^{2*}
Professor Frances S Mair^{1*}

*Joint senior author

Affiliations:

1. General Practice and Primary Care, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
2. Public Health, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
3. Health Economics and Health Technology Assessment, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

Corresponding author:

Dr Peter Hanlon
General Practice and Primary Care
Institute of Health and Wellbeing
University of Glasgow
1 Horselethill Road
Glasgow, G12 9LX

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

28 Peter.hanlon@glasgow.ac.uk
29 +44 141 330 8383

30 Word count: 2311

31 **Keywords:** Frailty, Diabetes Mellitus, Systematic review, Protocol

For peer review only

32 Abstract

33 Introduction:

34 Diabetes mellitus is common and growing in prevalence, and an increasing proportion of people with
35 diabetes are living to older age. Frailty is therefore becoming an important concept in diabetes.
36 Frailty is associated with older age and describes a state of increased susceptibility to
37 decompensation in response to physiological stress. A range of measures have been used to quantify
38 frailty. This systematic review aims to identify measures used to quantify frailty in people with
39 diabetes (any type); to summarize the prevalence of frailty in diabetes; and to describe the
40 relationship between frailty and adverse clinical outcomes in people with diabetes.

41 Methods and analysis:

42 Three electronic databases (Medline, Embase and Web of Science) will be searched from 2000 to
43 November 2019 and supplemented by citation searching of relevant articles and hand-searching of
44 reference lists. Two reviewers will independently review titles, abstracts and full texts. Inclusion
45 criteria include: (1) Adults with any type of diabetes mellitus; (2) Quantify frailty using any validated
46 frailty measure; (3) Report the prevalence of frailty and/or the association between frailty and
47 clinical outcomes in people with diabetes; (4) Studies that assess generic (e.g. mortality, hospital
48 admission, falls) or diabetes specific outcomes (e.g. hypoglycaemic episodes, cardiovascular events,
49 diabetic nephropathy, diabetic retinopathy); (5) Cross-sectional and longitudinal observational
50 studies. Study quality will be assessed using the Newcastle-Ottawa scale for observational studies.
51 Clinical and methodological heterogeneity will be assessed, and a random effects meta-analysis
52 performed if appropriate. Otherwise, a narrative synthesis will be performed.

1
2
3
4 53 **Ethics and dissemination:**

5
6
7 54 This manuscript describes the protocol for a systematic review of observational studies and does not
8
9 55 require ethical approval.

10
11
12
13 56 **Registration number:**

14
15
16 57 PROSPERO CRD42020163109.
17
18
19
20
21 58

22
23
24
25
26 59 **Strengths and Limitations**

27
28
29
30 60 This systematic review will provide a comprehensive overview of the prevalence and implications of
31
32 61 frailty in people with diabetes.

33
34
35 62 We will include a broad range of frailty definitions and clinical outcomes relevant to diabetes.

36
37
38 63 There is likely to be significant heterogeneity between population characteristics and frailty
39
40 64 definitions in included studies.

41
42
43 65 By including only English language articles, there is a chance of language bias in the results of the
44
45 66 review.

46
47
48 67 We exclude Grey literature, which may lead to publication bias.
49
50
51
52
53
54
55
56
57
58
59
60

68 Introduction

69 Diabetes mellitus (hereafter “diabetes”) describes a collection of metabolic disorders, with distinct
70 pathological processes, that are characterised by elevated blood glucose.(1) The most common are
71 type 1 diabetes and type 2 diabetes. Type 1 diabetes is caused by insulin deficiency resulting from
72 destruction of pancreatic beta cells, usually by an autoimmune process.(2) Type 2 diabetes describes
73 a relative insulin deficiency caused by beta-cell dysfunction and insulin resistance of target
74 organs.(2) Both are associated with a range of complications including macrovascular disease,
75 retinopathy, nephropathy and neuropathy.(3) The prevalence of diabetes is increasing across the
76 world.(4) Population demographics are also shifting towards an ageing population.(5) Among people
77 above the age of 65, the prevalence of diabetes can be as high as 30%.(6) Diabetes in older people is
78 therefore a growing clinical and public health priority. One factor with important implications for
79 disease management in older age is frailty.(7)

80 Frailty is a state characterised by reduced functional reserve across multiple physiological
81 systems.(8) People living with frailty have impaired resolution of homeostasis following physiological
82 stressors.(8) Frailty therefore carries an increased risk of a range of adverse health outcomes, such
83 as falls, cognitive decline, hospital admission and mortality.(9) Frailty is widely recognised to be a
84 multidimensional and dynamic state, associated with older age and with a range of non-
85 communicable diseases.(9) However, there is no single universally accepted operational definition of
86 frailty. Rather, a wide range of definitions have been utilized in both research and clinical
87 practice.(10)

88 The two dominant paradigms in the frailty literature are the frailty phenotype and the frailty index.
89 The frailty phenotype, described by *Fried et al* in 2001, defines frailty as the presence of three or
90 more out of five features: low hand-grip strength, unintentional weight loss, low physical activity,
91 exhaustion, and slow walking pace.(11) The presence of one or two of these features is classified as

1
2
3 92 a pre-frail state. The frailty index, described by Rockwood and Mitnitski in 2007, is based on a
4
5 93 cumulative-deficit model of frailty whereby frailty is identified by counting the number of health
6
7 94 'deficits' present in an individual.(12) At least 30 deficits are required to construct a frailty index, all
8
9
10 95 of which must increase in prevalence with age, be associated with poor health, and not saturate too
11
12 96 early (i.e. be universally present among older people).(13) Both the frailty phenotype and frailty
13
14 97 index have been associated with adverse health outcomes in a range of older populations, however
15
16 98 the populations identified as frail by each are different.(14) Since their original description, a wide
17
18 99 range of other frailty instruments, as well as adaptations of the frailty index and phenotype, have
19
20
21 100 been developed for both epidemiological studies and for clinical practice.(9, 10)

22
23
24 101 The relationship between diabetes and frailty is complex. Diabetes is associated with a higher
25
26 102 prevalence of frailty.(15-18) Both type 1 and type 2 diabetes lead to microvascular and
27
28 103 macrovascular complications which have important physical, cognitive and functional consequences,
29
30 104 that may contribute to the development of frailty.(6) Hyperglycaemia is also recognized to directly
31
32
33 105 impact muscle mass and quality, exacerbating age-related sarcopenia and, in turn, physical
34
35 106 function.(19) However, the association between frailty and poor functional outcomes in people with
36
37 107 diabetes is only partially explained by direct complications of diabetes.(17, 20)

38
39
40 108 The importance of frailty in the context of diabetes is increasingly recognised in clinical guidelines.(7)
41
42 109 Specifically, higher HbA1c targets are recommended in the context of frailty, in part due to the
43
44 110 increased risks associated with hypoglycaemia.(21) Despite this, up to 40% of older people with
45
46 111 diabetes may be over-treated (with HbA1c <7%).(22, 23) Conversely, poor glycaemic control and
47
48 112 associated vascular complications risk causing, or accelerating the progression of, frailty.(24)

49
50
51
52 113 One recent meta-analysis demonstrated a consistent relationship between frailty and mortality,
53
54 114 hospitalisation, and cardiovascular events in the context of diabetes.(25) We are not aware of any
55
56 115 systematic review to assess the prevalence of frailty in diabetes, or to consider a broader range of
57
58
59 116 outcomes relevant to the management of diabetes. Given the risks of both over- and under-

1
2
3 117 treatment of diabetes in the context of frailty, understanding the range of potential associations is
4
5 118 required to inform clinical decisions and to underpin future research.
6
7
8 119 To enhance understanding of the implications and management of diabetes within an ageing
9
10 120 population, it is important to fully describe the association between diabetes and frailty. Given the
11
12 121 risks of both over- and under-treatment of diabetes in the context of frailty, it is important to
13
14 122 understand the associations between frailty and a range of potential outcomes in diabetes. This
15
16 123 includes generic outcomes such as mortality and hospitalisation and disability and disease specific
17
18 124 outcomes such as retinopathy, neuropathy, and hypoglycaemic events. An understanding of the
19
20 125 range and complexity of these associations is required to inform clinical decisions around treatment
21
22 126 priorities and to underpin future research. This includes quantifying the prevalence of frailty in
23
24 127 people with diabetes, and the impact that different frailty definitions might have on this prevalence.
25
26 128 This manuscript describes the protocol of a systematic review aiming to synthesise existing evidence
27
28 129 relating to these questions.
29
30
31
32
33

34 130 Aims

35
36
37 131 The systematic review will aim to:

- 38 132 • Identify which frailty measures have been used to assess frailty in people with diabetes (any
39 133 type, including mixed/unspecified)
 - 40 134 • Quantify the prevalence of frailty among people with diabetes
 - 41 135 • Describe the association between frailty and both generic (e.g. mortality) and disease
42 136 specific (e.g. hypoglycaemia) clinical outcomes in the context of diabetes
- 43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

137 **Methods and analysis**

138 This protocol is registered with PROSPERO (CRD42020163109). The review will be conducted and
 139 reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
 140 (PRISMA) statement.⁽²⁶⁾ Where a meta-analysis is undertaken, we will report findings according to
 141 the Meta-analyses Of Observational Studies in Epidemiology checklist.

142 **Eligibility criteria for inclusion**

143 The eligibility criteria for this review are summarized in table 1 and explained in more detail below.

Table 1. Inclusion Criteria	
PECOS component	Description
Population	Adults (≥ 18 years old) Diabetes (any type, including mixed or unspecified)
Exposure	Frailty as assessed by any frailty measure
Comparator	People with diabetes not classified as frail
Outcomes	Generic: <ul style="list-style-type: none"> • Mortality • Major Adverse Cardiovascular Events • Hospital admission • Admission to long-term care facility • Falls • Number of clinic attendances • Quality of life • Disability/functional status Diabetes specific:

	<ul style="list-style-type: none"> • HbA1c (cross sectional association, or longitudinal) • Glycaemic variability • Hypoglycaemic episodes • Diabetic retinopathy (cross sectional association, or longitudinal) • Diabetic nephropathy (cross sectional association, or longitudinal) <ul style="list-style-type: none"> ○ Include development of end-stage renal disease • Diabetic foot complications (cross sectional association, or longitudinal) • Treatment burden (e.g. Diabetic Treatment Burden Questionnaire)
Settings	Community (including care home/nursing home) Outpatient clinic Inpatient
Study design	Cross sectional or longitudinal Cohort
Other exclusions	Conference abstracts, letters, review articles, intervention studies, Grey literature

144 **Population**

145 We will include studies analysing data from people with any form of diabetes.

146 While frailty is a state associated with increasing age, there is evidence that frailty is identifiable in
 147 relatively younger people, particularly in certain contexts such as multimorbidity (2 or more co-
 148 existing long-term conditions) or in areas of high socioeconomic deprivation. We will therefore
 149 include studies of adults of any age (≥18 years). However, we anticipate that most studies will focus
 150 predominantly on ‘older’ populations.

1
2
3 151 From an initial scoping of the literature, it is likely that many studies describing frailty in population-
4
5 152 based studies measure unspecified 'diabetes' rather than explicitly type 1 or type 2 diabetes. We will
6
7 153 therefore include any study which includes people with any type of diabetes (including type 1, type 2
8
9 154 diabetes, secondary or monogenic diabetes, or people with unspecified diabetes). Given that frailty
10
11 155 is a state associated with older age, and that type 2 diabetes is both more prevalent than type 1
12
13 156 diabetes and becomes more prevalent with age, it is likely that most (but not all) people with
14
15 157 diabetes in the relevant populations will have type 2 diabetes. Studies of type 1 diabetes, type 2
16
17 158 diabetes and those of unspecified diabetes will be considered separately in any subsequent analysis.
18
19
20
21 159 We will include studies focusing purely on people with diabetes, or population-based studies that
22
23 160 report results for people with diabetes separately.
24
25
26

27 161 Exposure

28
29
30 162 The 'exposure' of interest is frailty. Many epidemiological measures and clinical tools have been
31
32 163 developed to identify frailty for research or clinical practice.(10)
33
34
35 164 To be eligible for inclusion, a study must use a measure which explicitly seeks to quantify frailty. We
36
37 165 will include measures developed primarily as epidemiological tools (e.g. the frailty phenotype frailty
38
39 166 index).(11, 12) We will also include measures designed primarily for clinical practice (e.g. the Clinical
40
41 167 Frailty Scale).(27)
42
43
44
45 168 Studies focusing solely on comorbidity (i.e. no additional measures to identify 'frailty') will be
46
47 169 excluded unless these are explicitly operationalised as a 'frailty index'. In this case studies would
48
49 170 generally be expected to include additional deficits (such as symptoms, functional limitations,
50
51 171 laboratory measures etc.). Studies which use a single parameter as a proxy for frailty (e.g. grip
52
53 172 strength alone, self-rated health) will be excluded.
54
55
56
57
58
59
60

173 **Comparator**

174 Studies that report the prevalence of frailty will be eligible for inclusion if they report the prevalence
175 of frailty in diabetes only. Studies should report the number or proportion of participants with and
176 without frailty (or with varying degrees of frailty, depending on the measure used).

177 For assessing the association between frailty and clinical outcomes in the context of diabetes,
178 studies should report the association between frailty and the outcome of interest. This may be
179 reported either as the association with the presence or absence of frailty (in the case of a binary or
180 categorical measure) or the association between the degree of frailty and the outcome (in the case
181 of a continuous or ordinal measure of frailty).

182 **Outcomes**

183 Outcomes of interest are summarized in table 1. We will include studies assessing any of these
184 outcomes as long as the association is specifically quantified in people with diabetes and frailty.

185 **Setting**

186 We will include studies of community-dwelling patients, outpatient populations or hospital
187 inpatients.

188 For the purposes of this review, given the focus on frailty, people living in long-term care facilities
189 (e.g. care-homes, nursing-homes) will be considered to be 'community-dwelling'. Therefore, any
190 study including, or specifically recruiting, nursing home residents will be eligible for inclusion.

1
2
3
4 191 **Identification of studies**

5
6
7
8 192 **Electronic searches**

9
10
11 193 Medline, Embase, and Web of Science (Core collection) databases will be search using a combination
12
13 194 of Medical Subject Headings (MeSH) and keyword searches (Supplementary file 1). The terms used
14
15 195 for the medline search are shown in table 2. These terms will be adapted for the other databases.
16
17 196 Searches will be from 2000 to November 2019. The year 2000 was chosen as the start date as the
18
19 197 first seminal paper operationalising the concept of frailty in an epidemiological study was published
20
21 198 in 2001. Articles published prior to this date are therefore unlikely to be relevant. No language
22
23 199 restriction will be applied to the search, but only English language articles will be included at the
24
25 200 screening level. This language restriction is a pragmatic decision, however we acknowledge that this
26
27 201 may lead to a language bias in the results, potentially excluding relevant studies published in other
28
29 202 languages.
30
31
32
33

34
35 Table 2: Medline Search

- | |
|--|
| <p>36
37 1. Exp Frailty/
38
39 2. Exp Frail Elderly/
40
41 3. Frail*.tw
42
43 4. 1 or 2 or 3
44
45 5. Exp Diabetes Mellitus
46
47 6. Diabet*.tw
48
49 7. (IDDM or NIDDM or MODY or T1DM, or T2DM or T1D or T2D).tw
50
51 8. (non insulin* depend* or non insulin depend* or non insulin?depend* or non
52
53 insulin ?depend).tw
54
55 9. (insulin* depend* or insulin ?depend*).tw
56
57
58
59 10. 5 or 6 or 7 or 8 or 9
60</p> |
|--|

1
2
3 11. Exp Diabetes Insipidus/
4

5 12. Diabet* insipidus.tw
6

7 13. 11 or 12
8

9 14. 10 not 13
10

11 15. 4 and 14
12
13
14
15
16

17 203 Identifying additional articles

18
19
20 204 Electronic searches will be supplemented by hand searching reference lists of relevant articles. A
21
22
23 205 citation search of all relevant articles will also be carried out using the Web of Science citation search
24
25 206 tool.
26
27

28 207 Data collection and analysis

29 30 31 32 208 Selection of studies

33
34
35
36 209 Two reviewers, working independently, will screen all titles and abstracts of records identified in the
37
38 210 database searches. PECOS criteria outlined above will be used to determine eligibility. Where there
39
40 211 is disagreement, studies will be retained for full-text screening.
41
42

43 212 Full texts of all potentially eligible studies will be screened independently by two reviewers.
44

45 213 Disagreements about eligibility will be resolved by consensus, involving a third reviewer where
46
47 214 necessary.
48
49
50

51 215 Data extraction

52
53
54 216 A standard data extraction form will be designed and piloted before being applied to each of the
55
56 217 included studies. Extracted data will include:

57
58
59 218 Study details
60

- 1
2
3 219 • Author
4
5 220 • Year
6
7
8 221 • Location
9
10 222 • Setting (community, outpatient, residential care)
11
12 223 • Method of recruitment (e.g. random sample, postal invitation, consecutive patients)
13
14 224 • Method of assessment (face-to-face, survey, linkage to healthcare records)
15
16
17 225 Population
18
19
20 226 • Age
21
22 227 • Sex
23
24 228 • Ethnicity
25
26 229 • Socioeconomic status
27
28 230 • Comorbidities
29
30 231 • Medications
31
32 232 • Social circumstances (e.g. living independently, requiring carers, family support etc)
33
34 233 • Smoking status
35
36 234 • Physical activity
37
38
39 235 Diabetes details
40
41
42 236 • Type of diabetes
43
44 237 • Method of confirmation (self-report, medical records, clinical assessment)
45
46 238 • Measure of control (e.g. HbA1c)
47
48 239 • Medication (e.g. proportion taking insulin, oral antidiabetics etc.)
49
50 240 • Presence and severity of complications (e.g. retinopathy, nephropathy, neuropathy,
51
52 ulceration, Charcot arthropathy)
53
54 241
55
56 242 Frailty definition
57
58
59
60

- 1
2
3 243 • Frailty measure used
4
5 244 • Definitions for each component of the frailty measure (e.g. cut-points used for continuous
6
7 245 measures, method of assessment (questionnaire, interview etc.))
8
9

10 246 Frailty prevalence
11
12

13 247 Outcomes (generic):
14
15

- 16 248 • Mortality
17
18 249 • Major Adverse Cardiovascular Events
19
20 250 • Hospital admission
21
22 251 • Admission to long-term care facility
23
24 252 • Falls
25
26 253 • Number of clinic attendances
27
28 254 • Quality of life
29
30 255 • Disability/functional status
31
32
33

34 256 Outcomes (diabetes specific):
35
36
37

- 38 257 • HbA1c (cross sectional association, or longitudinal)
39
40 258 • Glycaemic variability
41
42 259 • Hypoglycaemic episodes
43
44 260 • Diabetic retinopathy (cross sectional association, or longitudinal)
45
46 261 • Diabetic nephropathy (cross sectional association, or longitudinal)
47
48 262 • Diabetic foot complications (cross sectional association, or longitudinal)
49
50 263 • Treatment burden (e.g. Diabetic Treatment Burden Questionnaire)
51
52
53

54 264 As we include a wide range of outcomes, it is likely that the way outcomes are assessed will vary
55
56 265 depending on the outcome in question. Studies may also assess similar outcomes (e.g. hospital
57
58 266 admission) in different ways (e.g. number of admissions over specified follow-up, time to first
59
60

1
2
3 267 admission, presence of absence of admission during follow-up). For the outcomes listed above, we
4
5 268 will extract data regardless of the method of assessment. Heterogeneity in the way outcome data
6
7 269 were collected will be used to inform the approach to data synthesis (i.e. meta-analysis versus
8
9
10 270 narrative synthesis). For each outcome reported we will record

- 11
12
13 271 • The method of outcome assessment (e.g. linkage to healthcare records, face-to-face
14
15 272 assessment, questionnaire etc.)
16
17 273 • Method of analysis (e.g. time-to-event, mean difference etc.)
18
19 274 • The association between frailty and the outcome (e.g. prevalence, odds ratio, hazard ratio
20
21 etc.)
22 275
23
24 276 • Adjustment for any potential confounders
25
26 277 • Length of follow-up over which the outcome was assessed
27
28
29 278 • Method of analysis of competing risks when assessing each outcome.
30

31 279 Where available, we will also extract data on both relative (e.g. hazard ratios) and absolute (e.g.
32
33 280 events per 1000 people) associations with outcomes.
34
35
36

37 281 **Assessment of methodological quality**

38
39

40 282 The Newcastle-Ottawa scale will be used to assess the risk of bias for each study (Supplementary file
41
42 283 2).(28) This scale is widely used for the assessment of observational studies, and has frequently been
43
44 284 adapted to the context of specific systematic reviews. We have adapted the criteria in order to be
45
46 285 explicit about how the 'exposure assessment' related to frailty: specifically, awarding one point for
47
48 286 the use of a validated frailty assessment measure. For cross-sectional studies, only the first 5
49
50 287 elements of the scale were relevant to quality assessment (the remainder concerning the
51
52 288 longitudinal assessment of outcomes). We will use this subsection of the Newcastle-Ottawa scale to
53
54 289 assess the quality of cross-sectional studies to allow direct comparability with the baseline
55
56 290 assessments of longitudinal studies (from which we will also extract data on frailty prevalence). In
57
58
59
60

1
2
3 291 assessing the comparability of frail/non-frail groups, age will be taken as the most important factor
4
5 292 for which studies should account.
6
7
8

9 293 Data synthesis

10
11
12 294 The appropriate method of data synthesis will be determined after assessment of the heterogeneity
13
14 295 of the included studies, in terms of population selection and demographics, frailty definition, and
15
16 296 method of outcome assessment.
17

18
19
20 297 With regards to the prevalence of frailty, different frailty measures will be considered separately (i.e.
21
22 298 we will not perform a meta-analysis of frailty prevalence measured using different scales). We will
23
24 299 also consider community studies separately from studies focussing on outpatient clinic populations
25
26 300 (as these may represent people with more severe diabetes), inpatients or people living in residential
27
28 301 care. We will also assess the inclusion criteria and demographics of the sample population, with
29
30 302 particular attention to age (as frailty is strongly associated with age) and sex (as women tend to have
31
32 303 a higher prevalence of frailty than men) to determine the most appropriate method of synthesis.
33

34
35 304 Where samples have been drawn from populations with a markedly different age/sex structure, a
36
37 305 pooled estimate of the mean prevalence of frailty across these studies is unlikely to be a meaningful
38
39 306 summary. Similarly, other inclusion criteria used by the individual studies (such as excluding
40
41 307 'institutionalised' people, people with cognitive impairment, of people with impaired mobility
42
43 308 unable to attend an assessment) may disproportionately impact on the estimation of frailty
44
45 309 prevalence. The appropriateness, or otherwise, of a meta-analysis of frailty prevalence will be
46
47 310 judged only after examination of these aspects of the included studies.
48

49
50
51 311 For the assessment of outcomes, the approach to synthesis will also be judged based on
52
53 312 heterogeneity of the method of outcome assessment and the analytic approach. As above, different
54
55 313 frailty measures will be considered separately.
56
57
58
59
60

1
2
3 314 If appropriate, we will combine these in a random effects meta-analysis (anticipating heterogeneity
4
5 315 in the true association). As well as a pooled estimate and 95% confidence intervals, we will also
6
7 316 calculate the prediction interval to assess the range of plausible estimates from the observed data.
8
9
10 317 Heterogeneity will be quantified using the I^2 statistic. Where heterogeneity is present, we will
11
12 318 attempt to explore potential sources of heterogeneity using subgroup analyses (e.g. by method of
13
14 319 determining frailty, age of sample population, method of outcome assessment). By doing so, we
15
16 320 propose to explore factors that may influence the estimates reported in observational studies in the
17
18 321 presence of heterogeneity, rather than provide a definitive single estimate.(29) We will use funnel
19
20 322 plots to assess for potential publication bias.
21
22

23
24 323 Only those studies that are judged to be sufficiently comparable will be included in meta-analyses.
25
26 324 For outcomes where there are too few studies, or the included studies are too heterogenous to
27
28 325 permit a meaningful meta-analysis (for example, in terms of outcome definition or method of
29
30 326 assessing frailty), we will perform a narrative synthesis of the study findings. This will report the
31
32 327 methods used to identify frailty along with the prevalence and association with outcomes, to explore
33
34 328 the impact of the method of assessment on the observed relationship. This will be reported
35
36 329 alongside detail of the recruitment strategy, age profile, and characteristics of each sample included.
37
38
39

40 330 Patient and public involvement

41
42
43
44 331 No patients were involved in the development of this review.
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

332 Ethics and dissemination

333 This systematic review will provide an overview of the prevalence of frailty in diabetes, and the
334 relationship between frailty and adverse health outcomes in people with diabetes.

335 As the prevalence of both frailty and diabetes increase, it will become increasingly important for
336 clinical guidelines for the treatment of diabetes to explicitly consider the needs of people living with
337 frailty.(7) Quantifying the prevalence of frailty in diabetes will allow the scale of this challenge to be
338 better appreciated. By including any reported definition of frailty within our inclusion criteria, this
339 review will demonstrate which of the wide range of frailty instruments and measures have been
340 used to study frailty in diabetes. It will also be possible to compare if and how prevalence and
341 association with outcomes differs depending on the frailty definition used.

342 Given the likely heterogeneity in frailty definitions, as well as inherent differences in the populations
343 studied, it may not be possible to undertake a meta-analysis of the findings of this review. If this is
344 the case, we propose to conduct a detailed narrative synthesis, systematically describing and
345 synthesizing details of the populations under study as well as the details of frailty definitions used.

346 We also propose to search for and extract data for a wide range of clinical outcomes. Given the
347 multidimensional nature of frailty,(8) and the vulnerability to decompensation that is inherent to any
348 frailty definition,(9) it is likely that frailty will be associated with a range of adverse outcomes. The
349 challenge in translating these associations into meaningful recommendations is understanding the
350 balance of these risks, and how they might inform clinical decisions and recommendations. The
351 balance of risks in diabetes, and treatment priorities, may differ depending on the degree of frailty
352 experienced by an individual. The associations may also differ in their nature or magnitude
353 depending on the method used to identify frailty. This review will aim to provide an overview of
354 what is known about the relationship between frailty and both generic and disease specific

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

355 outcomes. This is likely to inform priorities for future research into the consequences of frailty in
356 diabetes.
357 As this project is a systematic review, ethical approval is not required. Patients or the public were
358 not involved in the development of this protocol.

For peer review only

359 **Author contributions**

360 All authors (PH, IF, NC, EB, JL, DM and FM) contributed to the conception and design of the proposed
361 study. PH, DM and FM developed the data sources and search strategy. PH, IF, NC, DM and FM
362 refined the inclusion criteria. PH, IF, NC, DM and FM developed the data extraction template which
363 was piloted by PH, IF and NC. PH and IF wrote the first draft. All authors critically reviewed this and
364 subsequent drafts. All authors approved the final version of the manuscript for submission. FM is the
365 guarantor of the review. All authors accept accountability for the accuracy of the protocol.

366 **Funding statement**

367 Dr Peter Hanlon was funded by a Medical Research Council Clinical Research Training Fellowship
368 (Grant reference MR/S021949/1) entitled "Understanding prevalence and impact of frailty in chronic
369 disease and implications for clinical management. The funder had no role in protocol development.

370 **Competing interests statement**

371 The authors declare no competing interests.

372

373 **References**

- 374 1. Moini J. *Epidemiology of Diabetes*: Elsevier; 2019.
- 375 2. Ozougwu J, Obimba K, Belonwu C, Unakalamba C. The pathogenesis and pathophysiology of
376 type 1 and type 2 diabetes mellitus. *Journal of physiology and pathophysiology*. 2013;4(4):46-57.
- 377 3. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history
378 of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study
379 experience. *Diabetes*. 2006;55(5):1463-9.
- 380 4. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and
381 2030. *Diabetes research and clinical practice*. 2010;87(1):4-14.
- 382 5. United Nations. *World Population Ageing [Report] 2015* [Available from:
383 [https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.](https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf)
384 [pdf](https://www.un.org/en/development/desa/population/publications/pdf/ageing/WPA2015_Report.pdf).
- 385 6. Sinclair AJ, Rodriguez-Manas L. Diabetes and Frailty: Two Converging Conditions? *Canadian*
386 *journal of diabetes*. 2016;40(1):77-83.
- 387 7. Sinclair AJ, Abdelhafiz A, Dunning T, Izquierdo M, Manas LR, Bourdel-Marchasson I, et al. An
388 international position statement on the management of frailty in diabetes mellitus: summary of
389 recommendations 2017. *The Journal of frailty & aging*. 2018;7(1):10-20.
- 390 8. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *The Lancet*.
391 2013;381(9868):752-62.
- 392 9. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for
393 clinical practice and public health. *The Lancet*. 2019;394(10206):1365-75.
- 394 10. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, Singh-Manoux A, et al. Measures of
395 frailty in population-based studies: an overview. *BMC Geriatrics*. 2013;13(1):64.
- 396 11. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in Older
397 Adults: Evidence for a Phenotype. *The Journals of Gerontology: Series A*. 2001;56(3):M146-M57.
- 398 12. Rockwood K, Mitnitski A. Frailty in Relation to the Accumulation of Deficits. *The Journals of*
399 *Gerontology: Series A*. 2007;62(7):722-7.
- 400 13. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating
401 a frailty index. *BMC Geriatrics*. 2008;8(1):24.
- 402 14. Santos-Eggimann B, Sirven N. Screening for frailty: older populations and older individuals.
403 *Public health reviews*. 2016;37(1):7.
- 404 15. Kotsani M, Chatziadamidou T, Economides D, Benetos A. Higher prevalence and earlier
405 appearance of geriatric phenotypes in old adults with type 2 diabetes mellitus. *Diabetes Research*
406 *and Clinical Practice*. 2018;135:206-17.
- 407 16. Thein FS, Li Y, Nyunt MSZ, Gao Q, Wee SL, Ng TP. Physical frailty and cognitive impairment is
408 associated with diabetes and adversely impact functional status and mortality. *Postgraduate*
409 *medicine*. 2018;130(6):561-7.
- 410 17. Castro-Rodriguez M, Carnicero JA, Garcia-Garcia FJ, Walter S, Morley JE, Rodriguez-Artalejo
411 F, et al. Frailty as a Major Factor in the Increased Risk of Death and Disability in Older People With
412 Diabetes. *Journal of the American Medical Directors Association*. 2016;17(10):949-55.
- 413 18. Hanlon P, Hannigan L, Fischbacker C, Welton N, Dias S, Mair F, et al. Representation of
414 people with comorbidity and multimorbidity in clinical trials of novel drug therapies; an individual-
415 level participant data analysis. *BMC Medicine* (in press). 2019.
- 416 19. Yoon JW, Ha Y-C, Kim KM, Moon JH, Choi SH, Lim S, et al. Hyperglycemia Is Associated with
417 Impaired Muscle Quality in Older Men with Diabetes: The Korean Longitudinal Study on Health and
418 Aging. *Diabetes Metab J*. 2016;40(2):140-6.
- 419 20. Maggi S, Noale M, Gallina P, Marzari C, Bianchi D, Limongi F, et al. Physical disability among
420 older Italians with diabetes. *The ILSA Study*. *Diabetologia*. 2004;47(11):1957-62.

- 1
2
3 421 21. Scherthner G, Scherthner-Reiter MH. Diabetes in the older patient: heterogeneity
4 422 requires individualisation of therapeutic strategies. *Diabetologia*. 2018;61(7):1503-16.
5 423 22. Formiga F, Franch-Nadal J, Rodriguez L, Ávila L, Fuster E. Inadequate glycaemic control and
6 424 therapeutic management of adults over 65 years old with type 2 diabetes mellitus in Spain. *The*
7 425 *journal of nutrition, health & aging*. 2017;21(10):1365-70.
8 426 23. Braun AK, Kubiak T, Kuntsche J, Meier-Höfig M, Müller UA, Feucht I, et al. SGS: a structured
9 427 treatment and teaching programme for older patients with diabetes mellitus—a prospective
10 428 randomised controlled multi-centre trial. *Age and ageing*. 2009;38(4):390-6.
11 429 24. Quartuccio M, Buta B, Kalyani RR. Comparative effectiveness for glycemic control in older
12 430 adults with diabetes. *Current geriatrics reports*. 2017;6(3):175-86.
13 431 25. Ida S, Kaneko R, Imataka K, Murata K. Relationship between frailty and mortality,
14 432 hospitalization, and cardiovascular diseases in diabetes: a systematic review and meta-analysis.
15 433 *Cardiovascular Diabetology*. 2019;18(1):81.
16 434 26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews
17 435 and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535.
18 436 27. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical
19 437 measure of fitness and frailty in elderly people. *Canadian Medical Association Journal*.
20 438 2005;173(5):489.
21 439 28. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality
22 440 of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*. 2010;25(9):603-5.
23 441 29. Mueller M, D'Addario M, Egger M, Cevallos M, Dekkers O, Mugglin C, et al. Methods to
24 442 systematically review and meta-analyse observational studies: a systematic scoping review of
25 443 recommendations. *BMC Medical Research Methodology*. 2018;18(1):44.
26
27
28
29 444
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Medline Search Strategy

Search Terms

1. Exp Frailty/
2. Exp Frail Elderly/
3. Frail*.tw
4. 1 or 2 or 3
5. Exp Diabetes Mellitus
6. Diabet*.tw
7. (IDDM or NIDDM or MODY or T1DM, or T2DM or T1D or T2D).tw
8. (non insulin* depend* or non insulin depend* or non insulin?depend* or non insulin ?depend).tw
9. (insulin* depend* or insulin ?depend*).tw
10. 5 or 6 or 7 or 8 or 9
11. Exp Diabetes Insipidus/
12. Diabet* insipidus.tw
13. 11 or 12
14. 10 not 13
15. 4 and 14

Language restriction

None applied to search (non-English language studies excluded at screening stage)

Years searched

2001-November 2019

The Newcastle-Ottawa Scale

Adaptation for studies assessing the prevalence and impact of frailty in diabetes

1 – Representativeness of the exposed (i.e. frail) cohort

- a) Truly representative (one star)
- b) Somewhat representative (one star)
- c) Selected group
- d) No description of the derivation of the cohort

2 – Selection of the non-exposed (i.e. non-frail) cohort

- a) Drawn from the same community as the exposed cohort (one star)
- b) Drawn from a different source
- c) No description of the derivation of the non-exposed cohort

3 – Ascertainment of exposure

- a) Validated measurement tool for frailty (two stars)
- b) Non-validated measurement tool, but the tool is available or described (one star)
- c) No description of measurement tool

4 – Non-respondents

- a) Comparability between respondents and non-respondents' characteristics is established, and the response rate is satisfactory (one star)
- b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory
- c) No description of the response rate of the characteristics of the responders and non-responders

5 – Demonstration that outcome of interest was not present at the start of the study

- a) Yes (one star)
- b) No

Comparability:

1 – Comparability of the cohorts on the basis of the design or analysis being controlled for confounders

- a) The study controls for age and sex (one star)
- b) The study controls for other factors (one star)
- c) Cohorts are not comparable on the basis of the design or analysis controlled for confounders

1
2 Outcomes:

3
4 1 – Assessment of outcomes

5 a) Independent assessment (one star)

6
7 b) Record linkage (one star)

8
9 c) Self-report

10
11 d) No description

12
13 e) Other

14
15
16 2 – Follow-up long enough for outcomes to occur

17 a) Yes (one star)

18
19 b) No

20
21
22 3 – Adequacy of follow-up of cohorts

23 a) Complete follow-up: all subjects accounted for (one star)

24
25 b) Subjects lost to follow-up unlikely to introduce bias – number lost less than or equal to 20% or
26 description of those lost suggested no different from those followed (one star)

27
28 c) Follow-up rate less than 80% and no description of those lost

29
30 d) No statement
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

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

For peer review only

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page
		Reporting Item	Number
Title			
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	n/a

1 **Registration**
2
3

4 [#2](#) If registered, provide the name of the registry (such as 3
5
6 PROSPERO) and registration number
7
8

9
10 **Authors**
11

12
13 **Contact** [#3a](#) Provide name, institutional affiliation, e-mail address of all 1
14
15 protocol authors; provide physical mailing address of
16
17 corresponding author
18

19
20 **Contribution** [#3b](#) Describe contributions of protocol authors and identify the 18
21
22 guarantor of the review
23
24

25
26 **Amendments**
27

28
29 [#4](#) If the protocol represents an amendment of a previously n/a
30
31 completed or published protocol, identify as such and list
32
33 changes; otherwise, state plan for documenting important
34
35 protocol amendments
36
37

38
39 **Support**
40

41
42 **Sources** [#5a](#) Indicate sources of financial or other support for the review 18
43
44

45 **Sponsor** [#5b](#) Provide name for the review funder and / or sponsor 18
46
47

48 **Role of sponsor or** [#5c](#) Describe roles of funder(s), sponsor(s), and / or 18
49
50 funder
51 institution(s), if any, in developing the protocol
52

53 **Introduction**
54
55
56
57
58
59
60

1	Rationale	#6	Describe the rationale for the review in the context of what is	4,5
2			already known	
3				
4				
5				
6	Objectives	#7	Provide an explicit statement of the question(s) the review	6
7			will address with reference to participants, interventions,	
8			comparators, and outcomes (PICO)	
9				
10				
11				
12				
13				
14	Methods			
15				
16				
17	Eligibility criteria	#8	Specify the study characteristics (such as PICO, study	7-10
18			design, setting, time frame) and report characteristics (such	
19			as years considered, language, publication status) to be	
20			used as criteria for eligibility for the review	
21				
22				
23				
24				
25				
26				
27	Information	#9	Describe all intended information sources (such as	10
28			electronic databases, contact with study authors, trial	
29	sources		registers or other grey literature sources) with planned dates	
30			of coverage	
31				
32				
33				
34				
35				
36				
37	Search strategy	#10	Present draft of search strategy to be used for at least one	10-11
38			electronic database, including planned limits, such that it	
39			could be repeated	
40				
41				
42				
43				
44				
45	Study records -	#11a	Describe the mechanism(s) that will be used to manage	11
46			records and data throughout the review	
47	data management			
48				
49				
50	Study records -	#11b	State the process that will be used for selecting studies	11-12
51			(such as two independent reviewers) through each phase of	
52	selection process		the review (that is, screening, eligibility and inclusion in	
53			meta-analysis)	
54				
55				
56				
57				
58				
59				
60				

1	Study records -	#11c	Describe planned method of extracting data from reports	12-13
2				
3	data collection		(such as piloting forms, done independently, in duplicate),	
4				
5	process		any processes for obtaining and confirming data from	
6				
7			investigators	
8				
9				
10				
11	Data items	#12	List and define all variables for which data will be sought	12-13
12				
13			(such as PICO items, funding sources), any pre-planned	
14				
15			data assumptions and simplifications	
16				
17				
18				
19	Outcomes and	#13	List and define all outcomes for which data will be sought,	13-14
20				
21	prioritization		including prioritization of main and additional outcomes, with	
22				
23			rationale	
24				
25				
26	Risk of bias in	#14	Describe anticipated methods for assessing risk of bias of	14
27				
28	individual studies		individual studies, including whether this will be done at the	
29				
30			outcome or study level, or both; state how this information	
31				
32			will be used in data synthesis	
33				
34				
35				
36	Data synthesis	#15a	Describe criteria under which study data will be	14-15
37				
38			quantitatively synthesised	
39				
40				
41				
42	Data synthesis	#15b	If data are appropriate for quantitative synthesis, describe	14-15
43				
44			planned summary measures, methods of handling data and	
45				
46			methods of combining data from studies, including any	
47				
48			planned exploration of consistency (such as I ² , Kendall's τ)	
49				
50				
51	Data synthesis	#15c	Describe any proposed additional analyses (such as	n/a
52				
53			sensitivity or subgroup analyses, meta-regression)	
54				
55				
56				
57				
58				
59				
60				

1	Data synthesis	#15d	If quantitative synthesis is not appropriate, describe the type	15
2			of summary planned	
3				
4				
5				
6	Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as	n/a
7			publication bias across studies, selective reporting within	
8			studies)	
9				
10				
11				
12				
13				
14	Confidence in	#17	Describe how the strength of the body of evidence will be	n/a
15	cumulative		assessed (such as GRADE)	
16	evidence			
17				
18				
19				
20				
21				

22 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution
23 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool
24 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60