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The effect of frailty on Quality of Life in elderly patients after hip fracture: a longitudinal study

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36 Abstract

37 **Objective:** The aims of this study were to examine the pattern of changes over time in health status
38 (HS) and Quality of Life (QoL) in the first year after hip fracture and to quantify the association
39 between frailty at the onset of hip fracture and the change in HS and QoL one year later. The major
40 hypothesis was that frailty, a clinical state of increased vulnerability, is a good predictor of QoL in
41 patients recovering from hip fracture.

42 **Design:** Prospective observational follow-up cohort study.

43 **Setting:** Secondary care. Ten participating centres in Brabant, the Netherlands.

44 **Participants:** 1091 patients entered the study and 696 patients completed the study. Patients with a
45 hip fracture aged 65 years and older or proxy respondents for patients with cognitive impairment were
46 included in this study.

47 **Main outcome measures:** The primary outcomes were HS (EuroQol-5 Dimensions questionnaire;
48 EQ-5D) and capability wellbeing (ICEpop CAPability measure for Older People; ICECAP-O). Pre-
49 fracture frailty was defined with the Groningen Frailty Indicator (GFI), with $GFI \geq 4$ indicating frailty.
50 Participants were followed up at one month, three months, six months and one year after hospital
51 admission.

52 **Results:** In total, 371 patients (53.3%) were considered frail. Frailty was negatively associated with
53 HS (β -0.333; 95% CI -0.366, -0.299), self-rated health (β -21.9; 95% CI -24.2, -19.6), and capability
54 wellbeing (β -0.296; 95% CI -0.322, -0.270) in elderly patients one year after hip fracture. After
55 adjusting for confounders, including death, pre-fracture HS, age, pre-fracture residential status, pre-
56 fracture mobility, ASA and dementia, associations were weakened but remained significant.

57 **Conclusions:** We revealed that frailty is negatively associated with QoL one year after hip fracture,
58 even after adjusting for confounders. This finding suggests that early identification of pre-fracture
59 frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the
60 tailoring of treatment.

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63 **Strengths and limitations of this study:**

- 64 - This study addresses the paucity of knowledge of frailty in elderly patients with a hip fracture
- 65 - This multicenter prospective cohort study included a large number of participants and proxy
66 participants in different geographic locations, which increases the generalizability of this study.
- 67 - Participants may not accurately recall their status prior to the fracture, which might affect the results
68 of the GFI and the EQ-5D at baseline.
- 69 - This results from this study shows that pre-fracture frailty in patients with a hip fracture is important
70 for prognostic counseling, care planning, and the tailoring of treatment.

71 Introduction

72 A hip fracture is a serious event in the elderly population. It is associated with high mortality,
73 morbidity and disability for those who survive¹⁻³. Hip fracture risks rise exponentially with increasing
74 age. With the rising longevity across the globe, it seems reasonable that hip fractures will remain an
75 important global health problem with substantial socioeconomic costs^{4,5}. A hip fracture has a major
76 impact on health status (HS) and Quality of Life (QoL)⁶. HS represents the perceived impact of a
77 disease on the level of patients' physical, emotional and social functioning⁷. Several factors are
78 negatively associated with HS in elderly patients with a hip fracture, including female gender,
79 comorbidity, poor nutritional status, severe post-surgical pain perception, long duration of hospital
80 stay, postoperative complications, and low physical or psychosocial functioning at pre-fracture,
81 including cognitive dysfunction⁶. QoL is a multidimensional concept including both positive and
82 negative aspects of life, and it measures patients' evaluation of functioning in line with their
83 expectations⁸. QoL in older people is limited by an individuals' loss of ability to pursue different
84 attributes with regard to attachment, role, enjoyment, security and control⁹. This multidimensional
85 concept can be measured with a capability wellbeing instrument in frail older adults following a hip
86 fracture^{10,11}.

87 Inconclusive evidence was found for the predictive value of older age⁶. However, aging is associated
88 with a decline in physiological reserves, which impedes the body's ability to withstand and recover
89 from major and minor challenges, e.g., a hip fracture. This phenomenon is defined as frailty, a clinical
90 state of increased vulnerability, and it interacts with psychological factors, such as emotional state,
91 coping style and sociological state¹².

92 A systematic review from Lin and colleagues demonstrated that frailty is associated with adverse
93 outcomes in older post-surgery patients, including prolonged length of stay, complications and
94 postoperative mortality¹³. However, the relationship between frailty and HS, and between frailty and
95 capability wellbeing, is unknown. The aims of this study were to (i) compare HS by frailty status at the
96 time of hip fracture, (ii) describe the patterns of HS and capability wellbeing in the first year after hip
97 fracture, and (iii) quantify the association between frailty at the onset of hip fracture and the patterns in
98 HS and capability wellbeing one year following a hip fracture. We hypothesized that frail hip-
99 fractured patients would experience a higher likelihood of poor HS and capability wellbeing, even
100 after accounting for traditionally measured clinical risk factors.

101 **Materials and Methods**

102 *Study design and participants*

103 The Brabant Injury Outcome Surveillance (BIOS), a multicenter prospective observational follow-up
104 cohort study, was conducted to obtain data at one week and one, three, six and twelve months after hip
105 fracture. Full details of the study, objectives and methods are described in detail elsewhere¹⁴. Ethical
106 approval was received from the Medical Ethics Committee Brabant, the Netherlands (project number
107 NL50258.028.14). This report has been prepared in accordance with the STROBE guidelines¹⁵.
108 All participants were included between August 2015 and November 2016 from the ten participating
109 Dutch hospitals and were invited during hospital admission or within several days post-trauma by
110 mail. Both patients aged 65 years and older and proxy respondents for patients with cognitive
111 impairment were eligible for inclusion. Proxy participants could participate from one month onwards.
112 Exclusion criteria were as follows: (i) pathological hip fractures, (ii) patients and proxy respondents
113 being unable or unwilling to give written informed consent, and (iii) patients with insufficient
114 knowledge of the Dutch language.

115 116 *Data collection*

117 Baseline pre-fracture information (T0) was gathered one week or one month after hip fracture by self-
118 or proxy-reported questionnaires. The following data were collected at baseline within one month after
119 hip fracture: demographic characteristics (age, gender, educational level), American Society of
120 Anesthesiologists (ASA) grading, mobility, degree of frailty and HS. All participants were followed-
121 up at one week (T1), one month (T2), three months (T3), six months (T4) and one year (T5) after
122 hospital admission. At follow-up sessions, questionnaires were sent to the participant or proxy. In
123 cases of no return, they were contacted by telephone several times. If this method failed, the
124 participant or proxy was considered to be a non-responder at that follow-up time point.

125 126 *Patient and public involvement*

127 Patients were involved in the recruitment to and conduct of the study. In a small pilot before inclusion
128 in the BIOS, patients were asked their findings about the questionnaire and outcomes. We made small
129 adjustments and results were disseminated to study participants who want to receive information by a
130 newsletter.

131 132 *Outcome assessment questionnaires*

133 The Groningen Frailty Indicator (GFI) questionnaire was used to identify elderly individuals
134 as being frail (supplementary file). The GFI is a 15-item self-reported instrument and screens for the
135 loss of function and resources in four domains of functioning: physical, cognitive, social and
136 psychological¹⁶. The sum score of the GFI ranges from 0 to 15, with a score of ≥ 4 indicating frailty.

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3 137 The study of Peters et al. concluded that the GFI is a feasible, reliable and valid self-assessment in
4 138 home-dwelling and institutionalized elderly people by detecting those at high risk for poor outcomes¹⁷.

5 139 The score on the EuroQol-5 Dimensions (EQ-5D), a generic health utility instrument, is used
6 140 to measure HS¹⁸. The EQ-5D has two parts: a visual analogue scale (VAS), which measures self-rated
7 141 health, and an instrument along five health domains related to daily activities, including mobility, self-
8 142 care, usual activities, pain and discomfort, and anxiety and depression. A respondent's EQ-VAS
9 143 presents self-rated health on a vertical scale with two endpoints, i.e., 'best imaginable health state'
10 144 (100) and 'worst imaginable health state' (0). Each dimension consists of a three-level response: no
11 145 problems, moderate problems or severe problems. A scoring algorithm is available by which each
12 146 health status description can be expressed into an overall score using a published utility algorithm for
13 147 the Dutch population¹⁹. The EQ-5D has good measurement properties and could be used to measure
14 148 outcomes for patients recovering from hip fracture¹¹. The dimensions of the EQ-5D were
15 149 dichotomized in this study, with 0 indicating no problems and 1 indicating moderate and severe
16 150 problems.

17 151 The ICEpop CAPability measure for Older People (ICECAP-O) provides a broad assessment
18 152 of capability wellbeing as it measures an individual's ability to 'do' and 'be' the things that are
19 153 important in life²⁰. This index of capability focuses on wellbeing defined in a broader sense, rather
20 154 than defined by health, and covers the following five attributes: attachment (love and friendship),
21 155 security (thinking about the future without concern), role (doing things that make you feel valued),
22 156 enjoyment (enjoyment and pleasure), and control (independence). These attributes are used to
23 157 calculate a tariff between 0, meaning no capability, and 1, representing full capability. The ICECAP-O
24 158 has been validated in different elderly populations^{21,22}. The questionnaire shows good convergent
25 159 validity with health and wellbeing instruments and is able to discriminate between elderly individuals
26 160 with various health profiles^{21,23,24}.

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28 162 *Statistical analysis*

29 163 The descriptive statistics of the cohort were presented as the means with standard deviations (SDs) for
30 164 continuous variables and as numbers and percentages for dichotomous or categorical variables.
31 165 Missing baseline characteristics and missing sum scores in EQ-5D and ICECAP-O were imputed
32 166 according to multiple imputation, using the multivariate imputation by chained equations (MICE)
33 167 procedure²⁵. The dataset was imputed 15 times with 5 iterations. Patient demographics (age, gender)
34 168 were compared between responders and non-responders. Univariate and multivariable linear
35 169 regression models were used to compare HS by frailty status at time of hip fracture. To assess the
36 170 association between frailty and QoL over one year, we used linear mixed model analyses for EQ-5D
37 171 utility scores and ICECAP-O scores, and we used binary logistic mixed model analyses for domains of
38 172 the EQ-5D. Multicollinearity was assessed with the variance inflation factor (VIF). After univariate
39 173 analyses, we performed adjusted analyses in which confounders (pre-fracture HS, sociodemographic

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3 174 variables and comorbidity) were included in the model. Because the mortality of study participants
4 175 caused drop-out (loss to follow-up), we performed death-adjusted analyses to adjust for overly
5 176 optimistic estimates of patient outcomes. According to Parsons et al., we assumed that the EQ-5D
6 177 score ranges from zero to death; these observations were then carried forward to subsequent
7 178 assessment occasions²⁶. Effects were expressed as regression coefficients (Beta; β), odds ratios (ORs),
8 179 and adjusted ORs (aORs) with 95% confidence intervals (CI), representing the longitudinal
9 180 association between frailty and HS and between frailty and capability wellbeing over time, reflecting
10 181 both the within- and between-subject relationship²⁷. Statistical test results were considered significant
11 182 at a level of $p < 0.05$. The statistical analyses were performed in SPSS version 24.0 (IBM Statistical
12 183 Package for Social Sciences, Armonk, NY, USA) and R version 3.4.0 (The R Project for Statistical
13 184 Computing).

185 **Results**186 *Study population*

187 Figure 1 shows the flow diagram of study participants. Only patients who completed the pre-fracture
 188 questionnaire, including the GFI, were included in this study. No significant differences were found in
 189 patient demographics (age: $p=0.215$; sex: $p=0.183$) between responders and non-responders. In total,
 190 696 patients were included, and 371 patients (53.3%) were considered frail. Table 1 shows patients'
 191 characteristics and clinical parameters, divided into frail and non-frail participants. In total, the mean
 192 age was 80.3 years, and 70.4% of the sample was female. Furthermore, 216 (31.0%) proxy
 193 participants were included.

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Table 1. Demographic and clinical baseline characteristics of the cohort.

Variables	Total	Frail	Non-frail
N	696	371 (53.3)	325 (46.7)
Female (N,%)	490 (70.4)	279 (75.2)	211 (64.9)
Age (mean, SD)	80.27 (8.62)	83.7 (7.67)	76.4 (7.94)
BMI (mean, SD)	24.7 (4.92)	24.3 (4.61)	25.2 (5.19)
Educational level ^a (N,%)			
<i>Low</i>	495 (71.1)	284 (76.5)	211 (64.9)
<i>Middle</i>	107 (15.4)	57 (15.4)	50 (15.4)
<i>High</i>	94 (13.5)	30 (8.1)	64 (19.7)
Pre-fracture living in institution (N,%)	151 (21.7)	140 (37.7)	11 (3.4)
Pre-fracture mobility (N,%)			
<i>Dependent</i>	360 (51.7)	94 (25.3)	266 (81.8)
<i>Mobile with aid</i>	212 (30.5)	158 (42.6)	54 (16.7)
<i>Independent (immobile)</i>	124 (17.8)	119 (32.1)	5 (1.5)
ASA			
1	63 (9.1)	9 (2.4)	54 (16.6)
2	348 (50.0)	137 (36.9)	211 (64.9)
3	273 (39.2)	216 (58.3)	57 (17.6)
4-5	12 (1.7)	9 (2.4)	3 (0.9)
Dementia (N,%)	159 (22.8)	153 (41.2)	6 (1.8)
Proxy respondents (N,%)	216 (31.0)	197 (53.1)	19 (5.8)
Type of treatment (N,%)			
<i>Non-operative</i>	21 (3.0)	13 (3.5)	8 (2.4)
<i>Intramedullary fixation</i>	255 (36.6)	162 (43.7)	93 (28.6)
<i>Cannulated Hip Screws</i>	57 (8.2)	23 (6.2)	34 (10.5)
<i>Hemi-arthroplasty</i>	288 (41.4)	157 (42.3)	131 (40.3)
<i>Total hip arthroplasty</i>	75 (10.8)	16 (4.3)	59 (18.2)

Type of fracture (N,%)			
<i>Intracapsular</i>	440 (63.2)	208 (56.1)	232 (71.4)
<i>Extracapsular</i>	256 (36.8)	163 (43.9)	93 (28.6)
Length of hospital stay (mean, SD)	8.28 (5.67)	9.46 (6.79)	6.92 (3.67)
Discharge to home (yes, %)	392 (56.3)	164 (44.2)	228 (70.2)
1-year mortality (N, %)	98 (14.1)	86 (23.2)	12 (3.7)
GFI score (mean, SD)	4.78 (4.12)	8.01 (2.78)	1.09 (1.07)
EQ-5D pre-fracture utility score (mean, SD)	0.72 (0.28)	0.55 (0.26)	0.91 (0.13)
EQ-5D pre fracture VAS (mean, SD)	69.7 (20.6)	57.6 (17.7)	83.4 (13.6)

^a Educational level: Low = no diploma, primary education, preparatory secondary vocational education; Middle = university preparatory education, senior general secondary education, senior secondary vocational education and training; High = universities of applied sciences: associate degree or university degree.

Abbreviations: N=number; SD: Standard Deviation; BMI: body-mass index; ASA: American Society of Anesthesiologists grading; EQ-5D: Euroqol 5 dimensions; VAS: visual analogue scale

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198 *The longitudinal association between frailty and HS*

199 There were significant differences in health status between frail and non-frail patients during all
 200 follow-up time points ($p < 0.0001$; Figure 2). Pre-fracture frailty was associated with pre-fracture HS,
 201 adjusted for residential status as a confounder ($\beta = -0.29$; SE 0.02; $p < 0.001$; 95% CI -0.33, -0.26).

202 The pattern of recovery trajectories in the prevalence of reported problems in the domains of the EQ-
 203 5D during the first year period after hip fracture differed between the frail and non-frail patients
 204 (Figure 3a/3b). For pre-fracture, a significantly higher proportion of patients in the frail group had
 205 problems with mobility, self-care and usual activities, and experienced more pain and signs of
 206 anxiety/depression ($p < 0.001$; Table 2). The percentage of patients with problems of anxiety/depression
 207 in the frail group was 54.7% at 1 week and 58.3% at 1 year, compared with 18.9% at 1 week and
 208 14.2% at 1 year in the non-frail group. The aOR of the domain anxiety/depression revealed a 1.346-
 209 fold increase in problems (95% CI 1.045, 1.734) experienced by frail patients over one year, compared
 210 with the problems in the non-frail group.

Table 2. Mixed model analyses of change in EQ-3D-3L for frail patients compared to non-frail patients (=reference group) over time

EQ-5 Domain	Crude			Adjusted ^a		
	OR	95% CI	p	OR	95% CI	p
Mobility	1.970	1.501, 2.590	<0.001	1.186	0.877, 1.605	0.268
Self-care	2.210	1.737, 2.812	<0.001	1.272	0.980, 1.653	0.071
Usual activities	2.545	1.909, 3.393	<0.001	1.165	0.859, 1.579	0.326
Pain/discomfort	1.394	1.089, 1.785	0.008	1.179	0.909, 1.529	0.214
Anxiety/depression	1.928	1.507, 2.468	<0.001	1.346	1.045, 1.734	0.022

Reference group= non-frail

^a Adjusted for pre-fracture status of the EQ-5D domain, age, pre-fracture residential status, ASA and dementia

Abbreviations: EQ: Euroqol; OR: odds ratio; CI: confidence interval

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214 The VIF before the final model analysis ranged from 1.23 to 1.69, indicating that there was no
 215 problem with multicollinearity. Frailty was negatively associated with HS (β -0.333; 95% CI -0.366, -
 216 0.299) and self-rated health (β -21.9; 95% CI -24.2, -19.6) in elderly patients one year after hip
 217 fracture. (Table 3). The estimated crude regression coefficient of -0.333 for frail patients in relation to
 218 health status can be interpreted as follows: a patient considered to be frail at baseline has a 0.333 lower
 219 EQ-5D utility score compared to non-frail patients. The regression coefficient was -0.115 (95% CI -
 220 0.160, -0.069) for the association between frailty and health status, adjusted for deceased drop-outs
 221 and for confounders, including pre-fracture EQ-5D score, age, pre-fracture residential status, pre-
 222 fracture mobility, ASA and dementia.

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Table 3. Analyses results on the association between frailty and health status/capability wellbeing over 1 year after hip fracture (reference group = non-frail)

	EQ-5D utility score (health status)			EQ-VAS (self-rated health)			ICECAP-O score (capability wellbeing)		
	β	95% CI	p	β	95% CI	p	β	95% CI	p
Crude	-0.333	-0.366, -0.299	<0.001	-21.90	-24.19, -19.61	<0.001	-0.296	-0.322, -0.270	<0.001
Adjusted ^a	-0.100	-0.143, -0.057	<0.001	-7.74	-10.73, -4.75	<0.001	-0.130	-0.164, -0.096	<0.001
Adjusted ^b	-0.357	-0.392, -0.322	<0.001	-26.40	-29.20, -23.61	<0.001	-0.347	-0.378, -0.316	<0.001
Adjusted ^c	-0.115	-0.160, -0.069	<0.001	-9.42	-13.09, -5.75	<0.001	-0.146	-0.187, -0.106	<0.001

Reference group= non-frail

^a Adjusted for pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia

^b Adjusted for death

^c Adjusted for death, and pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and

dementia

Abbreviations: EQ-5D: Euroqol 5 dimensions; EQ-VAS Euroqol Visual Analogue Scale; ICECAP-O: ICEpop CAPability measure for Older People; β : Regression coefficient; CI: confidence interval

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226 *The longitudinal association between frailty and capability wellbeing*

227 Figure 4 shows differences in capability wellbeing between frail and non-frail patients during all

228 follow-up time points ($p < 0.0001$). We found a significantly strong negative association on average

229 between frailty and capability wellbeing over time, with a death-adjusted regression coefficient that

230 included all confounders of $\beta -0.146$ (95% CI $-0.187, -0.106$; Table 3).

231

232 Discussion

233 *Summary of results*

234 It is well known that elderly patients with a hip fracture have poor QoL⁶. However, it is unknown how
235 much frailty affects patients' QoL. This longitudinal cohort study shows that (i) frail patients with a
236 hip fracture had poorer HS than non-frail patients at baseline, (ii) frail patients had poorer HS and
237 poorer capability wellbeing than non-frail patients over time, and (iii) frailty at the onset of hip
238 fracture was negatively associated with HS and capability wellbeing one year after hip fracture.
239 Confounders, such as pre-fracture HS, age, pre-fracture residential status, pre-fracture mobility, ASA
240 and dementia, weakened the association between frailty and QoL, but the association remained
241 significant and clinically relevant. Our findings demonstrate that pre-fracture frailty is significantly
242 associated with poor HS, self-rated health and capability wellbeing the first year after recovery from
243 hip fracture.

244

245 *Comparison with existing literature*

246 This study demonstrates that frailty is a common condition among elderly patients with a hip fracture.
247 In our study, 53.3% of the patients with a hip fracture were considered frail. This finding is in line
248 with that of a small pilot study of Kistler et al., who found that 51% of patients were considered frail²⁸.
249 Previous studies, summarized in a systematic review by Lin and colleagues, showed frailty to be
250 associated with adverse outcomes, such as prolonged length of stay and mortality in older surgical
251 patients¹³. This finding is in line with ours, showing a significant difference in length of stay between
252 frail and non-frail patients ($t(696)=-5.845$, $p<0.001$). In line with the findings of Patel et al.²⁹ and
253 Dayama et al.³⁰, we also found increased 1-year mortality rates in frail patients with a hip fracture.
254 However, apart from these associations, our results showed that frailty is also negatively associated
255 with QoL. This finding is of major importance because frailty not only seems to influence patients'
256 postoperative outcomes, such as mortality and complications, but also has a perceived impact on the
257 level of patients' physical, emotional and social functioning.
258 In our study, HS and capability wellbeing do not improve substantially within six months after hip
259 fracture for both frail and non-frail patients. This finding is in line with that of the prospective cohort
260 study of Griffins et al., who also revealed an initial marked decline in HS after hip fracture, followed
261 by improvement within four months and no return to baseline at 1 year after hip fracture³¹. However,
262 in our study, we showed the pattern of QoL and distinguished between frail and non-frail patients. We
263 revealed a significantly more prominent decline in HS, self-rated health and capability wellbeing for
264 frail patients compared to non-frail patients the first year of recovery from hip fracture. To show that
265 our findings are clinically relevant, Walters et al. published the minimum clinically important
266 difference of 0.074 for the utility score of the EQ-5D³².
267 It is remarkable that in the non-frail group, a high percentage of individuals do not return to pre-
268 fracture levels within a year on all domains of the EQ-5D. In particular, the domains mobility, pain

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3 269 and usual activities showed major differences between the percentage of non-frail patients and that of
4 270 frail patients reporting problems at baseline and 1 year after hip fracture . However, the same did not
5 271 apply to the EQ-5D domain anxiety and depression, which revealed a strong positive association
6 272 between frailty and anxiety/depression. Until now, the literature revealed a prevalence rate of 10% of
7 273 patients reporting depressive symptoms after hip fracture³³. Future research should provide insight into
8 274 whether frailty is a predictor of psychological distress, characterized by symptoms of anxiety,
9 275 symptoms of depression and symptoms of posttraumatic stress.
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14 277 *Limitations and strengths*

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16 278 This study had several limitations. First, participants may not accurately recall their status prior to the
17 279 fracture, which might affect the results of the GFI and the EQ-5D at baseline. To minimize recall bias,
18 280 the pre-fracture frailty status and HS data were only collected in patients who flowed into the study
19 281 until one month had passed. In addition, because of the length of the questionnaire, we did not ask the
20 282 items of the ICECAP-O prior to the fracture, and we could not compare this longitudinal outcome with
21 283 pre-fracture capability wellbeing. Second, frail patients showed a higher capability wellbeing score at
22 284 one-week follow-up than at one-month follow-up. This is probably due to selection bias because frail
23 285 patients in relatively good condition were able to complete the questionnaire at this early follow-up
24 286 time point. Therefore, the overall QoL of patients after a hip fracture, especially in the frail group, is
25 287 probably worse than that presented in this study. On the other hand, an early follow-up time point at
26 288 one week is unique in prospective research in hip fracture populations, and we adjusted for
27 289 confounding variables in our mixed model analyses. Third, it is well known that surgery for hip
28 290 fractures is frequently followed by complications³⁴. However, information about complications after
29 291 hip fractures was not collected in this multicenter study, and complications could have affected
30 292 patients' QoL.

31 293 A strength of this study is the setup in the form of a multicenter prospective cohort study. We could
32 294 include a large number of participants in different geographic locations, along with the possibility of
33 295 including a wider range of hip-fracture population groups, which increases the generalizability of this
34 296 study. We also included proxy participants in case a patient was unable to participate in this study for
35 297 several reasons, including cognitive impairment. Particularly, this group is essential to include in this
36 298 study because a major proportion of the frail group (41.2%) was suffering from dementia. Another
37 299 strength of this study is that we reported death-adjusted outcomes according to Parsons et al²⁶. When
38 300 reporting QoL for patients after a hip fracture, excluding patients who die during follow-up leads to
39 301 overly optimistic estimates of patient outcomes and is likely to cause bias.
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53 303 *Implication for clinical practice*

54 304 The findings of this study support the hypothesis that pre-fracture frailty has an unfavorable effect on
55 305 HS, self-rated health and capability wellbeing after a hip fracture. Pre-operative frailty assessment can

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3 306 be valuable in informing patients and their relatives about the impact of hip fracture on patients'
4 307 physical, emotional and social functioning in the recovery period after a hip fracture. This frailty
5 308 assessment could classify patients at high risk for unfavorable outcomes regarding poor QoL. It could
6 309 support clinicians in tailoring treatment for medical decision making at an early phase. A clinically
7 310 easy-to-use and universal frailty indicator, such as the GFI, could have important implications in
8 311 prognostic counseling and care planning among older adults with hip fracture.
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313 **Conclusions**

314 Our results show that frailty is negatively associated with patients' QoL one year after hip fracture,
315 even after adjusting for pre-fracture HS, age, pre-fracture residential status, pre-fracture mobility, ASA
316 and dementia. This study highlights hip fracture as a major cause of burden and morbidity, especially
317 in frail patients. This finding suggests that early identification of pre-fracture frailty in patients with a
318 hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment.
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3 319 **Contribution of authors:**

4 320 CR, NK, LM, TG and MJ contributed to conception and design of this study. CR, ML, NK and LM
5 321 contributed to the data collection. CR, ML, NK, LM and MJ contributed to the analyses and
6 322 interpretation. CR, ML, NK, LM, JS, TG and MJ contributed to preparation of the manuscript. The
7 323 final version of the article was approved by all the authors.
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11 325 **Competing interests:** CR declares that he has no competing interest. ML declares that she has no
12 326 competing interest. NK declares that she has no competing interest. LM declares that she has no
13 327 competing interest. JS declares that she has no competing interest. TG declares that he has no
14 328 competing interest. MJ declares that she has no competing interest.
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18
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21 332 role in the investigation.
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25 334 **Ethical approval:** All procedures performed in studies involving human participants were in
26 335 accordance with the ethical standards of the institutional and/or national research committee and with
27 336 the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study
28 337 has been approved by the Medical Ethics Committee Brabant, the Netherlands (project number
29 338 NL50258.028.14).
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34 340 **Data sharing statement:** Data could be shared after consultation with BIOS study group
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343 **References**

- 344 1. Johnell O, Kanis J. An estimate of the worldwide prevalence, mortality and disability associated
345 with hip fracture. *Osteoporosis Int.* 2004;15(11):897-902.
- 346 2. Hu F, Jiang C, Shen J, Tang P, Wang Y. Preoperative predictors for mortality following hip fracture
347 surgery: A systematic review and meta-analysis. *Injury.* 2012;43(6):676-685.
- 348 3. Keene GS, Parker MJ, Pryor GA. Mortality and morbidity after hip fractures. *BMJ.*
349 1993;307(6914):1248-1250.
- 350 4. Marks R. Hip fracture epidemiological trends, outcomes, and risk factors, 1970-2009. *Int J Gen*
351 *Med.* 2010;3:1-17.
- 352 5. Johnell O. The socioeconomic burden of fractures: Today and in the 21st century. *Am J Med.*
353 1997;103(2):S20-S26.
- 354 6. Peeters CM, Visser E, Van de Ree, Cornelis LP, Gosens T, Den Oudsten BL, De Vries J. Quality of
355 life after hip fracture in the elderly: A systematic literature review. *Injury.* 2016.
- 356 7. De Vries J. Quality of life assessment. *Assessment in behavioral medicine.* 2001:353-370.
- 357 8. Whoqol Group. Development of the world health organization WHOQOL-BREF quality of life
358 assessment. *Psychol Med.* 1998;28(3):551-558.
- 359 9. Grewal I, Lewis J, Flynn T, Brown J, Bond J, Coast J. Developing attributes for a generic quality of
360 life measure for older people: Preferences or capabilities? *Soc Sci Med.* 2006;62(8):1891-1901.
- 361 10. van Leeuwen KM, Bosmans JE, Jansen AP, et al. Comparing measurement properties of the EQ-
362 5D-3L, ICECAP-O, and ASCOT in frail older adults. *Value Health.* 2015;18(1):35-43.
- 363 11. Parsons N, Griffin XL, Achten J, Costa ML. Outcome assessment after hip fracture: Is EQ-5D the
364 answer? *Bone Joint Res.* 2014;3(3):69-75.

- 1
2
3 365 12. Xue Q. The frailty syndrome: Definition and natural history. *Clin Geriatr Med.* 2011;27(1):1-15.
4
5
6 366 13. Lin H, Watts J, Peel N, Hubbard R. Frailty and post-operative outcomes in older surgical patients:
7
8 367 A systematic review. *BMC geriatrics.* 2016;16(1):157.
9
10
11 368 14. de Jongh MA, Kruihof N, Gosens T, et al. Prevalence, recovery patterns and predictors of quality
12
13 369 of life and costs after non-fatal injury: The brabant injury outcome surveillance (BIOS) study. *Inj*
14
15 370 *Prev.* 2017;23(1):59-2016-042032. Epub 2016 May 6.
16
17
18 371 15. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies
19
20 372 in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS medicine.*
21
22 373 2007;4(10):e296.
23
24
25 374 16. Steverink N, Slaets J, Schuurmans H, Van Lis M. Measuring frailty: Development and testing of
26
27 375 the groningen frailty indicator (GFI). *Gerontologist.* 2001;41(1):236.
28
29
30 376 17. Peters LL, Boter H, Buskens E, Slaets JP. Measurement properties of the groningen frailty
31
32 377 indicator in home-dwelling and institutionalized elderly people. *Journal of the American Medical*
33
34 378 *Directors Association.* 2012;13(6):546-551.
35
36
37 379 18. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. *Health*
38
39 380 *Policy.* 1990;16(3):199-208.
40
41
42 381 19. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The dutch tariff: Results and
43
44 382 arguments for an effective design for national EQ-5D valuation studies. *Health Econ.*
45
46 383 2006;15(10):1121-1132.
47
48
49 384 20. Coast J, Flynn TN, Natarajan L, et al. Valuing the ICECAP capability index for older people. *Soc*
50
51 385 *Sci Med.* 2008;67(5):874-882.
52
53
54
55
56
57
58
59
60

- 1
2
3 386 21. Makai P, Koopmanschap MA, Brouwer WB, Nieboer AA. A validation of the ICECAP-O in a
4 387 population of post-hospitalized older people in the netherlands. *Health and quality of life outcomes*.
5 388 2013;11(1):57.
- 6
7
8
9
10 389 22. Couzner L, Ratcliffe J, Lester L, Flynn T, Crotty M. Measuring and valuing quality of life for
11 390 public health research: Application of the ICECAP-O capability index in the australian general
12 391 population. *International journal of public health*. 2013;58(3):367-376.
- 13
14
15
16
17 392 23. Coast J, Peters TJ, Natarajan L, Sproston K, Flynn T. An assessment of the construct validity of
18 393 the descriptive system for the ICECAP capability measure for older people. *Quality of Life Research*.
19 394 2008;17(7):967-976.
- 20
21
22
23
24 395 24. Makai P, Brouwer WB, Koopmanschap MA, Nieboer AP. Capabilities and quality of life in dutch
25 396 psycho-geriatric nursing homes: An exploratory study using a proxy version of the ICECAP-O.
26 397 *Quality of life research*. 2012;21(5):801-812.
- 27
28
29
30
31 398 25. Van Buuren S. *Flexible imputation of missing data*. CRC press; 2012.
- 32
33
34 399 26. Parsons N, Griffin XL, Achten J, Chesser TJ, Lamb SE, Costa ML. Modelling and estimation of
35 400 health-related quality of life after hip fracture: A re-analysis of data from a prospective cohort study. .
36 401 ;*Bone Joint Res* 2018;7:1–5.
- 37
38
39
40
41 402 27. Twisk JW. *Applied longitudinal data analysis for epidemiology: A practical guide*. Cambridge
42 403 University Press; 2013.
- 43
44
45
46 404 28. Kistler EA, Nicholas JA, Kates SL, Friedman SM. Frailty and short-term outcomes in patients with
47 405 hip fracture. *Geriatric orthopaedic surgery & rehabilitation*. 2015;6(3):209-214.
- 48
49
50
51 406 29. Patel KV, Brennan KL, Brennan ML, Jupiter DC, Shar A, Davis ML. Association of a modified
52 407 frailty index with mortality after femoral neck fracture in patients aged 60 years and older. *Clinical*
53 408 *Orthopaedics and Related Research*®. 2014;472(3):1010-1017.
- 54
55
56
57
58
59
60

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2
3 409 30. Dayama A, Olorunfemi O, Greenbaum S, Stone ME,Jr, McNelis J. Impact of frailty on outcomes
4 410 in geriatric femoral neck fracture management: An analysis of national surgical quality improvement
5 411 program dataset. *Int J Surg*. 2016;28:185-190.
6
7
8
9
10 412 31. Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML. Recovery of health-related quality of
11 413 life in a united kingdom hip fracture population. the warwick hip trauma evaluation--a prospective
12 414 cohort study. *Bone Joint J*. 2015;97-B(3):372-382.
13
14
15
16 415 32. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state
17 416 utility measures: EQ-5D and SF-6D. *Quality of life research*. 2005;14(6):1523-1532.
18
19
20
21 417 33. Cristancho P, Lenze E, Avidan M, Rawson K. Trajectories of depressive symptoms after hip
22 418 fracture. *Psychol Med*. 2016;46(7):1413-1425.
23
24
25
26
27 419 34. Flikweert E, Wendt K, Diercks R, et al. Complications after hip fracture surgery: Are they
28 420 preventable? *European Journal of Trauma and Emergency Surgery*. 2017:1-8.
29
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3 423 **Figure 1.** Flow diagram of study participants. Participants who missed some of the measurements are
4 424 indicated as 'no show'.
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6 425 **Figure 2.** Patterns of health status according to frailty status over time.
7 426 **Figure 3.** Percentage of frail (a) and non-frail (b) patients reporting problems on each EQ-5D-3L.
8 427 questionnaire item at each follow-up time point.
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10 428 **Figure 4.** Patterns of capability wellbeing according to frailty status over time.
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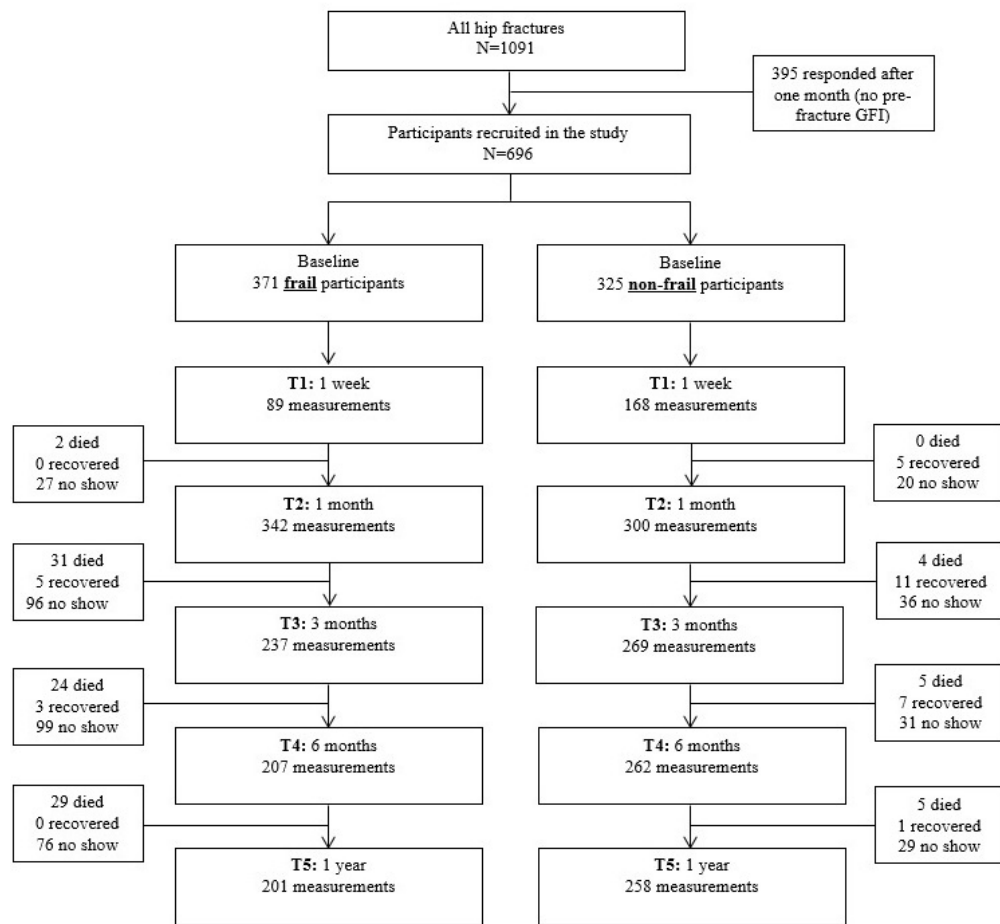


Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'.

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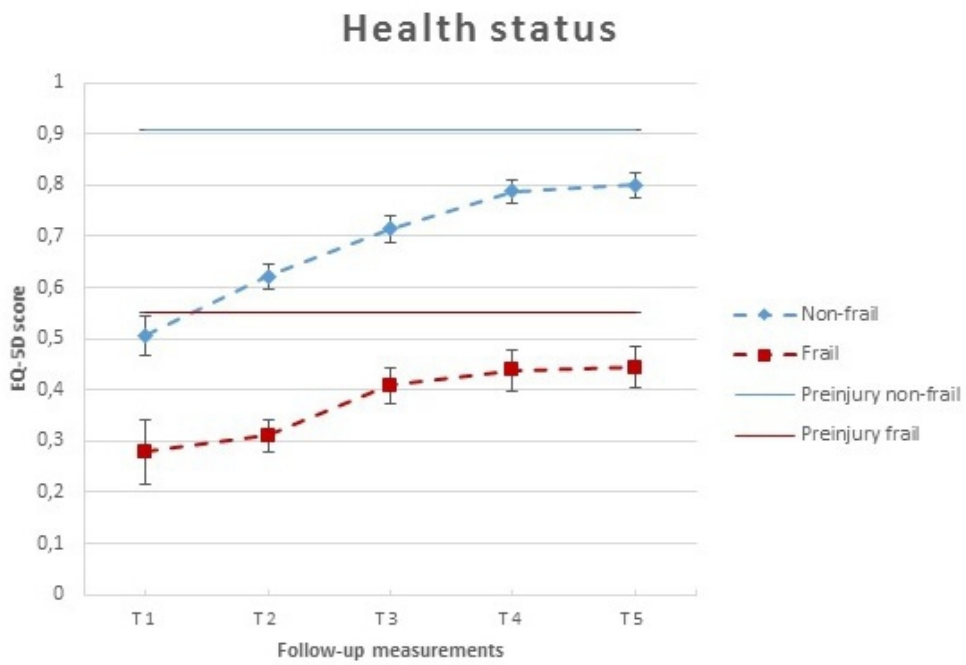


Figure 2. Patterns of health status according to frailty status over time.

47x33mm (300 x 300 DPI)

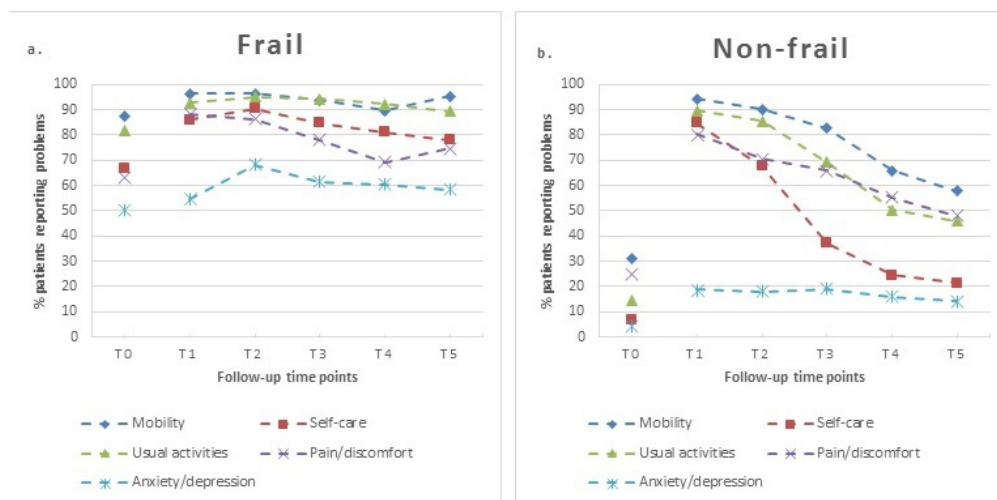


Figure 3. Percentage of frail (a) and non-frail (b) patients reporting problems on each EQ-5D-3L questionnaire item at each follow-up time point.

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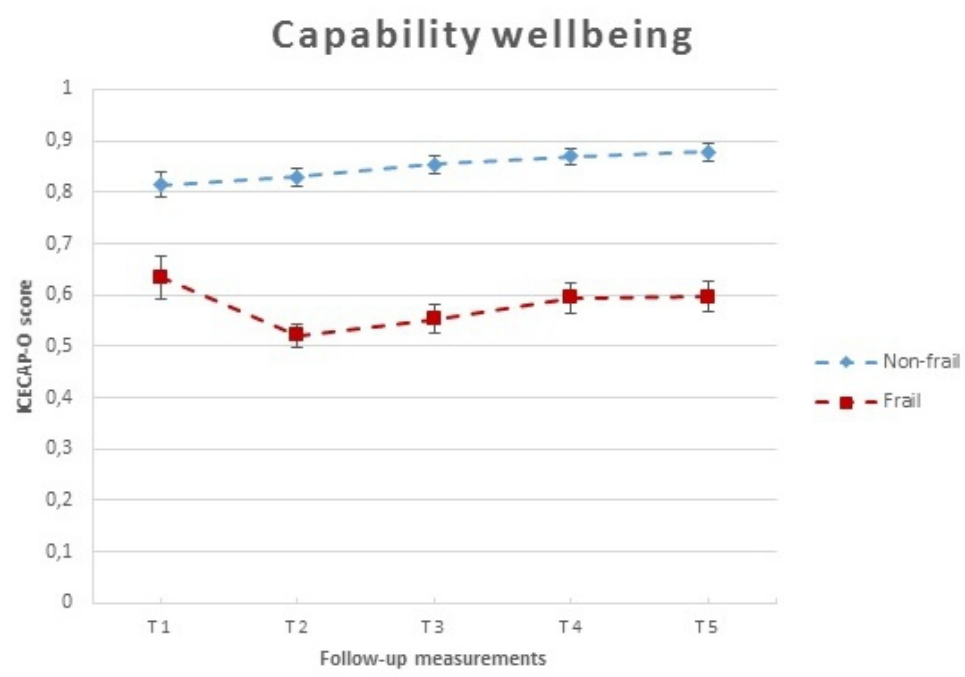


Figure 4. Patterns of capability wellbeing according to frailty status over time.

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APPENDIX 1: Groningen Frailty Indicator

Physical domain

Are you able to carry out these tasks single handedly and without any help? (The use of help resources, such as a walking stick, walking frame, or wheelchair, is considered to be independent.)

1. Shopping
2. Walking around outside (around the house or to the neighbors)
3. Dressing and undressing
4. Going to the toilet
5. What mark do you give yourself for physical fitness? (scale 0 to 10)
6. Do you experience problems in daily life because of poor vision?
7. Do you experience problems in daily life because of being hard of hearing?
8. Have you lost a lot of weight in the last 6 months? (3 kg in 1 month or 6 kg in 2 months)
9. Do you take 4 or more different types of medicine?

Cognitive domain

10. Do you have any complaints about your memory?

Social domain

11. Do you have ever experienced an emptiness around you?
12. Do you long for other people (to socialize with)?
13. Do you feel abandoned?

Psychological domain

14. In the past 4 weeks, did you feel downhearted or sad?
15. In the past 4 weeks, did you feel anxious or nervous?

Scoring:

Questions 1-4: → Yes = 0; no = 1

Question 5: → 0-6 = 1; 7-10 = 0

Questions 6-9: → No = 0; yes = 1

Question 10: → No = 0; sometimes = 0; yes = 1

Questions 11-15: → Yes = 1; sometimes = 1; no = 0

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5-6
		(b) Describe any methods used to examine subgroups and interactions	5-6
		(c) Explain how missing data were addressed	5
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	6
		(e) Describe any sensitivity analyses	

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-10
		(b) Indicate number of participants with missing data for each variable of interest	7-10
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7-10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-
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Generalisability	21	Discuss the generalisability (external validity) of the study results	12-
			13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The effect of frailty on Quality of Life in elderly patients after hip fracture: a longitudinal study

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Primary Subject Heading:	Surgery
Secondary Subject Heading:	Geriatric medicine, Patient-centred medicine
Keywords:	hip fracture, frailty, Quality of Life, elderly

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3 1 **Title:** The effect of frailty on Quality of Life in elderly patients after hip fracture: a longitudinal study

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37 33 **Keywords:** hip fracture, frailty, Quality of Life, elderly
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39 35 **Word count:** 3253
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36 Abstract

37 **Objective:** The aims of this study were to examine the pattern of changes over time in health status
38 (HS) and Quality of Life (QoL) in the first year after hip fracture and to quantify the association
39 between frailty at the onset of hip fracture and the change in HS and QoL one year later. The major
40 hypothesis was that frailty, a clinical state of increased vulnerability, is a good predictor of QoL in
41 patients recovering from hip fracture.

42 **Design:** Prospective observational follow-up cohort study.

43 **Setting:** Secondary care. Ten participating centres in Brabant, the Netherlands.

44 **Participants:** 1091 patients entered the study and 696 patients completed the study. Patients with a
45 hip fracture aged 65 years and older or proxy respondents for patients with cognitive impairment were
46 included in this study.

47 **Main outcome measures:** The primary outcomes were HS (EuroQol-5 Dimensions questionnaire;
48 EQ-5D) and capability wellbeing (ICEpop CAPability measure for Older People; ICECAP-O). Pre-
49 fracture frailty was defined with the Groningen Frailty Indicator (GFI), with $GFI \geq 4$ indicating frailty.
50 Participants were followed up at one month, three months, six months and one year after hospital
51 admission.

52 **Results:** In total, 371 patients (53.3%) were considered frail. Frailty was negatively associated with
53 HS (β -0.333; 95% CI -0.366, -0.299), self-rated health (β -21.9; 95% CI -24.2, -19.6), and capability
54 wellbeing (β -0.296; 95% CI -0.322, -0.270) in elderly patients one year after hip fracture. After
55 adjusting for confounders, including death, pre-fracture HS, age, pre-fracture residential status, pre-
56 fracture mobility, ASA and dementia, associations were weakened but remained significant.

57 **Conclusions:** We revealed that frailty is negatively associated with QoL one year after hip fracture,
58 even after adjusting for confounders. This finding suggests that early identification of pre-fracture
59 frailty in patients with a hip fracture is important for prognostic counseling, care planning, and the
60 tailoring of treatment.

62 Strengths and limitations of this study:

- 63 - This study addresses the paucity of knowledge of frailty in elderly patients with a hip fracture
- 64 - This is multicenter prospective cohort study included a large number of subjects
- 65 - Patients and proxy participants were included in different geographic locations, which increases the
66 generalizability of this study.
- 67 - Participants may not accurately recall their health status prior to the fracture, which might affect the
68 results.
- 69 - The frail group contained more no-show cases, which could resulted in selective drop-out.

70 Introduction

71 A hip fracture is a serious event in the elderly population. It is associated with high mortality, morbidity
72 and disability for those who survive¹⁻³. Hip fracture risks rise exponentially with increasing age. With
73 the rising longevity across the globe, it seems reasonable that hip fractures will remain an important
74 global health problem with substantial socioeconomic costs^{4,5}. A hip fracture has a major impact on
75 health status (HS) and Quality of Life (QoL)⁶. HS represents the perceived impact of a disease on the
76 level of patients' physical, emotional and social functioning⁷. Several factors are negatively associated
77 with HS in elderly patients with a hip fracture, including female gender, comorbidity, poor nutritional
78 status, severe post-surgical pain perception, long duration of hospital stay, postoperative complications,
79 and low physical or psychosocial functioning at pre-fracture, including cognitive dysfunction⁶. QoL is
80 a multidimensional concept including both positive and negative aspects of life, and it measures patients'
81 evaluation of functioning in line with their expectations⁸. QoL in older people is limited by an
82 individuals' loss of ability to pursue different attributes with regard to attachment, role, enjoyment,
83 security and control⁹. This multidimensional concept can be measured with a capability wellbeing
84 instrument in frail older adults following a hip fracture^{10,11}.

85 Inconclusive evidence was found for the predictive value of older age⁶. However, aging is associated
86 with a decline in physiological reserves, which impedes the body's ability to withstand and recover
87 from major and minor challenges, e.g., a hip fracture. This phenomenon is defined as frailty, a clinical
88 state of increased vulnerability, and it interacts with psychological factors, such as emotional state,
89 coping style and sociological state¹².

90 A systematic review from Lin and colleagues demonstrated that frailty is associated with adverse
91 outcomes in older post-surgery patients, including prolonged length of stay, complications and
92 postoperative mortality¹³. However, the relationship between frailty and HS, and between frailty and
93 capability wellbeing, is unknown. The aims of this study were to (i) compare HS by frailty status at the
94 time of hip fracture, (ii) describe the patterns of HS and capability wellbeing in the first year after hip
95 fracture, and (iii) quantify the association between frailty at the onset of hip fracture and the patterns in
96 HS and capability wellbeing one year following a hip fracture. We hypothesized that frail hip-
97 fractured patients would experience a higher likelihood of poor HS and capability wellbeing, even
98 after accounting for traditionally measured clinical risk factors.

99 **Materials and Methods**

100 *Study design and participants*

101 The Brabant Injury Outcome Surveillance (BIOS), a multicenter prospective observational follow-up
102 cohort study, was conducted to obtain data at one week and one, three, six and twelve months after hip
103 fracture. Full details of the study, objectives and methods are described in detail elsewhere¹⁴. Ethical
104 approval was received from the Medical Ethics Committee Brabant, the Netherlands (project number
105 NL50258.028.14). This report has been prepared in accordance with the STROBE guidelines¹⁵.

106 All participants were included between August 2015 and November 2016 from the ten participating
107 Dutch hospitals and were invited during hospital admission or within several days post-trauma by
108 mail. Both patients aged 65 years and older and proxy respondents for patients with cognitive
109 impairment were eligible for inclusion. Proxy participants could participate from one month onwards.
110 Exclusion criteria were as follows: (i) pathological hip fractures, (ii) patients and proxy respondents
111 being unable or unwilling to give written informed consent, and (iii) patients with insufficient
112 knowledge of the Dutch language.

114 *Data collection*

115 Baseline pre-fracture information (T0) was gathered one week or one month after hip fracture by self-
116 or proxy-reported questionnaires. The following data were collected at baseline within one month after
117 hip fracture: demographic characteristics (age, gender, educational level), American Society of
118 Anesthesiologists (ASA) grading, mobility, degree of frailty and HS. All participants were followed-
119 up at one week (T1), one month (T2), three months (T3), six months (T4) and one year (T5) after
120 hospital admission. At follow-up sessions, questionnaires were sent to the participant or proxy. In
121 cases of no return, they were contacted by telephone several times. If this method failed, the
122 participant or proxy was considered to be a non-responder at that follow-up time point.

124 *Patient and public involvement*

125 Patients were involved in the recruitment to and conduct of the study. In a small pilot before inclusion
126 in the BIOS, patients were asked their findings about the questionnaire and outcomes. We made small
127 adjustments and results were disseminated to study participants who want to receive information by a
128 newsletter.

130 *Outcome assessment questionnaires*

131 The Groningen Frailty Indicator (GFI) questionnaire was used to identify elderly individuals
132 as being frail. The GFI is a 15-item self-reported instrument and screens for the loss of function and
133 resources in four domains of functioning: physical, cognitive, social and psychological (supplementary
134 file)¹⁶. The sum score of the GFI ranges from 0 to 15, with a score of ≥ 4 indicating frailty. The study

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3 135 of Peters et al. concluded that the GFI is a feasible, reliable and valid self-assessment in home-
4 136 dwelling and institutionalized elderly people by detecting those at high risk for poor outcomes¹⁷.

6 137 The score on the EuroQol-5 Dimensions (EQ-5D), a measure of HS¹⁸. The EQ-5D has two
7
8 138 parts: a visual analogue scale (VAS), which measures self-rated health, and an instrument along five
9
10 139 health domains related to daily activities, including mobility, self-care, usual activities, pain and
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12 140 discomfort, and anxiety and depression. A respondent's EQ-VAS presents self-rated health on a
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14 141 vertical scale with two endpoints, i.e., 'best imaginable health state' (100) and 'worst imaginable
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16 142 health state' (0). Each dimension consists of a three-level response: no problems, moderate problems
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18 143 or severe problems. A scoring algorithm is available by which each health status description can be
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20 144 expressed into an overall score using a published utility algorithm for the Dutch population. HS was
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22 145 assessed with the utility score (EQ-5D™ utility), ranging from 0 representing death to 1 for full health.
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24 146 A negative utility score indicates a health status worse than death. The Dutch tariffs were used for this
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26 147 study to calculate EQ-5D-3L™ preference weights¹⁹. The EQ-5D has good measurement properties
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28 148 and could be used to measure outcomes for patients recovering from hip fracture¹¹.

25 149 The ICEpop CAPability measure for Older People (ICECAP-O) provides a broad assessment
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27 150 of capability wellbeing as it measures an individual's ability to 'do' and 'be' the things that are
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29 151 important in life²⁰. This index of capability focuses on wellbeing defined in a broader sense, rather
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31 152 than defined by health, and covers the following five attributes: attachment (love and friendship),
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33 153 security (thinking about the future without concern), role (doing things that make you feel valued),
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35 154 enjoyment (enjoyment and pleasure), and control (independence). These attributes are used to
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37 155 calculate a tariff between 0, meaning no capability, and 1, representing full capability. The ICECAP-O
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39 156 has been validated in different elderly populations and for this study the population of Makai et al. of
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41 157 post-hospitalized older people in the Netherlands was used to compare scores^{21,22}. The questionnaire
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43 158 shows good convergent validity with health and wellbeing instruments and is able to discriminate
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45 159 between elderly individuals with various health profiles^{21,23,24}.

44 161 *Statistical analysis*

46 162 The descriptive statistics of the cohort were presented as the means with standard deviations (SDs) for
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48 163 continuous variables and as numbers and percentages for dichotomous or categorical variables.
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50 164 Missing baseline characteristics and missing sum scores in EQ-5D and ICECAP-O were imputed
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52 165 according to multiple imputation, using the multivariate imputation by chained equations (MICE)
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54 166 procedure²⁵. There were no variables with 5% or more missing values. The dataset was imputed 15
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56 167 times with 5 iterations. Patient demographics (age, gender) were compared between responders and
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58 168 non-responders. Univariate and multivariable linear regression models were used to compare HS by
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60 169 frailty status at time of hip fracture. To assess the association between frailty and QoL over one year,
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61 170 we used linear mixed model analyses for EQ-5D utility scores and ICECAP-O scores, and we used
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63 171 binary logistic mixed model analyses for domains of the EQ-5D. Multicollinearity was assessed with

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3 172 the variance inflation factor (VIF). After univariate analyses, we performed adjusted analyses in which
4 173 confounders (pre-fracture HS, sociodemographic variables and comorbidity) were included in the
5 174 model. Because the mortality of study participants caused drop-out (loss to follow-up), we performed
6 175 death-adjusted analyses to adjust for overly optimistic estimates of patient outcomes. According to
7 176 Parsons et al., we assumed that the EQ-5D score ranges from zero to death; these observations were
8 177 then carried forward to subsequent assessment occasions²⁶. Effects were expressed as regression
9 178 coefficients (Beta; β), odds ratios (ORs), and adjusted ORs (aORs) with 95% confidence intervals
10 179 (CI), representing the longitudinal association between frailty and HS and between frailty and
11 180 capability wellbeing over time, reflecting both the within- and between-subject relationship²⁷.
12 181 Statistical test results were considered significant at a level of $p < 0.05$. The statistical analyses were
13 182 performed in SPSS version 24.0 (IBM Statistical Package for Social Sciences, Armonk, NY, USA)
14 183 and R version 3.4.0 (The R Project for Statistical Computing).

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3 **184 Results**

4 **185 Study population**

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6 **186** Figure 1 shows the flow diagram of study participants. Only patients who completed the pre-fracture
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8 **187** questionnaire, including the GFI, were included in this study. No significant differences were found in
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10 **188** patient demographics (age: $p=0.215$; sex: $p=0.183$) between responders and non-responders. In total,
11 **189** 696 patients were included, and 371 patients (53.3%) were considered frail. Table 1 shows patients'
12
13 **190** characteristics and clinical parameters, divided into frail and non-frail participants. In total, the mean
14 **191** age was 80.3 years, and 70.4% of the sample was female. Furthermore, 216 (31.0%) proxy
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16 **192** participants were included.
17
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19 **194**

Table 1. Demographic and clinical baseline characteristics of the cohort.

Variables	Total	Frail	Non-frail
N	696	371 (53.3)	325 (46.7)
Female (N,%)	490 (70.4)	279 (75.2)	211 (64.9)
Age (mean, SD)	80.27 (8.62)	83.7 (7.67)	76.4 (7.94)
BMI (mean, SD)	24.7 (4.92)	24.3 (4.61)	25.2 (5.19)
Educational level ^a (N,%)			
<i>Low</i>	495 (71.1)	284 (76.5)	211 (64.9)
<i>Middle</i>	107 (15.4)	57 (15.4)	50 (15.4)
<i>High</i>	94 (13.5)	30 (8.1)	64 (19.7)
Pre-fracture living in institution (N,%)	151 (21.7)	140 (37.7)	11 (3.4)
Pre-fracture mobility (N,%)			
<i>Dependent</i>	360 (51.7)	94 (25.3)	266 (81.8)
<i>Mobile with aid</i>	212 (30.5)	158 (42.6)	54 (16.7)
<i>Independent (immobile)</i>	124 (17.8)	119 (32.1)	5 (1.5)
ASA			
1	63 (9.1)	9 (2.4)	54 (16.6)
2	348 (50.0)	137 (36.9)	211 (64.9)
3	273 (39.2)	216 (58.3)	57 (17.6)
4-5	12 (1.7)	9 (2.4)	3 (0.9)
Dementia (N,%)	159 (22.8)	153 (41.2)	6 (1.8)
Proxy respondents (N,%)	216 (31.0)	197 (53.1)	19 (5.8)
Type of treatment (N,%)			
<i>Non-operative</i>	21 (3.0)	13 (3.5)	8 (2.4)
<i>Intramedullary fixation</i>	255 (36.6)	162 (43.7)	93 (28.6)
<i>Cannulated Hip Screws</i>	57 (8.2)	23 (6.2)	34 (10.5)
<i>Hemi-arthroplasty</i>	288 (41.4)	157 (42.3)	131 (40.3)
<i>Total hip arthroplasty</i>	75 (10.8)	16 (4.3)	59 (18.2)

Type of fracture (N,%)			
<i>Intracapsular</i>	440 (63.2)	208 (56.1)	232 (71.4)
<i>Extracapsular</i>	256 (36.8)	163 (43.9)	93 (28.6)
Length of hospital stay (mean, SD)	8.28 (5.67)	9.46 (6.79)	6.92 (3.67)
Discharge to home (yes, %)	392 (56.3)	164 (44.2)	228 (70.2)
1-year mortality (N, %)	98 (14.1)	86 (23.2)	12 (3.7)
GFI score (mean, SD)	4.78 (4.12)	8.01 (2.78)	1.09 (1.07)
EQ-5D pre-fracture utility score (mean, SD)	0.72 (0.28)	0.55 (0.26)	0.91 (0.13)
EQ-5D pre fracture VAS (mean, SD)	69.7 (20.6)	57.6 (17.7)	83.4 (13.6)

^a Educational level: Low = no diploma, primary education, preparatory secondary vocational education; Middle = university preparatory education, senior general secondary education, senior secondary vocational education and training; High = universities of applied sciences: associate degree or university degree.
 Abbreviations: N=number; SD: Standard Deviation; : BMI: body-mass index; ASA: American Society of Anesthesiologists grading; EQ-5D: Euroqol 5 dimensions; VAS: visual analogue scale

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197 *The longitudinal association between frailty and HS*

198 There were significant differences in health status between frail and non-frail patients during all
 199 follow-up time points ($p < 0.0001$; Figure 2). Pre-fracture frailty was associated with pre-fracture HS,
 200 adjusted for residential status as a confounder ($\beta -0.29$; SE 0.02; $p < 0.001$; 95% CI -0.33, -0.26).
 201 The pattern of recovery trajectories in the prevalence of reported problems in the domains of the EQ-
 202 5D during the first year period after hip fracture differed between the frail and non-frail patients
 203 (Figure 3a/3b). For pre-fracture, a significantly higher proportion of patients in the frail group had
 204 problems with mobility, self-care and usual activities, and experienced more pain and signs of
 205 anxiety/depression ($p < 0.001$; Table 2). The percentage of patients with problems of anxiety/depression
 206 in the frail group was 54.7% at 1 week and 58.3% at 1 year, compared with 18.9% at 1 week and
 207 14.2% at 1 year in the non-frail group. The aOR of the domain anxiety/depression revealed a 1.346-
 208 fold increase in problems (95% CI 1.045, 1.734) experienced by frail patients over one year, compared
 209 with the problems in the non-frail group.

Table 2. Mixed model analyses of change in EQ-3D-3L for frail patients compared to non-frail patients (=reference group) over time

EQ-5 Domain	Crude			Adjusted ^a		
	OR	95% CI	p	OR	95% CI	p
Mobility	1.970	1.501, 2.590	<0.001	1.186	0.877, 1.605	0.268
Self-care	2.210	1.737, 2.812	<0.001	1.272	0.980, 1.653	0.071
Usual activities	2.545	1.909, 3.393	<0.001	1.165	0.859, 1.579	0.326
Pain/discomfort	1.394	1.089, 1.785	0.008	1.179	0.909, 1.529	0.214
Anxiety/depression	1.928	1.507, 2.468	<0.001	1.346	1.045, 1.734	0.022

Reference group= non-frail

^a Adjusted for pre-fracture status of the EQ-5D domain, age, pre-fracture residential status, ASA and dementia

Abbreviations: EQ: Euroqol; OR: odds ratio; CI: confidence interval

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213 The VIF before the final model analysis ranged from 1.23 to 1.69, indicating that there was no
 214 problem with multicollinearity. Frailty was negatively associated with HS (β -0.333; 95% CI -0.366, -
 215 0.299) and self-rated health (β -21.9; 95% CI -24.2, -19.6) in elderly patients one year after hip
 216 fracture. (Table 3). The estimated crude regression coefficient of -0.333 for frail patients in relation to
 217 health status can be interpreted as follows: a patient considered to be frail at baseline has a 0.333 lower
 218 EQ-5D utility score compared to non-frail patients. The regression coefficient was -0.115 (95% CI -
 219 0.160, -0.069) for the association between frailty and health status, adjusted for deceased drop-outs
 220 and for confounders, including pre-fracture EQ-5D score, age, pre-fracture residential status, pre-
 221 fracture mobility, ASA and dementia.

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Table 3. Analyses results on the association between frailty and health status/capability wellbeing over 1 year after hip fracture (reference group = non-frail)

	EQ-5D utility score (health status)			EQ-VAS (self-rated health)			ICECAP-O score (capability wellbeing)		
	β	95% CI	p	β	95% CI	p	β	95% CI	p
Crude	-0.333	-0.366, -0.299	<0.001	-21.90	-24.19, -19.61	<0.001	-0.296	-0.322, -0.270	<0.001
Adjusted ^a	-0.100	-0.143, -0.057	<0.001	-7.74	-10.73, -4.75	<0.001	-0.130	-0.164, -0.096	<0.001
Adjusted ^b	-0.357	-0.392, -0.322	<0.001	-26.40	-29.20, -23.61	<0.001	-0.347	-0.378, -0.316	<0.001
Adjusted ^c	-0.115	-0.160, -0.069	<0.001	-9.42	-13.09, -5.75	<0.001	-0.146	-0.187, -0.106	<0.001

Reference group= non-frail

^a Adjusted for pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia

^b Adjusted for death

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3 ^c Adjusted for death, and pre-fracture EQ-5D utility score, age, pre-fracture residential status, pre-fracture mobility, ASA and
4 dementia

5
6 *Abbreviations:* EQ-5D: Euroqol 5 dimensions; EQ-VAS Euroqol Visual Analogue Scale; ICECAP-O: ICEpop CAPability measure
7 for Older People; β : Regression coefficient; CI: confidence interval

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12 225 *The longitudinal association between frailty and capability wellbeing*

13 226 Figure 4 shows differences in capability wellbeing between frail and non-frail patients during all

14 227 follow-up time points ($p < 0.0001$). We found a significantly strong negative association on average

15 228 between frailty and capability wellbeing over time, with a death-adjusted regression coefficient that

16 229 included all confounders of β -0.146 (95% CI -0.187, -0.106; Table 3).

231 **Discussion**

232 *Summary of results*

233 It is well known that elderly patients with a hip fracture have poor QoL⁶. However, it is unknown how
234 much frailty affects patients' QoL. This longitudinal cohort study shows that (i) frail patients with a
235 hip fracture had poorer HS than non-frail patients at baseline, (ii) frail patients had poorer HS and
236 poorer capability wellbeing than non-frail patients over time, and (iii) frailty at the onset of hip
237 fracture was negatively associated with HS and capability wellbeing one year after hip fracture. The
238 pattern of recovery trajectories in the prevalence of reported problems in the domains of the EQ-5D
239 during the first year period after hip fracture differed between the frail and non-frail patients.
240 However, after adjustment for confounders, especially for the concerned pre-fracture status of the EQ-
241 5D domain, the major differences between frail and non-frail patients disappeared. Confounders, such
242 as pre-fracture HS, age, pre-fracture residential status, pre-fracture mobility, ASA and dementia,
243 weakened also the association between frailty and QoL, but the association remained significant and
244 clinically relevant. Our findings demonstrate that pre-fracture frailty is significantly associated with
245 poor HS, self-rated health and capability wellbeing the first year after recovery from hip fracture.

247 *Comparison with existing literature*

248 This study demonstrates that frailty is a common condition among elderly patients with a hip fracture.
249 In our study, 53.3% of the patients with a hip fracture were considered frail. This finding is in line
250 with that of a small pilot study of Kistler et al., who found that 51% of patients were considered frail²⁸.
251 Previous studies, summarized in a systematic review by Lin and colleagues, showed frailty to be
252 associated with adverse outcomes, such as prolonged length of stay and mortality in older surgical
253 patients¹³. This finding is in line with ours, showing a significant difference in length of stay between
254 frail and non-frail patients ($t(696)=-5.845$, $p<0.001$). In line with the findings of Patel et al.²⁹ and
255 Dayama et al.³⁰, we also found increased 1-year mortality rates in frail patients with a hip fracture.
256 However, apart from these associations, our results showed that frailty is also negatively associated
257 with QoL. This finding is of major importance because frailty not only seems to influence patients'
258 postoperative outcomes, such as mortality and complications, but also has a perceived impact on the
259 level of patients' physical, emotional and social functioning. In the Netherlands, there is no difference
260 in post-fracture treatments between frail and non-frail patients. However, frail patients have already
261 pre-fracture more problems with their mobility and selfcare, and therefore, this could have influenced
262 their post-fracture rehabilitation possibilities.
263 In our study, HS and capability wellbeing do not generally fully recover within 12 months after hip
264 fracture for both frail and non-frail patients. This finding is in line with that of the prospective cohort
265 study of Griffins et al., who also revealed an initial marked decline in HS after hip fracture, followed
266 by improvement within four months and no return to baseline at 1 year after hip fracture³¹. This is also
267 in line with the International Costs and Utilities Related to Osteoporotic fractures Study^{32,33}. However,

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3 268 in our study, we showed the pattern of QoL and distinguished between frail and non-frail patients. We
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5 269 revealed a significantly more prominent decline in HS, self-rated health and capability wellbeing for
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7 270 frail patients compared to non-frail patients the first year of recovery from hip fracture. To show that
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9 271 our findings are clinically relevant, Walters et al. published the minimum clinically important
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11 272 difference of 0.074 for the utility score of the EQ-5D³⁴.
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13 273 It is remarkable that in the non-frail group, a high percentage of individuals do not return to pre-
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15 274 fracture levels within a year on all domains of the EQ-5D. In particular, the domains mobility, pain
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17 275 and usual activities showed major differences between the percentage of non-frail patients and that of
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19 276 frail patients reporting problems at baseline and 1 year after hip fracture . However, the same did not
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21 277 apply to the EQ-5D domain anxiety and depression, which revealed a strong positive association
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23 278 between frailty and anxiety/depression. Until now, the literature revealed a prevalence rate of 10% of
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25 279 patients reporting depressive symptoms after hip fracture³⁵. Future research should provide insight into
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27 280 whether frailty is a predictor of psychological distress, characterized by symptoms of anxiety,
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29 281 symptoms of depression and symptoms of posttraumatic stress.
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32 283 *Limitations and strengths*

33 284 This study had several limitations. First, participants may not accurately recall their status prior to the
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35 285 fracture, which might affect the results of the GFI and the EQ-5D at baseline. To minimize recall bias,
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37 286 the pre-fracture frailty status and HS data were only collected in patients who flowed into the study
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39 287 until one month had passed. In addition, because of the length of the questionnaire, we did not ask the
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41 288 items of the ICECAP-O prior to the fracture, and we could not compare this longitudinal outcome with
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43 289 pre-fracture capability wellbeing. Second, frail patients showed a higher capability wellbeing score at
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45 290 one-week follow-up than at one-month follow-up. This is probably due to selection bias because frail
46
47 291 patients in relatively good condition were able to complete the questionnaire at this early follow-up
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49 292 time point. Furthermore, there were more no-show cases in the frail group, resulted in selective drop-
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51 293 out. Therefore, the overall QoL of patients after a hip fracture, especially in the frail group, is probably
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53 294 worse than that presented in this study. On the other hand, an early follow-up time point at one week is
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55 295 unique in prospective research in hip fracture populations, and we adjusted for confounding variables
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57 296 in our mixed model analyses. Third, it is well known that surgery for hip fractures is frequently
58
59 297 followed by complications³⁶. However, information about complications after hip fractures was not
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61 298 collected in this multicenter study, and complications could have affected patients' QoL.
62
63 299 A strength of this study is the setup in the form of a multicenter prospective cohort study. We could
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65 300 include a large number of participants in different geographic locations, along with the possibility of
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67 301 including a wider range of hip-fracture population groups, which increases the generalizability of this
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69 302 study. We also included proxy participants in case a patient was unable to participate in this study for
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71 303 several reasons, including cognitive impairment. Particularly, this group is essential to include in this
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73 304 study because a major proportion of the frail group (41.2%) was suffering from dementia. Gabbe et al.

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3 305 published in trauma patients that differences in HS between patient and proxy respondents showed
4 306 random variability rather than systematic bias³⁷. They concluded that group comparisons using proxy
5 307 responses are unlikely to be biased. Another strength of this study is that we reported death-adjusted
6 308 outcomes according to Parsons et al²⁶. When reporting QoL for patients after a hip fracture, excluding
7 309 patients who die during follow-up leads to overly optimistic estimates of patient outcomes and is
8 310 likely to cause bias.

311

312 *Implication for clinical practice*

313 The findings of this study support the hypothesis that pre-fracture frailty has an unfavorable effect on
314 HS, self-rated health and capability wellbeing after a hip fracture. Pre-operative frailty assessment can
315 be valuable in informing patients and their relatives about the impact of hip fracture on patients'
316 physical, emotional and social functioning in the recovery period after a hip fracture. This frailty
317 assessment could classify patients at high risk for unfavorable outcomes regarding poor QoL. It could
318 support clinicians in tailoring treatment for medical decision making at an early phase. A clinically
319 easy-to-use and universal frailty indicator, such as the GFI, could have important implications in
320 prognostic counseling and care planning among older adults with hip fracture.

321

322 **Conclusions**

323 Our results show that frailty is negatively associated with patients' QoL one year after hip fracture,
324 even after adjusting for pre-fracture HS, age, pre-fracture residential status, pre-fracture mobility, ASA
325 and dementia. This study highlights hip fracture as a major cause of burden and morbidity, especially
326 in frail patients. This finding suggests that early identification of pre-fracture frailty in patients with a
327 hip fracture is important for prognostic counseling, care planning, and the tailoring of treatment.

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2
3 328 **Contribution of authors:**

4 329 CR, NK, LM, TG and MJ contributed to conception and design of this study. CR, ML, NK and LM
5
6 330 contributed to the data collection. CR, ML, NK, LM and MJ contributed to the analyses and
7
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9
10 332 final version of the article was approved by all the authors.

11 333

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13
14 335 competing interest. NK declares that she has no competing interest. LM declares that she has no
15
16 336 competing interest. JS declares that she has no competing interest. TG declares that he has no
17
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25 342

26 343 **Ethical approval:** All procedures performed in studies involving human participants were in
27
28 344 accordance with the ethical standards of the institutional and/or national research committee and with
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30 345 the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study
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32 346 has been approved by the Medical Ethics Committee Brabant, the Netherlands (project number
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34 347 NL50258.028.14).

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36 349 **Data sharing statement:** Data could be shared after consultation with BIOS study group

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References

1. Johnell O, Kanis J. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. *Osteoporosis Int.* 2004;15(11):897-902.
2. Hu F, Jiang C, Shen J, Tang P, Wang Y. Preoperative predictors for mortality following hip fracture surgery: A systematic review and meta-analysis. *Injury.* 2012;43(6):676-685.
3. Keene GS, Parker MJ, Pryor GA. Mortality and morbidity after hip fractures. *BMJ.* 1993;307(6914):1248-1250.
4. Marks R. Hip fracture epidemiological trends, outcomes, and risk factors, 1970-2009. *Int J Gen Med.* 2010;3:1-17.
5. Johnell O. The socioeconomic burden of fractures: Today and in the 21st century. *Am J Med.* 1997;103(2):S20-S26.
6. Peeters CM, Visser E, Van de Ree, Cornelis LP, Gosens T, Den Oudsten BL, De Vries J. Quality of life after hip fracture in the elderly: A systematic literature review. *Injury.* 2016.
7. De Vries J. Quality of life assessment. *Assessment in behavioral medicine.* 2001:353-370.
8. Whoqol Group. Development of the world health organization WHOQOL-BREF quality of life assessment. *Psychol Med.* 1998;28(3):551-558.
9. Grewal I, Lewis J, Flynn T, Brown J, Bond J, Coast J. Developing attributes for a generic quality of life measure for older people: Preferences or capabilities? *Soc Sci Med.* 2006;62(8):1891-1901.
10. van Leeuwen KM, Bosmans JE, Jansen AP, et al. Comparing measurement properties of the EQ-5D-3L, ICECAP-O, and ASCOT in frail older adults. *Value Health.* 2015;18(1):35-43.
11. Parsons N, Griffin XL, Achten J, Costa ML. Outcome assessment after hip fracture: Is EQ-5D the answer? *Bone Joint Res.* 2014;3(3):69-75.

- 1
2
3 374 12. Xue Q. The frailty syndrome: Definition and natural history. *Clin Geriatr Med*. 2011;27(1):1-15.
4
5
6 375 13. Lin H, Watts J, Peel N, Hubbard R. Frailty and post-operative outcomes in older surgical patients:
7
8 376 A systematic review. *BMC geriatrics*. 2016;16(1):157.
9
10
11 377 14. de Jongh MA, Kruithof N, Gosens T, et al. Prevalence, recovery patterns and predictors of quality
12
13 378 of life and costs after non-fatal injury: The brabant injury outcome surveillance (BIOS) study. *Inj*
14
15 379 *Prev*. 2017;23(1):59-2016-042032. Epub 2016 May 6.
16
17
18
19 380 15. Von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies
20
21 381 in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *PLoS medicine*.
22
23 382 2007;4(10):e296.
24
25
26
27 383 16. Steverink N, Slaets J, Schuurmans H, Van Lis M. Measuring frailty: Development and testing of
28
29 384 the groningen frailty indicator (GFI). *Gerontologist*. 2001;41(1):236.
30
31
32 385 17. Peters LL, Boter H, Buskens E, Slaets JP. Measurement properties of the groningen frailty
33
34 386 indicator in home-dwelling and institutionalized elderly people. *Journal of the American Medical*
35
36 387 *Directors Association*. 2012;13(6):546-551.
37
38
39 388 18. Group TE. EuroQol-a new facility for the measurement of health-related quality of life. *Health*
40
41 389 *Policy*. 1990;16(3):199-208.
42
43
44
45 390 19. Lamers LM, McDonnell J, Stalmeier PF, Krabbe PF, Busschbach JJ. The dutch tariff: Results and
46
47 391 arguments for an effective design for national EQ-5D valuation studies. *Health Econ*.
48
49 392 2006;15(10):1121-1132.
50
51
52 393 20. Coast J, Flynn TN, Natarajan L, et al. Valuing the ICECAP capability index for older people. *Soc*
53
54 394 *Sci Med*. 2008;67(5):874-882.
55
56
57
58
59
60

- 1
2
3 395 21. Makai P, Koopmanschap MA, Brouwer WB, Nieboer AA. A validation of the ICECAP-O in a
4
5 396 population of post-hospitalized older people in the netherlands. *Health and quality of life outcomes*.
6
7 397 2013;11(1):57.
8
9
10 398 22. Couzner L, Ratcliffe J, Lester L, Flynn T, Crotty M. Measuring and valuing quality of life for
11
12 399 public health research: Application of the ICECAP-O capability index in the australian general
13
14 400 population. *International journal of public health*. 2013;58(3):367-376.
15
16
17
18 401 23. Coast J, Peters TJ, Natarajan L, Sproston K, Flynn T. An assessment of the construct validity of
19
20 402 the descriptive system for the ICECAP capability measure for older people. *Quality of Life Research*.
21
22 403 2008;17(7):967-976.
23
24
25 404 24. Makai P, Brouwer WB, Koopmanschap MA, Nieboer AP. Capabilities and quality of life in dutch
26
27 405 psycho-geriatric nursing homes: An exploratory study using a proxy version of the ICECAP-O.
28
29 406 *Quality of life research*. 2012;21(5):801-812.
30
31
32
33 407 25. Van Buuren S. *Flexible imputation of missing data*. CRC press; 2012.
34
35
36 408 26. Parsons N, Griffin XL, Achten J, Chesser TJ, Lamb SE, Costa ML. Modelling and estimation of
37
38 409 health-related quality of life after hip fracture: A re-analysis of data from a prospective cohort study. .
39
40 410 ;*Bone Joint Res* 2018;7:1–5.
41
42
43
44 411 27. Twisk JW. *Applied longitudinal data analysis for epidemiology: A practical guide*. Cambridge
45
46 412 University Press; 2013.
47
48
49 413 28. Kistler EA, Nicholas JA, Kates SL, Friedman SM. Frailty and short-term outcomes in patients with
50
51 414 hip fracture. *Geriatric orthopaedic surgery & rehabilitation*. 2015;6(3):209-214.
52
53
54
55 415 29. Patel KV, Brennan KL, Brennan ML, Jupiter DC, Shar A, Davis ML. Association of a modified
56
57 416 frailty index with mortality after femoral neck fracture in patients aged 60 years and older. *Clinical*
58
59 417 *Orthopaedics and Related Research®*. 2014;472(3):1010-1017.
60

- 1
2
3 418 30. Dayama A, Olorunfemi O, Greenbaum S, Stone ME, Jr, McNelis J. Impact of frailty on outcomes
4
5 419 in geriatric femoral neck fracture management: An analysis of national surgical quality improvement
6
7 420 program dataset. *Int J Surg*. 2016;28:185-190.
8
9
10 421 31. Griffin XL, Parsons N, Achten J, Fernandez M, Costa ML. Recovery of health-related quality of
11
12 422 life in a united kingdom hip fracture population. the warwick hip trauma evaluation--a prospective
13
14 423 cohort study. *Bone Joint J*. 2015;97-B(3):372-382.
15
16
17 424 32. Abimanyi-Ochom J, Watts J, Borgström F, et al. Changes in quality of life associated with fragility
18
19 425 fractures: Australian arm of the international cost and utility related to osteoporotic fractures study
20
21 426 (AusICUROS). *Osteoporosis Int*. 2015;26(6):1781-1790.
22
23
24 427 33. Svedbom A, Borgström F, Hernlund E, et al. Quality of life after hip, vertebral, and distal forearm
25
26 428 fragility fractures measured using the EQ-5D-3L, EQ-VAS, and time-trade-off: Results from the
27
28 429 ICUROS. *Quality of Life Research*. 2018;27(3):707-716.
29
30
31 430 34. Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state
32
33 431 utility measures: EQ-5D and SF-6D. *Quality of life research*. 2005;14(6):1523-1532.
34
35
36 432 35. Cristancho P, Lenze E, Avidan M, Rawson K. Trajectories of depressive symptoms after hip
37
38 433 fracture. *Psychol Med*. 2016;46(7):1413-1425.
39
40
41 434 36. Flikweert E, Wendt K, Diercks R, et al. Complications after hip fracture surgery: Are they
42
43 435 preventable? *European Journal of Trauma and Emergency Surgery*. 2017:1-8.
44
45
46 436 37. Gabbe BJ, Lyons RA, Sutherland AM, Hart MJ, Cameron PA. Level of agreement between patient
47
48 437 and proxy responses to the EQ-5D health questionnaire 12 months after injury. *Journal of Trauma and*
49
50 438 *Acute Care Surgery*. 2012;72(4):1102-1105.
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3 440 **Figure 1.** Flow diagram of study participants. Participants who missed some of the measurements are
4 441 indicated as 'no show'.

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6 442 **Figure 2.** Patterns of health status according to frailty status over time.

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8 443 **Figure 3.** Percentage of frail (a) and non-frail (b) patients reporting problems on each EQ-5D-3L.
9 444 questionnaire item at each follow-up time point.

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11 445 **Figure 4.** Patterns of capability wellbeing according to frailty status over time.
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For peer review only

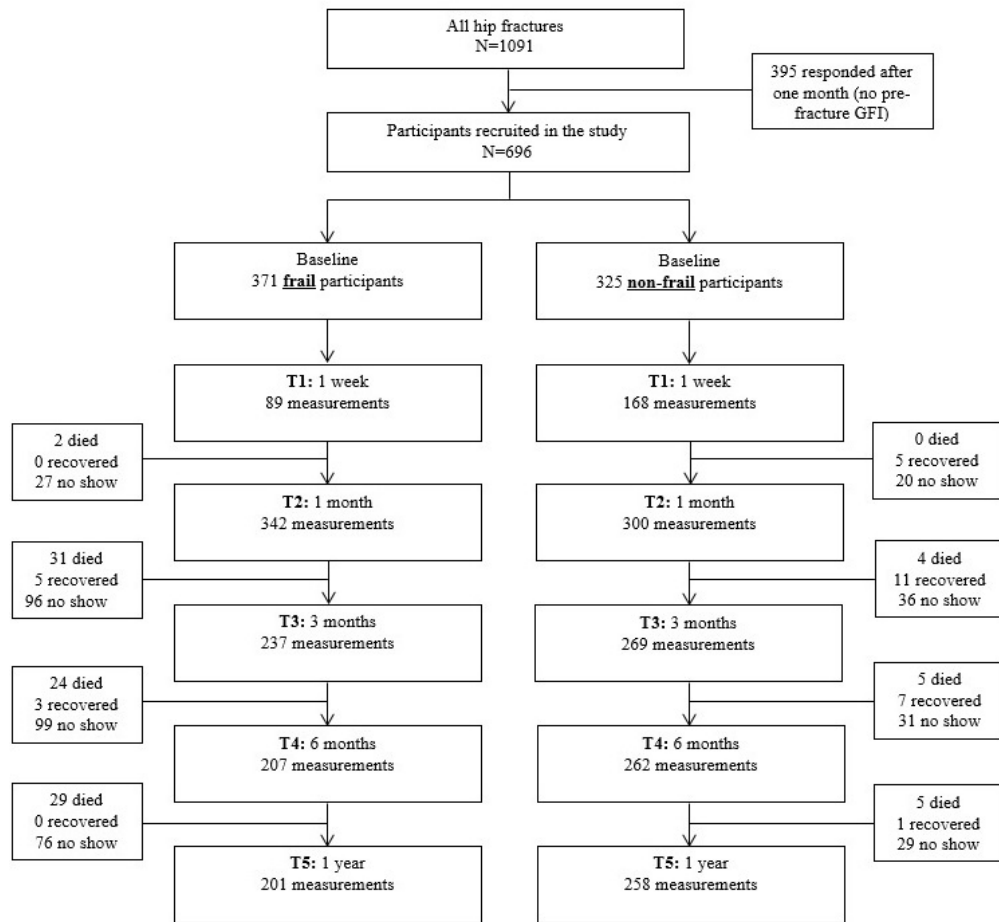


Figure 1. Flow diagram of study participants. Participants who missed some of the measurements are indicated as 'no show'.

63x60mm (300 x 300 DPI)

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Figure 2. Patterns of health status according to frailty status over time

47x33mm (300 x 300 DPI)

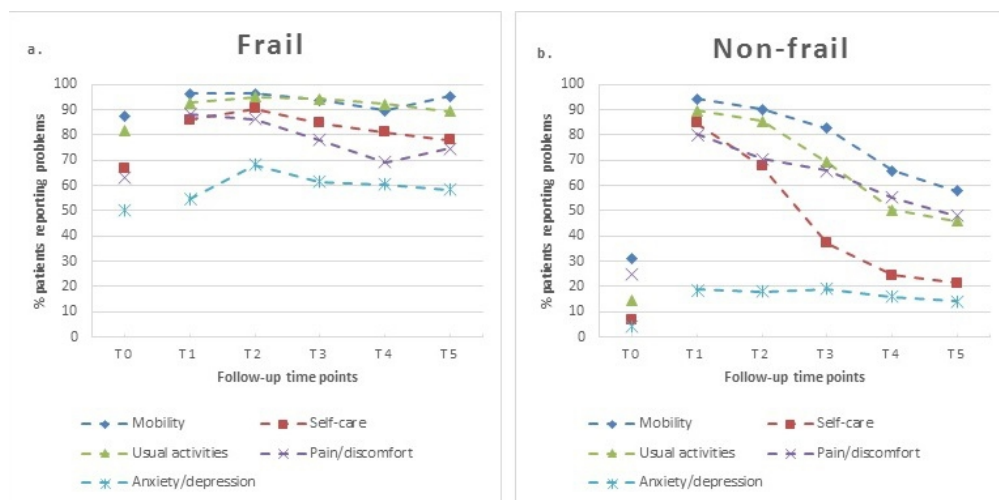
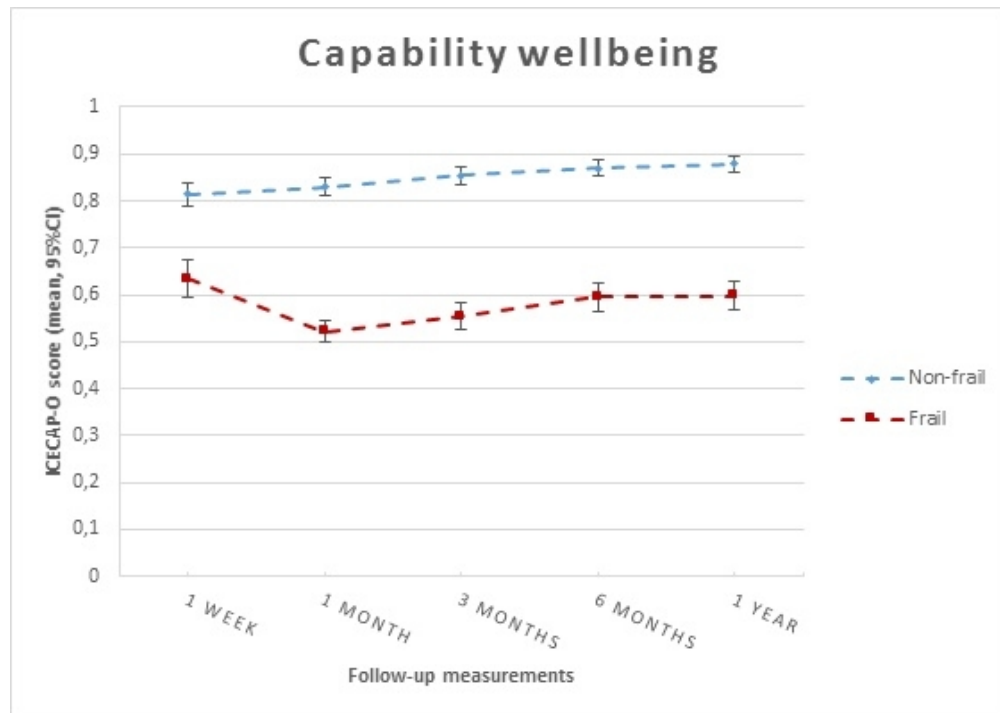


Figure 3. Percentage of frail (a) and non-frail (b) patients reporting problems on each EQ-5D-3L questionnaire item at each follow-up time point.

64x32mm (300 x 300 DPI)



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Figure 4. Patterns of capability wellbeing according to frailty status over time

47x33mm (300 x 300 DPI)

Supplementary file: Groningen Frailty Indicator

Physical domain

Are you able to carry out these tasks single handedly and without any help? (The use of help resources, such as a walking stick, walking frame, or wheelchair, is considered to be independent.)

1. Shopping
2. Walking around outside (around the house or to the neighbors)
3. Dressing and undressing
4. Going to the toilet
5. What mark do you give yourself for physical fitness? (scale 0 to 10)
6. Do you experience problems in daily life because of poor vision?
7. Do you experience problems in daily life because of being hard of hearing?
8. Have you lost a lot of weight in the last 6 months? (3 kg in 1 month or 6 kg in 2 months)
9. Do you take 4 or more different types of medicine?

Cognitive domain

10. Do you have any complaints about your memory?

Social domain

11. Do you have ever experienced an emptiness around you?
12. Do you long for other people (to socialize with)?
13. Do you feel abandoned?

Psychological domain

14. In the past 4 weeks, did you feel downhearted or sad?
15. In the past 4 weeks, did you feel anxious or nervous?

Scoring:

Questions 1-4: → Yes = 0; no = 1

Question 5: → 0-6 = 1; 7-10 = 0

Questions 6-9: → No = 0; yes = 1

Question 10: → No = 0; sometimes = 0; yes = 1

Questions 11-15: → Yes = 1; sometimes = 1; no = 0

Reference: 16. Steverink N, Slaets J, Schuurmans H, Van Lis M. Measuring frailty: Development and testing of the groningen frailty indicator (GFI). Gerontologist. 2001;41(1):236.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-6
Bias	9	Describe any efforts to address potential sources of bias	4-6
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	5-6
		(b) Describe any methods used to examine subgroups and interactions	5-6
		(c) Explain how missing data were addressed	5
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	6
		(e) Describe any sensitivity analyses	

Results			Page
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	7
		(c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7-10
		(b) Indicate number of participants with missing data for each variable of interest	7-10
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7-10
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	7-10
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9-10
		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	12-13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.