Transitions and trajectories in frailty states over time: a systematic review of the European Joint Action ADVANTAGE

Rónán O'Caoimh[1], **Lucia Galluzzo**[2], **Ángel Rodríguez-Laso**[3], **Johan Van der Heyden**[4], **Anette Hylen Ranhoff**[5], **Laure Carcaillon-Bentata**[6], **Nathalie Beltzer**[6], **Siobhán Kennelly**[1*], **Aaron Liew**[1] on behalf of Work Package 5 of the Joint Action ADVANTAGE

[1]*Health Service Executive of Ireland (Social Care Division) and National University of Ireland (Discipline of Medicine), Galway, Ireland*
[2]*Dipartimento Malattie Cardiovascolari, Dismetaboliche e Invecchiamento, Istituto Superiore di Sanità, Rome, Italy*
[3]*Fundación para la Investigación Biomédica del Hospital Universitario de Getafe, Getafe, Spain*
[4]*Sciensano, Brussels, Belgium*
[5]*Nasjonalt Folkehelseinstitutt (Norwegian Institute of Public Health), Oslo, Norway*
[6]*Santé Publique France, Saint-Maurice, France*
[*]*Siobhán Kennelly is not a member of the ADVANTAGE Joint Action*

Abstract
Introduction. Frailty is a dynamic syndrome and may be reversible. Despite this, little is known about trajectories or transitions between different stages of frailty.
Methods. A systematic review was conducted, selecting studies reporting frailty trajectories or transition states for adults in any settings in European ADVANTAGE Joint Action Member States.
Results. Only three papers were included. Data were from longitudinal community-based cohorts in the United Kingdom, Netherlands and Italy. The English study investigated the effect of physical activity on the progression of frailty over a 10-year period. Two presented data on the proportion of participants experiencing at least one frailty transition over time (32.6% in the Italian sample aged ≥ 65 years followed for 4.4 years; 34.3% in the Dutch sample aged 65-75 years, followed for 2 years).
Conclusions. Data on frailty trajectories and transition states were limited and heterogeneous. Well-designed prospective studies and harmonized approaches to data collection are now needed.

INTRODUCTION

As societies age, the prevalence of age-related conditions is expected to increase [1]. While there is as yet no widely-accepted consensus definition [2, 3], frailty is considered to be an age-associated syndrome of increased vulnerability resulting in a propensity for adverse healthcare outcomes [4]. Frailty is recognised as dynamic [5, 6] with a clearly identifiable prodromal state, usually referred to as pre-frailty [7]. Pre-frailty, before onset of established frailty, may be reversible [8] and has become a target for multi-domain interventions in community-dwelling older adults [7, 9-10]. Like frailty, there is no accepted definition of pre-frailty; instead

it is usually described by deficits on a frailty screening or classification instrument not reaching the threshold for frailty but not consistent with being non-frail or robust [7]. Recent systematic data suggests that frailty is prevalent in community-dwellers [11] including in European Union (EU) Member States (MS) [12]. Data from previous systematic reviews also suggest that pre-frailty is common with reported prevalence rates ranging from 41.6-49.3%, depending on the setting and populations assessed [11,13].

Over recent years multiple prospective, mainly cohort studies of ageing, have investigated the epidemiology of frailty. Most use either the Fried frailty criteria, focusing

Address for correspondence: Rónán O'Caoimh, Health Research Board Clinical Research Facility Galway, National University of Ireland, Galway, Geata an Eolais, University Road, Galway City, Ireland. E-mail: rocaoimh@hotmail.com.

on a physical phenotype as derived from the Cardiovascular Health Study (CHS) [14], or a Frailty Index (FI), based on the accumulation of deficits theory whereby individuals are scored on an index with the number of deficits present on the numerator and all possible deficits from a fixed inventory on the denominator [15]. The latter is commonly used in cross-sectional and longitudinal studies [16] and may be best to measure change over time [17]. Such longitudinal studies have shown that there is a natural or background rate of transition or deterioration in FI scores [18]. This differs between studies, with figures varying from a doubling of the FI score over 12.6 [19] to over 20 years [20]. Again, these rates may reflect the heterogeneity between samples [19]; rates of deficit accumulation over time are associated with increasing age [21], female gender [22] and lower socioeconomic status [23]. A gender paradox is evident with women more likely to accumulate but better able to tolerate deficits [22, 24]. In addition, a cohort effect has been postulated that may affect frailty trajectories; more recent cohorts, of equivalent age to previous ones, are living with higher levels of frailty, apparently driven by wealth disparities [23]. There may also be a ceiling effect, typically a maximum FI score of 0.70 [22, 25].

Despite its strong associations with age, frailty may not be inevitable and there is some, albeit limited, evidence of reversibility [6]. Frailty is a separate syndrome not synonymous with multi-morbidity and chronic disease [26] and there is evidence that changes in the initial frailty cycle could be observed before onset of functional decline and disability [6]. Epidemiological studies offer the potential to demonstrate these complex patterns to better understand them. Hence, the focus of recent research in this area is on recognising and describing the progression of frailty and identifying predictors likely to influence the transition to higher or lower frailty states, in order to appreciate the processes and dynamics underlying the development of frailty over time [27]; targeting these may allow appropriate public health systems' processes (screening, monitoring and surveillance programmes) and interventions to be put in place [28].

The Joint Action (JA) on Frailty Prevention (AD-VANTAGE) www.advantageja.eu is a co-funded project bringing together 33 partners from 22 EU MSs to develop a comprehensive strategic framework for the prevention and management of frailty in Europe. Although transitional states with bi-directional frailty trajectories are described in different countries and settings [5, 6], a clear understanding of these complex processes are still lacking. Given this, the aim of this study was to systematically review the scientific literature on trajectories and transitions between different stages of frailty in studies conducted in European JA ADVANTAGE MSs.

MATERIALS AND METHODS
Search strategy

A systematic search of the available literature relating to frailty transitions and trajectories was conducted. PubMed/MEDLINE, Embase, CINAHL, Opengrey and the Cochrane library databases were searched for articles published over fifteen years between January 2002 and April 2017. Grey literature and data from on-going or unpublished studies were sought. In addition, the reference lists of relevant articles were searched for pertinent papers. The review was published on the Prospero database of systematic reviews, protocol CRD42017071866, and undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [29]. The following search terms with truncations were used to identify possible citations: "Trajectories" OR "Trajectory" OR "Transition*"; AND "Elderly" OR "Aged" OR "Older adult*" OR "Older person*" OR "Geriatric*" AND "Frailty", OR "Frail".

Two pairs of reviewers independently screened citation' titles and abstracts for possible inclusion and removed all duplicates. Where required, a third reviewer settled disparities. Full papers were then retrieved and data from articles assessed as suitable for inclusion were extracted and analysed.

Selection criteria

For the purpose of this systematic review, trajectories were defined as clusters of individuals following a similar progression of frailty over time [30] and transitions were defined as changes between different stages of frailty over time (i.e. transition from robust, pre-frail, frail and back).

Papers were included only if they:
1) provided data relating to frailty using any accepted definition of frailty, irrespective of the screening or assessment instrument used to describe frailty or one of its transition states i.e. non-frail or pre-frail;
2) studied adult participants who were aged ≥18 at baseline;
3) described frailty trajectories or transitions independent of the setting the study was conducted in i.e. no restriction on setting provided the study was population-based. Population-based papers were defined as studies where the results could be extrapolated to a larger population defined in terms of e.g. age groups, geographical areas, or clinical setting.
4) described trajectories or transition states as defined *a priori*;
5) reported results exclusively from, and in any of the languages of, the 22 JA MSs;
6) published results between January 2002 and April 2017. Before 2002, relevant studies were only considered on a case-by-case basis when discovered opportunistically i.e. through searching reference lists.

Papers were excluded if they:
a) contained replicated data from the same study;
b) only provided data from a country that was not included among the 22 JA MSs;
c) were reported in a language other than that of a JA MS;
d) were published as conference abstracts, editorials and correspondence;
e) did not relate specifically to the topic or were not population based.

RESULTS

In total, 864 records were retrieved after the literature search and review of the grey literature. After the

removal of duplicates, 581 abstracts were screened. Of these, 3 full-text articles met inclusion criteria and were reviewed. The PRISMA flow diagram is presented in *Figure 1*. Most studies on trajectories or transitions between different stages of frailty were reported from non-JA MSs. The majority reported data from longitudinal population-based cohort studies. In all, only three papers presenting data on frailty trajectories or transitions from JA ADVANTAGE MSs were available. These were from the United Kingdom (UK) (n = 1) [31], Italy (n = 1) [32] and the Netherlands (n = 1) [33]. The characteristics of these studies are provided in detail in *Table 1*. In summary, two of the studies (in the UK and Italy) were community-based longitudinal studies [31, 32]; the Dutch study recruited patients from primary care [33]. The Italian and Dutch studies analysed frailty transitions, both providing data on the proportion of participants having at least one transition during the period of follow-up; the UK study provided data on the association between trajectories and physical activity. There was considerable variation in frailty instruments used; the Italian study used Fried's CHS criteria, the UK paper a 56-item FI and the Dutch study used the 15-question Groningen Frailty Indicator (GFI).

The UK study presented data on trajectories from the English Longitudinal Study of Ageing (ELSA) over the period from 2002 and 2010 [31]. The results showed that there were higher levels of frailty in women compared with men and that these differences persisted over time. The study found that moderate physical activity reduced the progression of frailty in some age groups, particularly those aged ≥ 65 and that vigorous activity significantly reduced the trajectory of frailty. However, mild physical activity was insufficient to slow progression [31]. The results also described the influence of socioeconomic factors on frailty trajectories with those in lower socioeconomic groups more likely to transition to frailty. The Progetto Veneto Anziani (Pro.V.A.) Longitudinal Study from Italy, found that 32.6% of participants had at least one frailty transition in any direction over 4.4 years of follow-up [32]. The authors identified several risk factors for transitions including older age, female gender, obesity, cardiovascular disease, osteoarthritis, hypovitaminosis D, hyperuricemia, smoking, vision loss, dependence in activities of daily living, cognitive impairment, low monthly income and poor physical performance, all of which were significantly associated with greater risk of becoming frail at end-point [32]. Improvements in frailty status in participants who were frail or pre-frail at baseline were associated with being overweight, having low-moderate alcohol consumption, higher educational level and living alone [32]. In the Personalised ICT Supported Service for Independent Living and Active Ageing (PERSSILAA) Study, older adults attending their general practitioner in the Enschede region of the Netherlands were screened with the GFI to categorise frailty at baseline and end-point over two years of follow-up [33]. The study found that most robust participants at baseline (78%) remained robust. Over half (52%) of
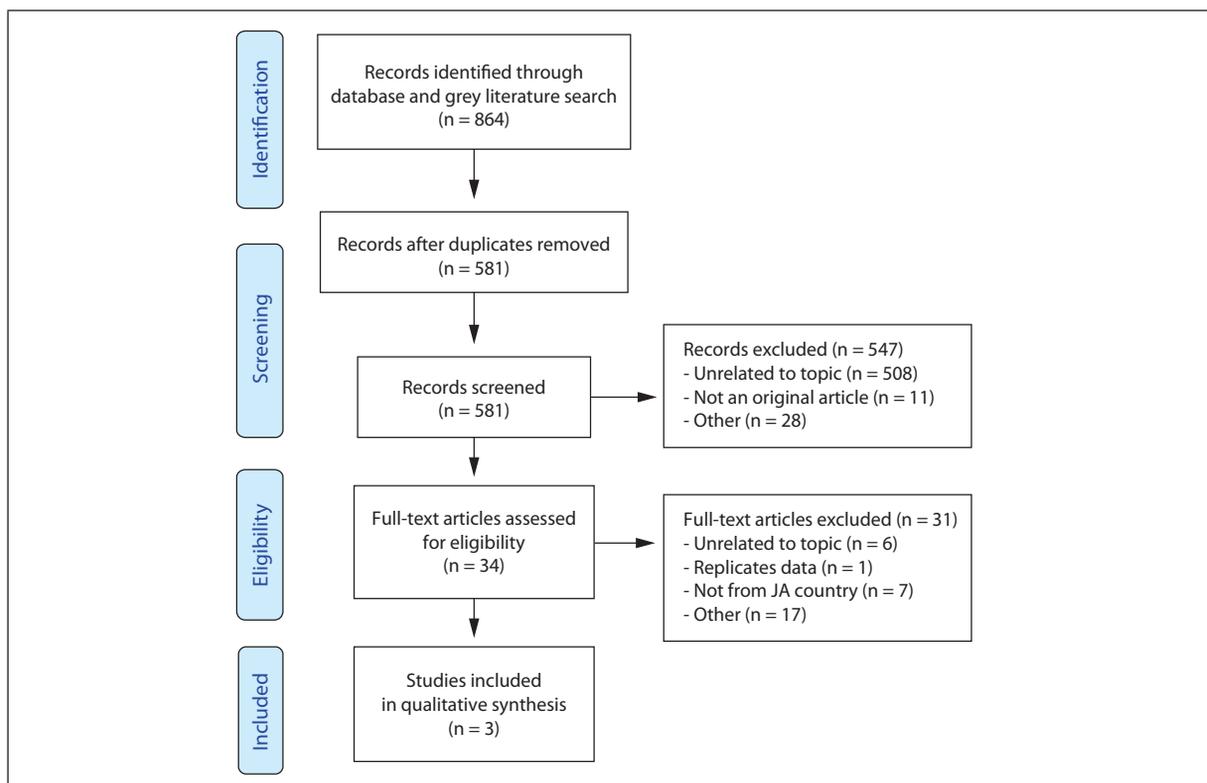
Figure 1
PRISMA flow diagram of the systematic review of studies of frailty trajectories or transition states at population level in the Joint Action ADVANTAGE European Member States.

Table 1
Characteristics of studies reporting transitions or trajectories of frailty at population-level in the Joint Action ADVANTAGE European Member States

Author, year	Number of participants	Age (years)	Women (%)	Setting & Design	Frailty definition	Sampling process	Results
UK							
Rogers et al., 2017 [31]	8649	≥50	53.2	Community based Longitudinal cohort study	FI, 56 variables	Representative sample of the population aged 50 and over, living in private households in England.	Average eleven-year frailty trajectories in five-year age cohorts (50-54; 55-59; 60-64; 65-69; 70-74; 75-79; 80+) of non-frail adults were assessed, predicted by baseline physical activity (PA) status. Compared with the sedentary reference group, mild PA was insufficient to significantly slow the progression of frailty, moderate physical activity reduced the progression of frailty in some age groups (particularly ages 65 and above) and vigorous activity significantly reduced the trajectory of frailty.
Italy							
Trevisan et al., 2017 [32]	2925	≥65	59.7	Community based Longitudinal cohort study	Fried criteria (CHS)	Randomly selected using a multistage stratified method.	Over 4.4 years of follow-up, 41.9% retained their baseline frailty status, 32.6% had one transition in their frailty status, and 25.5% died.
The Netherlands							
O'Caoimh et al., 2017 [33]	169	≥65	52	Primary care Longitudinal cohort study	GFI	Sampling from a representative sample of patients attending general practitioners offices. Two-step screening and assessment process. Only those with baseline and end-point data included.	During two years of follow-up, 78% of subjects remained robust, while over half remained stable as pre-frail (52%) or frail (52%). About a quarter transitioned back from either frail to pre-frail (26%) and from pre-frail to robust (25%). In all, 23% converted from pre-frailty to established frailty over two years (2014-2016). In all, 34.3% had one frailty transition.

CHS: Cardiovascular Health Study; FI: Frailty Index; GFI: Groningen Frailty Indicator

participants who were pre-frail or frail also remained stable. It was found that 26% of frail participants transitioned back to pre-frail while 25% of pre-frail participants transitioned to robust. Overall, 23% of the older adults examined converted from pre-frailty to established frailty over two years, and 34.3% (58/169) had at least one frailty transition in any direction. However, as highlighted by the PERSSILAA investigators, the numbers were small, duration of follow-up short and the classification of frailty based on the GFI, which may have been overly sensitive to change.

DISCUSSION

The results of this systematic review of frailty trajectories and transitions in JA MSs showed that available data were limited. The three studies found were extremely heterogeneous; one reporting trajectories and two providing data on transitions between different frailty states. Both papers reporting transitions provided the proportion of participants with at least one frailty transition noted during the period of follow-up. Indeed, while both studies reported data on a various array of possible transition states from robust (non-frail) to pre-frail, frail and back, this was the only consistent indicator. Findings appeared roughly similar; in the Pro.V.A Longitudinal study the proportion of participants with any frailty transition was 32.6% [32] versus 34.3% in PERSSILAA [7, 33] in cohorts both aged over 65 years. However, the duration of follow-up over which these outcomes were investigated varied markedly (ranging from 2 to 4.4 years) between studies, limiting comparability. Further, these also differed in sampling approach,

frailty classification, sample size and population characteristics.

This heterogeneity is similar to that reported in non-JA countries, where the proportions with any transition also vary considerably. The most consistent measure of progression reported appears to be the proportion of individuals with at least one frailty transition during follow-up, which has been reported to be as low as 22% over six years using the Vulnerable Elders Survey-13 questionnaire in a sample with a mean age of 79 years in Israel [34] to 61% over ten years using the Fried's CHS criteria in persons with a mean age of 78 years in the United States of America (USA) [35]. Acute illness and hospitalisation were identified in the USA [36] and polypharmacy in Australia [37] as the most common precipitating factors resulting in transitions to more severe frailty states.

Since this systematic review was conducted several new studies have been published, including an analysis from the Longitundinal Aging Study Amsterdam examining trajectories in those aged ≥65 years [19]. This paper presents mean changes in a 32-item FI score (including factors from physical, mental and cognitive domains) over 17 years. It could be argued that the use of such a sensitive, comprehensive, adaptable and continuous measure will allow for greater comparability [17], especially if this approach to capturing trajectories is more widely used.

Using similar frailty classifications and instruments is one approach to standardising results to provide more accurate and reliable data on trajectories and transitions. Developing broader consensus definitions on not only frailty but also pre-frailty are required to facilitate this [7]. There is also a need for well-designed prospective studies and harmonised approaches to gather reliable information on the epidemiology and progression of frailty. Ongoing longitudinal studies of ageing including the international Survey of Health and Retirement in Europe (SHARE) [38] and the Study on Global AGEing and Adult Health (SAGE) [39], which collect frailty data, are a good example of this. Nevertheless, these kinds of studies are subject to attrition bias, which may lead to relatively less frail samples over time and underestimation of rates at different time points, particularly if participants are followed over the prolonged periods necessary to demonstrate changes [40] especially at the early pre-frailty stage. Cohort effects may also introduce bias where different waves are considered in longitudinal data sets [19].

It is also important to conduct studies examining predictors of transitions to higher (or lower) levels of frailty, including those associated with more rapid trajectories. To date, a number of risk factors have been identified, which apart from age and gender, include a wide variety of social and behavioural factors [23]. These were echoed in the Italian study by Trevisan *et al.* [32], which highlighted the association between these and frailty transitions. Understanding how these determine rates of change including their impact on reversibility will also be important, particularly if evidence grows for the potential to improve frailty and transition to lower frailty states. Indeed, whether frailty is truly reversible remains a topic of discussion for over twenty years with little evidence yet available from population-level studies measuring frailty progression over time. Growing research is focused on preventing onset in community-dwellers at risk (i.e. pre-frail older adults) [7, 10]. However, while there is evidence that pre-frailty can be reduced in community-dwelling older adults [9], there is little evidence that this applies to those with established frailty, even in its early stages [41].

This study has several limitations. The focus was on EU JA countries as this was the remit of ADVANTAGE and no detailed analysis or meta-analysis was possible because of the paucity of papers retrieved in this context. Including papers from other countries, particularly the USA and Japan, where most studies examining frailty trajectories have been conducted, would allow a better insight into the topic, although this could introduce even more heterogeneity. Our search only included papers published since 2002 and our review of the grey literature in particular was not exhaustive so that some relevant studies may not have been included. Given the increased research focus on frailty trajectories and transitions and the growing number of publications dedicated to this, repeating this review in a global context would be worthwhile.

CONCLUSIONS

Few studies examining frailty trajectories or transitions were available from EU ADVANTAGE JA MSs. Given the importance of this information in planning public health interventions, there is a need to better support data collection and projects that measure frailty trajectories and transitions between different levels of frailty severity at population-level in the EU. Existing data from ongoing longitudinal studies of ageing such as SHARE and SAGE might be used to better understand these in Europe. More data on predictors and risk factors for transitions are also required; better knowledge about these can foster policy action to reduce frailty at population-level. Agreement on the timing of suitable intervals to assess frailty trajectories is important and recommendations to standardise these should be made. Well-designed incidence studies should also help inform this. Again, developing standardised approaches to defining and measuring frailty is important to ensure comparability of findings globally and across JA ADVANTAGE MSs.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

REFERENCES

1. Kingston A, Robinson L, Booth H, Knapp M, Jagger C; MODEM project. Projections of multi-morbidity in the older population in England to 2035: estimates from the Population Ageing and Care Simulation (PACSim) model. Age Ageing. 2018;47(3):374-80. DOI: 10.1093/ageing/afx201

2. Morley JE, Vellas B, Van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392-7. DOI: 10.1016/j.jamda.2013.03.022

3. Rodríguez-Mañas L, Féart C, Mann G, Viña J, Chatterji S, Chodzko-Zajko W, et al.; FOD-CC group (Appendix 1). Searching for an operational definition of frailty: a Delphi method based consensus statement: the frailty operative definition-consensus conference project. J Gerontol A Biol Sci Med Sci. 2013;68(1):62-7. DOI: 10.1093/gerona/gls119

4. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. Lancet. 2013;381(9868):752-62. DOI: 10.1016/S0140-6736(12)62167-9

5. Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Arch Intern Med. 2006;166(4):418-23.

6. Lang PO, Michel JP, Zekry D. Frailty syndrome: a transitional state in a dynamic process. Gerontology. 2009;55(5):539-49. DOI: 10.1159/000211949

7. O'Caoimh, R, Molloy DW, Fitzgerald C, Velsen LV, Cabrita M, Nassabi MH et al. ICT-supported interventions targeting pre-frailty: healthcare recommendations from the Personalised ICT Supported Service for Independent Living and Active Ageing (PERSSILAA) study. In: Röcker et al. (Eds.). Information and communication technologies for ageing well and e-health. Berlin: Springer Nature; 2018. doi.10.1007/978-3-319-93644-4_4

8. Sergi G, Veronese N, Fontana L, De Rui M, Bolzetta F, Zambon S, et al. Pre-frailty and risk of cardiovascular disease in elderly men and women: the Pro.V.A. study. J Am Coll Cardiol. 2015;65(10):976-83. DOI: 10.1016/j.jacc.2014.12.040

9. Puts MT, Toubasi S, Andrew MK, Ashe MC, Ploeg J, Atkinson E, et al. Interventions to prevent or reduce the level of frailty in community-dwelling older adults: a scoping review of the literature and international policies. Age Ageing. 2017;46(3):383-92. DOI: 10.1093/ageing/afw247

10. Serra-Prat M, Sist X, Domenich R, Jurado L, Saiz A, Roces A, et al. Effectiveness of an intervention to prevent frailty in pre-frail community-dwelling older people consulting in primary care: a randomised controlled trial. Age Ageing. 2017;46(3):401-7. DOI: 10.1093/ageing/afw242

11. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in community-dwelling older persons: a systematic review. J Am Geriatr Soc. 2012;60(8):1487-92. DOI: 10.1111/j.1532-5415.2012.04054.x

12. O'Caoimh R, Galluzzo L, Van der Heyden J, Carriazo AM, López Samaniego L, Koula Maria, et al. Frailty at population level: a systematic review [Report]. Available from: http://advantageja.eu/images/WP5-Frailty-at-Population-Level-a-Systematic-Review-.pdf.

13. Siriwardhana DD, Hardoon S, Rait G, Weerasinghe MC, Walters KR. Prevalence of frailty and prefrailty among community-dwelling older adults in low-income and middle-income countries: a systematic review and meta-analysis. BMJ Open. 20181;8(3):e018195. DOI: 10.1136/bmjopen-2017-018195

14. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56. DOI: org/10.1093/gerona/56.3.M146

15. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. J Gerontol A Biol Sci Med Sci. 2007;62(7):722-7. DOI: 10.1093/gerona/62.7.722

16. Drubbel I, de Wit NJ, Bleijenberg N, Eijkemans RJ, Schuurmans MJ, Numans ME. Prediction of adverse health outcomes in older people using a frailty index based on routine primary care data. J Gerontol A Biol Sci Med Sci 2013;68:301-8. DOI: 10.1093/gerona/gls161

17. Cesari M, Gambassi G, van Kan GA, Vellas B. The frailty phenotype and the frailty index: different instruments for different purposes. Age Ageing. 2014;43(1):10-2. DOI: 10.1093/ageing/aft160

18. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ. 2011;183(8):E487-94. DOI: 10.1503/cmaj.10127.

19. Hoogendijk EO, Rockwood K, Theou O, Armstrong JJ, Onwuteaka-Philipsen BD, Deeg DJH, et al. Tracking changes in frailty throughout later life: results from a 17-year longitudinal study in the Netherlands. Age Ageing. 2018; May 19. DOI: 10.1093/ageing/afy081

20. Mitnitski A, Rockwood K. The rate of aging: the rate of deficit accumulation does not change over the adult life span. Biogerontology. 2016;17(1):199-204. DOI: 10.1007/s10522-015-9583-y

21. Mitnitski A, Song X, Rockwood K. Improvement and decline in health status from late middle age: modeling age-related changes in deficit accumulation. Exp Gerontol. 2007;42(11):1109-15. DOI: 10.1016/j.exger.2007.08.002

22. Shi J, Yang Z, Song X, Yu P, Fang X, Tang Z, et al. Sex differences in the limit to deficit accumulation in late middle-aged and older Chinese people: results from the Beijing Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci. 2013;69(6):702-9. DOI: 10.1093/gerona/glt143

23. Marshall A, Nazroo J, Tampubolon G, Vanhoutte B. Cohort differences in the levels and trajectories of frailty among older people in England. J Epidemiol Community Health. 2015 Apr 1;69(4):316-21. DOI: 10.1136/jech-2014-204655.

24. Gordon EH, Peel NM, Samanta M, Theou O, Howlett SE, Hubbard RE. Sex differences in frailty: A systematic review and meta-analysis. Exp Gerontol. 2017 Mar;89:30-40. DOI: 10.1016/j.exger.2016.12.021.

25. Rockwood K, Mitnitski A. Limits to deficit accumulation in elderly people. Mech Ageing Dev. 2006 May; 127(5):494-6. DOI: 10.1016/j.mad.2006.01.002

26. Vetrano DL, Palmer K, Marengoni A, Marzetti E, Lattanzio F, Roller-Wirnsberger R, et al.; Joint Action ADVANTAGE WP4 group. Frailty and multimorbidity: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2018 May 3. DOI: 10.1093/gerona/gly110

27. Galluzzo L, O'Caoimh R, Rodríguez-Laso Á, Beltzer N, Ranhoff AH, Van der Heyden J, Lamprini-Koula M, Ciutan M, Lopez-Samaniego L, Liew A on behalf of Work Package 5 of the Joint Action ADVANTAGE. Incidence of frailty: a systematic review of scientific literature from a public health perspective. Ann Ist Super Sanità. 2018;54(3):239-245.

28. Rodríguez-Laso Á, O'Caoimh R, Galluzzo L, Carcaillon-Bentata L, Beltzer N, Macijauskiené J, Albaina Bacaicoa O, Ciutan M, Hendry A, López Samaniego L, Liew A, on

behalf of Work Package 5 of the Joint Action ADVAN-TAGE. Population screening, monitoring and surveillance for frailty: three systematic reviews and a grey literature review. Ann Ist Super Sanità. 2018;54(3):253-262.

29. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine. 200921;6(7):e1000100. DOI: 10.1136/bmj.b2700.

30. Chamberlain AM, Finney Rutten LJ, Manemann SM, Yawn BP, Jacobson DJ, Fan C, et al. Frailty Trajectories in an Elderly Population-Based Cohort. J Am Geriatr Soc. 2016 Feb;64(2):285-92. DOI: 10.1111/jgs.13944

31. Rogers NT, Marshall A, Roberts CH, Demakakos P, Steptoe A, Scholes S. Physical activity and trajectories of frailty among older adults: evidence from the English Longitudinal Study of Ageing. PLoS One. 2017;12(2):e0170878. DOI: 10.1371/journal.pone.0170878

32. Trevisan C, Veronese N, Maggi S, Baggio G, Toffanello ED, Zambon S, et al. Factors influencing transitions between frailty states in elderly adults: The Progetto Veneto Anziani Longitudinal Study. J Am Geriatr Soc. 2017;65(1):179-84. DOI: 10.1111/jgs.14515

33. O'Caoimh R, Molloy DW, Fitzgerald C, Van Velsen L, Cabrita M, Nassabi MH, et al. Healthcare recommendations from the personalised ICT supported service for independent living and active ageing (PERSSILAA) study. ICT4Ageing Well 2017; 2017 Apr 28-29. Porto, Portugal, 91-103. doi.org/10.5220/0006331800910103

34. Bentur N, Sternberg SA, Shuldiner J. Frailty transitions in community dwelling older people. Isr Med Assoc J. 2016;18(8):449-53.

35. Ottenbacher KJ, Graham JE, Snih SA, Raji M, Samper-Ternent R, Ostir GV, et al. Mexican Americans and frailty: findings from the Hispanic established populations epidemiologic studies of the elderly. Am J Public Health. 2009;99(4):673-9. DOI: 10.2105/AJPH.2008.143958

36. Gill TM, Gahbauer EA, Han L, Allore HG. The relationship between intervening hospitalizations and transitions between frailty states. J Gerontol A Biol Sci Med Sci. 2011;66(11):1238-43. DOI: 10.1093/gerona/glr142

37. Jamsen KM, Bell JS, Hilmer SN, Kirkpatrick CM, Ilomäki J, Couteur DL, et al. Effects of changes in number of medications and drug burden index exposure on transitions between frailty states and death: the concord health and ageing in men project cohort study. J Am Geriatr Soc. 2016;64(1):89-95. DOI: 10.1111/jgs.13877

38. Santos-Eggimann B, Cuénoud P, Spagnoli J, Junod J. Prevalence of frailty in middle-aged and older community-dwelling Europeans living in 10 countries. J Gerontol A Biol Sci Med Sci. 2009;64(6):675-81. DOI: 10.1093/gerona/glp012

39. Harttgen K, Kowal P, Strulik H, Chatterji S, Vollmer S. Patterns of frailty in older adults: comparing results from higher and lower income countries using the Survey of Health, Ageing and Retirement in Europe (SHARE) and the Study on Global AGEing and Adult Health (SAGE). PLoS One. 2013;8(10):e75847. DOI: 10.1371/journal.pone.0075847

40. Gustavson K, von Soest T, Karevold E, Røysamb E. Attrition and generalizability in longitudinal studies: findings from a 15-year population-based study and a Monte Carlo simulation study. BMC Public Health. 2012;12(1):918. DOI: 10.1186/1471-2458-12-918

41. Frost R, Belk C, Jovicic A, Ricciardi F, Kharicha K, Gardner B, et al. Health promotion interventions for community-dwelling older people with mild or pre-frailty: a systematic review and meta-analysis. BMC Geriatr. 2017;17(1):157. DOI: 10.1186/s12877-017-0547-8