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Original Article

Three year functional changes and long-term mortality hazard in community-dwelling older men

Stefanie De Buyser [a,*], Mirko Petrovic [a,**], Youri Taes [b], Kaatje Toye [b], Jean-Marc Kaufman [b], Stefan Goemaere [b], Bruno Lapauw [b]

[a] Department of Geriatrics, Ghent University Hospital, De Pintelaan 185 1K2, Ghent, Belgium
[b] Department of Endocrinology and Unit for Osteoporosis and Metabolic Bone Diseases, Ghent University Hospital, De Pintelaan 185 9K12, Ghent, Belgium

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ABSTRACT

Background: Low levels of physical function have been associated with higher mortality hazard in older persons. However, few studies have investigated the association between functional changes and subsequent mortality. This study aimed to examine whether 3-year functional changes independently predict subsequent all-cause mortality.

Methods: This population-based cohort study included 171 community-dwelling men aged ≥71 years at wave 2 (baseline of the present analysis), living in the semi-rural community of Merelbeke (Belgium). Physical function assessments included the Short Form-36 (SF-36) Physical Function Index, Grip strength, Chair rising, and Timed Up and Go. Changes over a 3-year time were calculated using data obtained at four annual visits.

Results: After a 15-year follow-up, 149 men (87%) died. Median survival time was 8.2 (4.2–12.4) years. Physical function assessed at a single time point (at wave 2 or wave 5) was significantly associated with subsequent mortality hazard, independently from future or preceding 3-year changes. Greater functional declines during the 3-year follow-up were associated with higher mortality hazards. These associations were 1) more pronounced within the first seven years, 2) independent from baseline age, polypharmacy, depression, disability, and physical function, and 3) no longer significant when closure physical function was taken into account.

Conclusion: Physical function assessed at a single time point is a robust predictor of all-cause long-term mortality in community-dwelling older men. Yet, repeated assessments of physical function can provide prognostic information beyond that available from single initial assessment. However, with repeated assessments, most prognostic information can be found in the final assessment of physical function.

1. Introduction

Low levels of physical function have been associated with higher mortality hazard in older persons [1–3]. These low levels of physical function include impairments (which may be detected through measurements of muscle strength), functional limitations (which can be assessed with physical performance measurements), as well as disabilities (which include reported measurements of activities of daily living and physical domains of health-related quality of life).

The majority of previous research used measurements of physical function at a single point in time to predict mortality. Nevertheless, physical function is dynamic and changes with time [4,5]. On average physical function declines with age [6–9]. According to the European Male Ageing Study, annual decline in Gait speed and Grip strength in community-dwelling men turns significant from the age of 70 years [10]. Functional decline in community-dwelling older persons has been associated with incident disability [11], but few studies have investigated its association with subsequent mortality and they have yielded inconsistent results. At present evidence is still lacking that functional changes would affect mortality hazard [2,12,13].

A better understanding of the clinical effects and consequences of functional changes would help to justify physical function as a relevant outcome in clinical trials and to adapt and tailor care in the clinical setting accordingly. Identifying persons at risk of death may allow interventions to be more targeted and efficient.

* Correspondence to: S. De Buyser, Department of Geriatrics, Ghent University Hospital, De Pintelaan 185, 6K12E, B-9000 Ghent, Belgium. Tel.: +32 9 332 19 61.
** Alternate corresponding author.
E-mail addresses: Stefanie.DeBuyser@UGent.be (S. De Buyser), Mirko.Petrovic@UGent.be (M. Petrovic).

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In this study, we aimed to examine whether 3-year functional changes – not caused by any active intervention – in four assessments of physical function (Short Form-36 (SF-36) Physical Function Index, Grip strength, Chair rising, and Timed Up and Go) independently predict subsequent long-term all-cause mortality in community-dwelling older men.

2. Methods

2.1. Study population

The study population consisted of participants who attended both the second and fifth waves of a cohort study, which was initiated to investigate the process of aging, mainly focusing on hormonal changes and bone metabolism. This population-based observational study started in 1996 with follow-up visits annually until 2000, one visit in 2003, and subsequent annual follow-up by postal questionnaires and telephone contacts (still ongoing) (Fig. 1). Ambulatory, non-institutionalized men aged 70 to 85 years were recruited from the population register of Merelbeke, a semi-rural community of ±20,000 inhabitants in East Flanders, Belgium. Details concerning recruitment have been described previously [1,14,15]. We used the second wave in 1997 as this analysis' baseline since the serial testing of physical performance by the same group of four study nurses began at this point. During each wave, all participants were assessed within 3.5 months. The study was performed according to the Declaration of Helsinki. All participants gave their written informed consent for participation in this study, which the ethics committee of Ghent University Hospital approved (project 96/22).

2.2. Measurements

Participants' weight (nearest 0.1 kg) and height (nearest 0.1 cm) were measured in light clothing without shoes. Body Mass Index (BMI) was calculated as weight in kilograms divided by squared height in meters. Participants were asked about their educational level, marital and residential status (living with spouse, with family or alone), recreational physical activity (how much time during the week they were exercising in the past years), concomitant medication use (range 0–8 +; polypharmacy was defined as ≥5 medications), and history of falls in the previous year. Standing balance was evaluated by instructing participants to stand in three positions (parallel, semi-tandem, and tandem stands) first with the eyes open and then closed for up to 10 s each (range 0–6). Cognition was evaluated through a 5-item recall performed three times (range 0–15). Higher scores indicate better cognitive status. The 30-item Geriatric Depression Scale (GDS) was used to evaluate depressive symptoms (range 0–30, a score ≥ 11 is a possible indicator of depression) [16], the first part of the Rapid Disability Rating Scale-2 (RDRS-2) to rate the amount of assistance required in

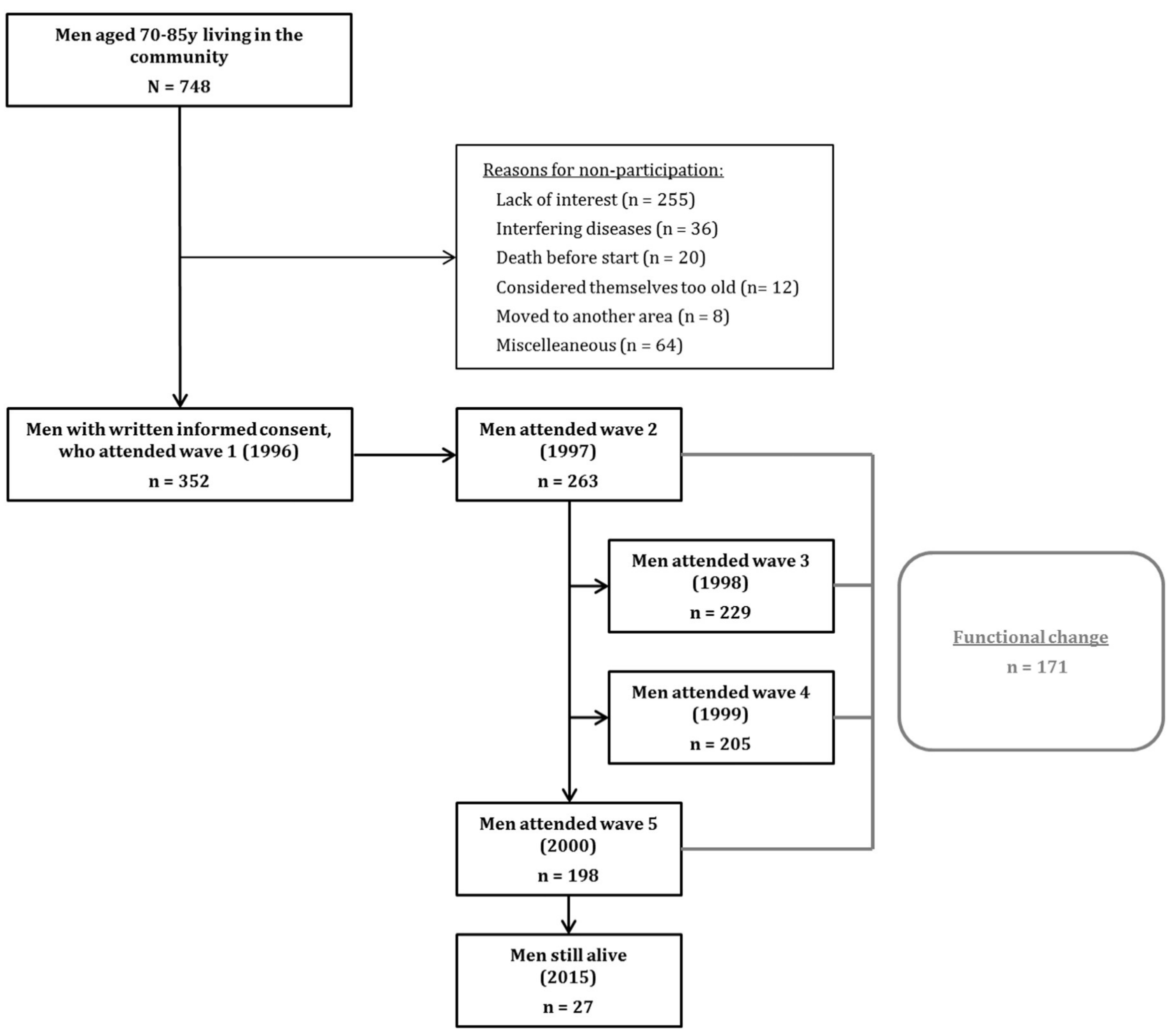

Fig. 1. Study design.

eight activities of daily living (range 8–32, higher scores indicate more assistance needed, a score > 8 is considered an indicator of disability) [17] and the SF-36 to evaluate self-reported health and physical function (range 0–100) [18].

Educational level was recorded at the first visit, whereas the other correlates were assessed by four dedicated study nurses at the second visit, which is our analysis' baseline.

2.3. Assessments of physical function

Assessments of physical function were performed at each wave by the same group of study nurses. Self-reported physical function was assessed using the 'Physical Function Index' of the SF-36 questionnaire [19], which consists of ten items asking about mobility limitations at the present time. The total sum of the 3-point scale responses is transformed to a total score ranging between 0 and 100 with higher values indicating better physical function.

Performance-based physical function was assessed using the Grip strength, Chair rising, and Timed Up and Go tests.

Grip strength was measured with a Smedley type hand dynamometer (Smith & Nephew Rolyan Inc., Germantown, WI, USA). Participants were in a standing position with the elbow in full extension, moving the shoulder from 180° to 0° flexion while squeezing as hard as possible. Assessors were trained study nurses who gave encouragement during the assessment. The used score was the second result of two consecutive trials (with unstandardized interval) of the dominant hand, expressed to the nearest kilogram [20,21]. Performance on the Chair Stand test was assessed twice in a row, using a standard chair with seat height of 45 cm. Participants were instructed to complete five full stands from seated position as quickly as possible (fastest time expressed to the nearest hundredth of a second) [22,23]. The Timed Up and Go test was assessed according to the method described by Podsiadlo & Richardson [24]. Participants were instructed to stand up from an armchair (seat height of 45 cm), walk at a comfortable and secure pace to a line on the floor 3 m away, turn, return to the chair and sit down again (time expressed to the nearest hundredth of a second).

2.4. Functional change

Functional change over four assessment points within three years was estimated for each participant separately using the formula for the slope of an ordinary least-squares regression line.

$$Three-year\ change = \frac{3*365*\sum_{i=1}^{n}\left(PF_i-\overline{PF}\right)\left(days_i-\overline{days}\right)}{\sum_{i=1}^{n}\left(days_i-\overline{days}\right)^2}$$

PF	physical function
n	number of assessment points in time
days	number of days since baseline assessment at wave 2

Assessments were completed at all four waves in 158 men, at three waves in 12 men and at two waves in 1 man. Missing data for in-between assessments were not replaced, instead the slope of change was estimated without these data.

2.5. Mortality

We obtained data on all-cause mortality through yearly postal questionnaires and by contacting proxies and the treating general practitioners via telephone. Survival time was calculated as the number of months from assessment in 2000 until death or up to 15 years of follow-up (until 1 January 2015 if there was a response to the postal questionnaire (n = 14), until 8 July 2015 if the proxy or treating general practitioner was contacted by telephone (n = 7), until last date of contact if the participant was lost to follow-up in 2015 (n = 1)).

2.6. Statistical analysis

Normally distributed data are presented as mean (standard deviation (SD)) [25], and differences between groups were compared using independent-samples T tests. Non-normally distributed data are presented as median (25th–75th percentile), and differences between groups were compared using Mann–Whitney U. Countable variables are presented as total number and percentage of the sample. Differences between groups were compared using Chi-square.

Cox proportional hazard models were used to analyze associations with all-cause mortality. Date of participants' fifth visit was considered as zero time for subsequent survival. For participants who did not attend the fifth wave (and were included in the sensitivity analyses), July 1st 2000 was considered as zero time. Interaction terms between baseline physical function and functional change were not significant. The proportional hazard assumption which requires coefficients not to change over time was assessed by plotting estimates of $\beta(t)$ and by using the cox.zph function in RStudio. Because the effect of decline in SF-36 Physical Function Index, Grip strength, and Chair rising was not constant over time, a time-dependent covariate was constructed using the time-transform functionality of coxph in RStudio and additional analyses were performed examining the associations with shorter-term (7 years) mortality [26]. Hazard ratios for continuous measures are computed in such a way as to correspond with a unit of worse function/functional decline. Wald statistics were provided to indicate the models' fit. All analyses were performed using RStudio, Version 0.99.484 — © 2009–2015 RStudio, Inc. Statistical significance was indicated by a P value <0.05.

3. Results

A total of 198 men attended both the second and fifth waves of this longitudinal study. However, assessment of functional changes was incomplete due to protocol deviations for 27 men (Fig. 1). Participants' characteristics at baseline are shown in Table 1. Participants included in our analysis (n = 171) differed from excluded men who had missing data (n = 57) or who died before the fifth wave (n = 35) in terms of younger age, higher likelihood to perform at least 2 h of recreational physical activity per week, lesser likelihood to have fallen in the previous year and to have balance problems, higher self-reported Physical Function Index, and faster Timed Up and Go time. In addition, compared with the men who died before the fifth wave, included men had lower scores on the GDS, lesser likelihood for depression and disability, and higher self-reported general health.

Median (25th–75th percentile) survival time after the second wave was 11.3 (7.3–15.4) years for included participants, 2.1 (1.5–2.5) years for men who died before 2000 ($P < 0.001$) and 9.5 (6–12.4) years for men with missing data ($P = 0.035$).

Median (25th–75th percentile) 3-year change in SF-36 Physical Function Index was −4.71 (−18.58 to +0.11) points, in Grip strength +0.25 (−4.02 to +2.23) kg, in Chair rising −0.85 (−2.14 to +0.15) seconds, and in Timed Up and Go −0.02 (−1.18 to +1.22) seconds.

After 15 years of follow-up, 149 out of 171 participants (87%) died. Median survival time after the fifth wave was 8.3 (4.3–12.4) years.

Cox proportional hazard models including a time-dependent object found a 3-year functional decline in SF-36 Physical Function Index ($\beta = 0.06$, HR = 1.06 (1.02–1.10)), Grip strength ($\beta = 0.20$, HR = 1.22 (1.06–1.41)), Chair rising ($\beta = 0.41$, HR = 1.50 (1.12–2.02)), and Timed Up and Go ($\beta = 0.26$, HR = 1.30 (1.05–1.61)) to be associated with mortality hazard at zero time, independent from age and baseline physical function. However, a significant time-attenuated effect for decline in SF-36 Physical Function Index ($\beta = -0.01$, HR = 0.99 (0.98–0.998)), Grip strength ($\beta = -0.04$, HR = 0.96 (0.93–0.998)), and Chair rising ($\beta = -0.08$, HR = 0.92 (0.85–0.995), but not Timed

Table 1
Characteristics of men at the second wave of this cohort study (n = 263).

Baseline characteristic	Participants in wave 2		
	Included in this analysis	Not included in this analysis[a]	Deceased before wave 5
N	171 (65%)	57 (22%)	35 (13%)
Age (y), mean (SD)	75.3 (3.4)	77.5 (4.1)***	77.8 (4.6)**
BMI (kg/m^2), mean (SD)	26.5 (3.3)	26.3 (4.0)	25.6 (3.7)
Low education (elementary or less), n (%)	81 (47)	37 (65)	18 (51)
Living alone, n (%)	31 (18)	8 (14)	8 (23)
Recreational physical activity (<2 h/week), n (%)	33 (19)	21 (37)*	12 (34)*
No. of medications, median (IQR)	2 (1–4)	2 (1–3)	3 (1–5)
Polypharmacy, n (%)	24 (14)	6 (11)	10 (29)
Any fall in previous year, n (%)	20 (12)	12 (21)*	9 (26)*
Balance <5/6 points, n (%)	18 (11)	18 (32)***	13 (37)***
Cognitive recall [0–15], median (IQR)	13 (12–14)	13 (11–14)	13 (12–14)
Cognitive recall <13/15, n (%)	61 (36)	23 (40)	15 (43)
GDS score [0–30], median (IQR)	4 (2–7)	6 (3–7)	6 (4–11)**
Depression, n (%)	21 (12)	6 (11)	10 (29)*
Disability, n (%)	18 (11)	5 (9)	11 (31)**
Self-reported health [0–100], median (IQR)	65 (55–80)	65 (55–75)	60 (45–70)*
Physical Function Index [0–100], median (IQR)	85 (75–95)	75 (60–93)**	70 (51–85)***
Grip strength (kg), mean (SD)	31.0 (7.5)	29.4 (7.7)	29.1(7.8)
Chair rising (s), median (IQR)	10.8 (9.5–12.4)	11.5 (10.0–13.8)	12.7 (11.1–17.2)***
Timed Up and Go (s), median (IQR)	10.4 (8.9–12.2)	11.9 (10.0–14.5)**	12.9 (10.6–16.9)***

***P < 0.001, **P < 0.01, *P < 0.05 compared with the men who were included in this analysis.
SD = standard deviation, BMI = Body Mass Index, IQR = interquartile range, GDS = Geriatric Depression Scale.
[a] This group consists of men with incomplete physical function data at the second and/or fifth waves.

Up and Go (β = −0.04, HR = 0.96 (0.91–1.02)) was detected. For example, a greater 3-year decline in Chair rising with one second/three years was associated with 50% higher mortality hazard at zero time, but with only 26% higher mortality hazard at 15 years (= exp(0.41–0.08 ∗ log(180 months)). This time-attenuated effect turned significant after 7 years for changes in SF-36 Physical Function, Grip strength, and Chair rising, but not for changes in Timed Up and Go.

Cox proportional hazard models with fixed covariates found both physical function at a single time point assessment (either baseline (M1 in Table 2) or closure at wave 5 (M3 and M 5 in Table 2)) and a 3-year functional decline estimated from repeated assessments (M1 in Table 2) to be associated with higher subsequent 7-year mortality hazard, independent from age. For example, men of similar age with a similar 3-year decline had on average a 16% higher mortality hazard for

Table 2
Seven-year all-cause mortality hazard predicted by physical function at single time point assessment (baseline or closure) and 3-year functional decline estimated from repeated assessments in community-dwelling older men (n = 171, deaths = 73).

Model	Function at wave 2		3-year functional decline		Function at wave 5		
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	Wald
SF-36 Physical Function (0–100)							
M1	1.02 (1.003–1.03)	0.011	1.02 (1.01–1.03)	0.002	–	–	29
M2*	1.01 (0.998–1.03)	0.086	1.02 (1.01–1.03)	0.003	–	–	33
M3	–	–	1.00 (0.98–1.02)	0.535	1.01 (1.003–1.03)	0.011	29
M4*	–	–	1.01 (0.99–1.03)	0.354	1.01 (0.998–1.03)	0.087	33
M5	1.00 (0.98–1.01)	0.622	–	–	1.02 (1.01–1.03)	0.003	29
M6*	0.99 (0.98–1.01)	0.433	–	–	1.02 (1.01–1.03)	0.003	32
Grip strength (kg)							
M1	1.04 (1.01–1.08)	0.014	1.09 (1.04–1.14)	<0.001	–	–	33
M2*	1.04 (1.001–1.08)	0.043	1.10 (1.05–1.15)	<0.001	–	–	39
M3	–	–	1.05 (0.99–1.11)	0.101	1.04 (1.001–1.07)	0.042	29
M4*	–	–	1.05 (0.995–1.12)	0.071	1.03 (0.995–1.07)	0.087	35
M5	0.97 (0.93–1.02)	0.272	–	–	1.07 (1.02–1.12)	0.004	27
M6*	0.96 (0.91–1.02)	0.17	–	–	1.08 (1.03–1.13)	0.003	33
Chair rising (s)							
M1	1.16 (1.08–1.25)	<0.001	1.20 (1.09–1.32)	<0.001	–	–	35
M2*	1.17 (1.08–1.27)	<0.001	1.23 (1.10–1.36)	<0.001	–	–	43
M3	–	–	1.04 (0.93–1.15)	0.504	1.15 (1.06–1.23)	<0.001	33
M4*	–	–	1.04 (0.94–1.14)	0.463	1.17 (1.08–1.27)	<0.001	43
M5	0.99 (0.90–1.09)	0.799	–	–	1.17 (1.06–1.28)	0.001	33
M6*	0.99 (0.90–1.07)	0.622	–	–	1.20 (1.09–1.32)	<0.001	42
Timed Up and Go (s)							
M1	1.15 (1.05–1.26)	0.003	1.16 (1.08–1.25)	<0.001	–	–	37
M2*	1.16 (1.04–1.29)	0.008	1.18 (1.08–1.28)	<0.001	–	–	41
M3	–	–	1.02 (0.92–1.14)	0.659	1.14 (1.04–1.25)	0.01	34
M4*	–	–	1.03 (0.93–1.15)	0.568	1.14 (1.02–1.27)	0.017	40
M5	1.00 (0.90–1.11)	0.954	–	–	1.15 (1.07–1.25)	<0.001	34
M6*	0.99 (0.89–1.11)	0.908	–	–	1.17 (1.07–1.28)	<0.001	38

HR = hazard ratio, CI = confidence interval.
M1, M3, M5: adjusted models included age at wave 2.
M2*, M4*, M6*: fully adjusted models included age, polypharmacy, depression, and disability at wave 2.

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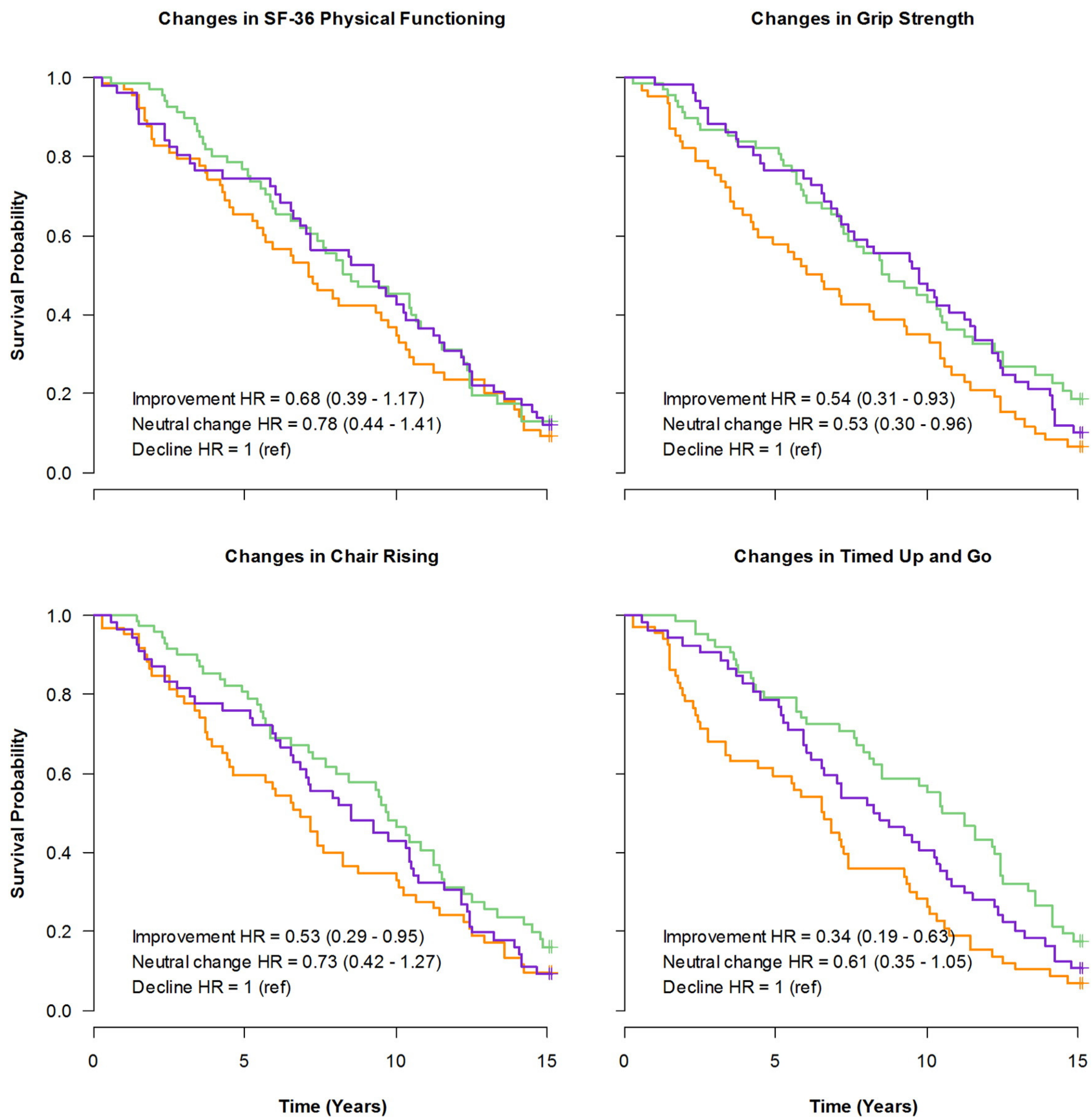

Fig. 2. Age- and baseline physical function-adjusted survival curves stratified by tertile of 3-year functional changes. Orange lines correspond with tertiles of the highest functional decline, purple lines with mid-tertiles of functional change, and green lines with tertiles of least functional decline/improvement. HR = hazard ratio, 95% confidence intervals are reported between brackets. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

every one second increase in baseline Chair rising performance. Men of similar age with a similar baseline Chair rising performance had on average 20% higher mortality hazard for every one second/three years greater decline in a 3-year Chair rising change.

Fig. 2 shows age- and baseline function-adjusted survival curves stratified by tertile of 3-year functional changes (SF-36 Physical Function Index [33rd percentile = −11.93; 66th percentile = −0.26], Grip strength [−2.65; 1.49 kg], Chair rising [−1.62; −0.27 s], Timed Up and Go [−0.79; 0.81 s]).

Associations between functional decline and 7-year mortality were still significant in supplementary analyses adjusted for baseline polypharmacy, disability, and depression in addition to age and physical function at baseline (M2* in Table 2), but were no longer significant when closure physical function at wave 5 was taken into account (M3 and M4* in Table 2).

Sensitivity analyses were performed including participants who attended wave 2 and had at least two measurements without protocol deviations (attendance of wave 5 was not specifically required). Similar results were obtained by these analyses, which included up to 30 extra participants (results not shown).

4. Discussion

In this study, the association of 3-year functional changes – not caused by any active intervention – with subsequent long-term all-cause mortality was evaluated in a sample of apparently healthy community-dwelling older men.

Physical function assessed at a single time point (either baseline or closure at wave 5) was significantly associated with subsequent mortality hazard, independently from future or preceding 3-year functional changes. Greater functional declines during the 3-year follow-up were associated with higher mortality hazards. These associations were 1) more pronounced within the first seven years, 2) independent from age, polypharmacy, depression, disability, and physical function at baseline, and 3) no longer significant when physical function at wave 5 was taken into account.

Few studies so far have examined the association between functional changes and subsequent mortality in healthy community-dwelling older persons and they have yielded inconsistent results [4,5,27–31]. In addition, there are many discrepancies regarding how functional change was evaluated, the time span over which change was assessed,

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and the duration of mortality follow-up. Different studies who included a self-reported measure of physical function derived from the SF-36 questionnaire found change [27] or at least decline [28] in the physical component summary score predicted 4-year mortality, but neither decline nor improvement on the Physical Function Index within one year was associated with a 5- or 8-year mortality [4,5]. Studies including a performance-based measure of physical function most often used Gait speed. Patterns of change [4,5,30], but not always slopes of Gait speed [29,31] were associated with subsequent mortality risk. When the Short Physical Performance Battery was used, patterns of decline but not of improvement within one year were associated with subsequent mortality rate [4,5]. In the Cardiovascular Health Study the highest quintile of Grip strength decline, but not of Chair rising decline was associated with higher subsequent 7-year mortality risk [29]. These inconsistent associations with mortality indicate the importance of which physical function assessment is considered and how its change over time is evaluated (number of assessments over time, patterns vs. slope of change).

Our findings have two important implications. First, physical function assessments at a single time point – baseline or closure – were significantly associated with mortality independently from future or preceding functional changes (Table 2), which supports their robustness and their use in clinical practice. Second, in addition to age and single baseline function, ensuing 3-year functional changes added significant value to the prediction of mortality. This indicates that assessing physical function repeatedly over time can provide prognostic information beyond that available from initial assessment [32]. In addition to closure physical function (at wave 5) preceding 3-year functional changes did no longer contribute to the prediction of mortality. This indicates that when physical function is repeatedly assessed over time, most prognostic information can be found in the final assessment. Our results are in line with the findings of Sabia et al. [31].

Further research questions emerging from our findings relate to the longitudinal use of the SF-36 Physical Function Index, Grip strength, Chair rising, and Timed Up and Go test as markers of (altered) mortality risk in older community-dwelling persons. Notably in this study, the observed functional changes were not caused by any active intervention. As such, it remains to be demonstrated whether functional changes, caused by active intervention, have similar predictive capacity and could therefore be used as surrogate end points of mortality hazard in clinical trials. It might also be further examined whether undergoing meaningful functional change or reaching a threshold for closure physical function is best associated with mortality.

Our study has several innovative aspects. It is to our knowledge the first European study in community-dwelling older men to report on the association between objectively measured performance change and subsequent mortality risk and is the first to assess rate of change in Timed Up and Go performance in that sense. Moreover, four assessment points over a 3-year time, performed by the same group of four dedicated and experienced study nurses, allow an accurate estimate of rate of functional change. The subsequent 15-year follow-up, which is the longest for any related mortality study, contributes to the high mortality rate of 86% in our analysis. The small number of survivors, who are censored in the analysis, reduces the risk of bias in estimates and standard errors.

Our study, however, has also some limitations. First, results might be influenced due to selection bias, because only men who participated in both the second and fifth waves of this longitudinal study could be included in the analyses (Table 1). Sensitivity analyses, including participants who attended wave 2 and had at least two measurements without protocol deviations led to similar results. Second, mortality was not confirmed by death registry data, but relied on communication with the treating general practitioner and/or proxy. Third, this study was performed in apparently healthy community-dwelling men, so our findings might not be generalizable to a more health-deprived population. Fourth, the study sample is relatively small. By adjusting only for age, polypharmacy, depression, disability, and physical function at baseline in the survival analyses, we might have omitted important confounders. Related to the time-attenuated effect we observed, Sabia and colleagues [31] similarly reported that the association of change in fast walking speed with mortality was more pronounced in the first four year compared to the full 8-year follow-up. Nevertheless, it possible that our observed attenuated effect results from the decreasing sample of men who are still alive after certain follow-up.

In conclusion, physical function assessed at a single time point is a robust predictor of all-cause long-term mortality in community-dwelling older men. Yet, repeated assessments of physical function can provide prognostic information beyond that available from single initial assessment for subsequent mortality hazard. However, with repeated assessments, most prognostic information lays in the final assessment of physical function.

Learning points

- Physical function assessments at a single time point are robust predictors of all-cause long-term mortality in community-dwelling older men.
- Nevertheless, older community-dwelling men can experience functional changes over a 3-year time, not caused by any active intervention.
- In this respect, repeated assessments of physical function can provide prognostic information beyond that available from single initial assessment for subsequent mortality hazard. However, with repeated assessments, most prognostic information lays in the final assessment of physical function.

Conflict of interests

The authors state that they have no conflicts of interest.

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