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Early identification of frailty: Developing an international Delphi consensus on pre-frailty

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Highlights

- Given the growing importance of the early identification of frailty to prevent subsequent functional decline and disability at both individual and population-level, we have conducted an international delphi study to identify defining characteristics of pre-frailty.
- The final consensus statement produced by this international collaboration of experts in the field describes pre-frailty as an aged-associated, multi-factorial, multi-dimensional, and non-linear prodromal risk-state associated with one or more of physical impairment, cognitive decline, nutritional deficiencies, and socioeconomic inequalities, predisposing to the development of frailty.
- Further study is required to fully operationalise this definition of pre-frailty for use in clinical practice including the development of improved screening and assessment tools.

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Early Identification of Frailty: Developing an International Delphi Consensus on Pre-frailty

Abstract

Background: Frailty is associated with a prodromal stage called pre-frailty, a potentially reversible and highly prevalent intermediate state before frailty becomes established. Despite being widely-used in the literature and increasingly in clinical practice, it is poorly understood.

Objective: To establish consensus on the construct and approaches to diagnose and manage pre-frailty.

Methods: We conducted a modified (electronic, two-round) Delphi consensus study. The questionnaire included statements concerning the concept, aspects and causes, types, mechanism, assessment, consequences, prevention and management of pre-frailty. Qualitative and quantitative analysis methods were employed. An agreement level of 70% was applied.

Results: Twenty-three experts with different backgrounds from 12 countries participated. In total 70 statements were circulated in Round 1. Of these, 52.8% were accepted. Following comments, 51 statements were re-circulated in Round 2 and 92.1% were accepted. It was agreed that physical and non-physical factors including psychological and social capacity are involved in the development of pre-frailty, potentially adversely affecting health and health-related quality of life. Experts considered pre-frailty to be an age-associated multi-factorial, multi-dimensional, and non-linear process that does not inevitably lead to frailty. It can be reversed or attenuated by targeted interventions. Brief, feasible, and validated tools and multidimensional assessment are recommended to identify pre-frailty.

Conclusions: Consensus suggests that pre-frailty lies along the frailty continuum. It is a multidimensional risk-state associated with one or more of physical impairment, cognitive decline, nutritional deficiencies and socioeconomic disadvantages, predisposing to the

development of frailty. More research is needed to agree an operational definition and optimal management strategies.

Keywords: Frailty, Geriatric Assessment, Consensus, Pre-frailty, Older people, Delphi.

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Introduction

Frailty is a highly prevalent [1] age-related syndrome associated with multimorbidity [2] and disability [3] that increases vulnerability to adverse healthcare outcomes, impacting negatively upon quality of life [2-8]. Pre-frailty is often described as a risk-state that may be evident before the onset of clinically identifiable frailty [9]. Increased awareness of pre-frailty has emerged as a consequence of the realisation that frailty is a dynamic condition along a continuum with transitions between different (higher and lower) frailty states over time [10], and from the operationalisation of scales to measure its severity [9,11]. In this context, pre-frailty can be considered as a 'prodromal' form of frailty (prodromal frailty) akin to mild cognitive impairment (prodromal dementia). Despite being widely-used in the academic literature [9] and increasingly in clinical practice, the nature and mechanism of pre-frailty as a precursor to frailty are not fully understood [12].

Pre-frailty is common in all healthcare settings; the global prevalence in community-dwelling adults aged ≥65 was reported to be 41.6% [13] with rates varying by setting, region and the assessment approach [1,13-16]. Current approaches to measure pre-frailty centre on using cut-off values on frailty scales, which fall below the threshold for established frailty. This approach is analogous to the use of cognitive screening instruments to separate mild cognitive impairment from dementia. The most widely-used frailty classifications are Fried et al.'s Physical Phenotype [17] (if one or two of five physical features are present, an individual is designated as pre-frail) and the accumulation of deficits theory of frailty (usually a score between 0.08 and 0.25 on a Frailty Index denotes pre-frailty) [18-20]. It is postulated that chronic inflammation and multiple metabolic and nutritional factors [3, 9, 12] play a role in its pathogenesis; however, there is no single widely-accepted process leading to the development of pre-frailty.

Research suggests that interventions, particularly those focusing on nutrition and physical exercise, may prevent onset of frailty in pre-frail individuals [21-23]. Studies addressing pre-frailty are difficult to compare because of the heterogeneous nature of the approaches used to define and measure the condition. Exploration of the term and development of a standardised definition are therefore important to improve the identification of those who may benefit from early intervention [24, 25].

To date, there is no agreed or commonly used definition available for pre-frailty and to our knowledge, no study has brought experts together to discuss its features including core concepts, causes, mechanisms and consequences. The objective of this study is to conduct an international Delphi consensus process to identify key characteristics that could contribute to a successful definition of pre-frailty or 'prodromal stage frailty' and aid in the development of a standard assessment approach to identify older adults before onset of established frailty.

Methods

This study followed a modified Delphi (e-Delphi) approach including two rounds of electronic surveys and an online consensus meeting (Figure 1). A Delphi consensus process includes methods to establish effective group communications, typically by soliciting opinions of a group of experts in order to identify possible solutions to a complex problem or a real-world issue [26, 27]. The Delphi technique is considered suitable for achieving consensus as it uses methods for linking/combining opinions gathered from individuals with expertise in certain areas related to a complex problem [27].

Selection of participants

Following a non-probabilistic sampling approach, a total of 27 international experts with different professional backgrounds from 12 countries were invited to participate in the study with the aim of gathering a broad range of opinions. Participants were included based on their reputation and involvement in research and or clinical practice related to pre-frailty and frailty. Specifically, invitees had published research articles or audits on the topic, led frailty education programmes, or were clinical practitioners who had recognised expertise in screening or assessment of pre-frailty and frailty. Participants ideally had to have published peer-reviewed research papers within the last five years in this area or had at least ten years' experience of providing care for pre-frail or frail patients. To ensure that the participation of experts in the study reflected the broad range of frailty domains, the backgrounds of participants included clinicians, academic researchers, and educators with expertise in different aspects of frailty. The core working group (…), based at the …, selected participants and sent invitations directly via email. Interested individuals were provided with additional information and invited to participate in one of two online introductory meetings using video-conferencing facilities to introduce and discuss the methods. Two meetings were conducted to suit participants from

multiple time zones. Time was allowed to consider participation before receipt of the first e-Delphi survey link. All participants provided informed consent. Ethical approval was granted in advance from the… Research Ethics Committee (Reference number …). *(Note: Identifiable details were removed to ensure anonymity during review – these will be added)*

Development and administration of the questionnaires

A systematic review was conducted prior to the Delphi to identify current definitions of pre-frailty in the literature [9]. This produced a list of 70 statements and one open-ended question, which were incorporated into the initial electronic survey. Questions were grouped into sections and sub-sections: 1. 'Pre-frailty as a concept' *(1.1. first stages, 1.2. frailty as a continuum – transitions and trajectories, and 1.3. frailty as a multi-factorial and multi-dimensional construct);* 2. 'Types of pre-frailty' *(2.1. physical, 2.2. social, 2.3. cognitive, and 2.4. nutritional);* 3. 'Multifactorial aspects and causes of pre-frailty'; 4. 'Mechanisms'; 5. 'Screening and assessment instruments supporting operational definitions and clinical assessment'; 6. 'Consequences of pre-frailty'; and 7. 'Prevention and management of pre-frailty' (see appendix for the full list of statements). Participants had three weeks to respond to each round. To improve the response rate, weekly reminders were sent to those who had not yet responded. An online cloud-based survey software tool was used to conduct the e-Delphi surveys. The survey was administered in English.

Delphi Rounds

Round one was circulated between 1st-21st February 2019 and Round 2 from 5th-26th March 2019. Participants rated the statements on a 5-item Likert scale from 1-strongly disagree to 5-strongly agree and were also able to add free-text comments. An agreement level of 70% was applied for accepting statements i.e. those rated as 4 "agree" or 5 "strongly agree" by ≥70% of

participants, provided they were not rated as 1 "strongly disagree" or 2 "disagree" by more than 15% [28-31]. Statements not meeting these criteria were automatically excluded. Entries in the open-ended comments sections in Round 1 were collated and mapped under existing statements or refined as new statements to be circulated in Round 2. The final set of statements was forwarded to participants in advance of the online consensus meeting.

Consensus meeting

Participants were invited to the online expert panel at the end of e-Delphi Round 2 on 15th April 2019 in order to refine the final statements to minimise duplication or repetition. Additional clinicians with expertise in frailty were invited to participate in the meeting as external experts to act as a sounding board.

Results

Round 1

Twenty-three participants from 12 countries contributed to Round 1 (response rate= 85.1%). Their backgrounds were in geriatric medicine, nursing, acute medicine and geriatrics, endocrinology and active ageing, medical education and curriculum development, physiotherapy and musculoskeletal health, primary care, psychology, public health and statistics, sociology, and telemedicine and e-health. More than half of the participants were geriatricians (n=13), the majority (n=17) were later stage researchers (≥10 years' experience) and most were based in Europe (n=18) (Table 1). A total of 52.8% of the statements were accepted (37/70) during this round. In summary, 27 statements were agreed outright by ≥70% of respondents and 10 required edits based on comments received (see appendix for distribution of the survey responses). Most of the excluded statements (n=11) were from section two ('Types of pre-frailty') and resulted in the social pre-frailty subsection being excluded from the survey. Eighty-eight comments received from participants were collated and mapped under

existing statements. Statements that did not meet the threshold level but were supported by feedback in the comments boxes were edited accordingly and included to be re-rated in Round 2 (n=9 statements). Finally, comments or suggestions that did not address existing statements were added as new statements. This included a single open-ended question where participants were asked to name the instrument (scale or questionnaire) that they considered optimal to identify pre-frailty. The most frequent response, the Physical Phenotype (reported by 8 of 23 participants), was incorporated into a new statement *"Applying the Fried (physical) frailty criteria is the optimal approach to assessing and classifying pre-frailty"*. These free-text responses resulted in the generation of new statements (n=7) for Round 2. In total, 51 statements were forwarded to be rated in Round 2 (Figure 2).

Round 2

Twenty-one individuals participated in Round 2; two with a background in geriatric medicine dropped out (response rate= 91.3%). In all, 92.1% of the statements were accepted (47 of 51) and were forwarded to be included in the consensus meeting for further discussion. Distribution of survey responses and the included statements are provided in the appendix. Excluded statements were from section three ('Multifactorial aspects and causes of pre-frailty', n=2), and section five, ('Screening and assessment instruments supporting operational definitions and clinical assessment', n=2).

Consensus meeting

The final stage was an online consensus meeting with participation of 10 experts from eight countries. In the meeting, the wordings of the statements were refined and they were merged where possible to shorten the final list of statements. For example, 'Types of pre-frailty', was merged with section three 'Multi-factorial aspects and causes'. Similarly, section five 'Consequences of pre-frailty' was merged with section one 'Pre-frailty as a concept'. Thus, the

final list of statements consisted of a total of five sections. A detailed summary of the re-phrasing and merger of statements is presented in the Appendix. The final multidimensional consensus statement formed is presented in Table 2.

Discussion

This e-Delphi study highlights different aspects of pre-frailty with participants agreeing upon five core areas to further understanding on this prodromal state. These incorporated the basic concept as well as multifactorial causes, the mechanism leading to pre-frailty, the importance of screening and assessment, and approaches to prevent and manage pre-frailty.

Concept

Participants agreed that while pre-frailty lies upon the frailty continuum, as the development of frailty is not a linear process, frailty might not be an inevitable outcome of pre-frailty. Therefore, what distinguishes this prodromal risk-state from 'very' mild frailty is that, as with mild cognitive impairment, the final outcome is not inevitable. In the literature, pre-frailty is often described as a state between being robust (non-frail) and frail [15], such that pre-frail individuals have a high risk of progressing to frailty [32]. Multiple studies support that pre-frailty is indeed a non-linear process that may be reversible, exhibiting dynamic transitions and trajectories between non-frail, pre-frail and frail states [10,33].

Most participants agreed that pre-frailty is age-associated, and might directly result in adverse outcomes without the need to transition to frailty. This is supported by several studies showing that pre-frailty results in increased healthcare utilisation [34], development of frailty [35], and higher mortality [36]. Consensus was established that pre-frailty is likely reversible and prevention of frailty is possible. They also agreed on the importance of early detection to prevent its negative consequences. Again, several studies show the potential for reversibility

[22, 37, 38] and suggest the benefits of early intervention [21, 23, 35]. Similarly, there is growing evidence that pre-frailty is not a single homogeneous biological syndrome and there is divergence in outcomes over time amongst those identified as pre-frail [39].

Multifactorial aspects and causes

Respondents indicated that pre-frailty is multi-factorial in its nature, broadly related to physical, cognitive, nutritional, socio-economic, and other causes. The participants suggested that assessment should therefore include physical, cognitive, social, nutritional, and other aspects of frailty in order not to miss its often subtle onset. Given that it exists on the frailty spectrum, pre-frailty would be expected to have the same multidimensional causes [10, 24, 40], though few studies have examined this. These include oxidative stress [38, 41], reduced resistance [42], nutritional deficiency [3], multimorbidity [36], obesity [36], smoking and alcohol consumption [36], and socioeconomic disadvantage [36].

There was some disagreement among participants at the end of Round 1 about the features of pre-frailty. This resulted in the exclusion of social isolation as a potential aspect and cause. Studies conducted in Japan introduced the term 'social frailty' into the literature, which is associated with living alone or a lack of social activities such as going out, visiting family and friends, or talking with someone every day [43, 44]. This is distinct from socio-economic causes of frailty, which are well established [45]. Participants suggested that there is insufficient evidence to include social isolation as a direct cause of pre-frailty or that such a subtype of pre-frailty exists. This is reflected in data from the English Longitudinal Study of Ageing that suggests that loneliness rather than social isolation may result in progression of (physical) frailty [46]. Nevertheless, participants indicated that social capital plays a role in the management of pre-frailty.

Mechanisms

The consensus was that the pathogenesis of pre-frailty is not well-understood currently. Nevertheless, in-keeping with pre-frailty as a prodrome to frailty i.e. a precursor or step in the

development of frailty, participants indicated that the primary mechanisms contributing to the development of pre-frailty were alterations in multiple body systems and reduced ability to maintain homeostasis. This vulnerability caused by impaired systems is in-keeping with previous studies examining the mechanism of frailty, which concluded that multisystem dysregulation, reduced adaptability, hormonal dysregulation [40], and oxidative and inflammatory processes are linked to the development of frailty [40-49]. However, the precise mechanisms that lead to dysregulation of pathways leading to frailty still remain unclear [47]. In this Delphi study, participants also suggested that non-physical factors such as psychological resilience and coping ability, as well as the social capacity (extent of support networks) contribute to pre-frailty.

Screening and assessment

Participants were not satisfied that existing screening and assessment tools (scales or questionnaires) adequately supported the operationalisation of pre-frailty. Nevertheless, in response to the open-ended question asking about their preference of instruments, physical phenotype measures were the most frequently named. Participants rationalised that as there is no widely accepted standard screening or assessment tool for frailty [24], it would have been too early to propose a consensus instrument for pre-frailty. However, a recently published consensus report on frailty assessment in primary care [50] recommends short frailty screening tools such as the Clinical Frailty Scale [51] or FRAIL scale [52] for initial identification of frail older adults. Nevertheless, no instrument for detecting pre-frail patients at risk of transitioning to frailty has been recommended. We suggest that research is needed to find an optimal approach for identifying pre-frailty and that this may require a widely-agreed operational definition of its own, similar to that produced here, rather than one defined by the currently available instrument cut-offs (for frailty).

At the consensus meeting, discussions also took place regarding the number of steps required in identifying pre-frailty. A two-step process was favoured by some participants using a brief screening instrument followed by a more multidimensional assessment such as a Comprehensive Geriatric Assessment (CGA) for confirmation. This is consistent with a study from the community in the Netherlands [35] and a paper summarising recent studies examining the relationship between frailty and CGA [53] that recommend that frailty screening is an efficient way to identify high-risk older adults who need detailed frailty assessment using CGA (if appropriate resources and environment are available). In this way, frailty screening supports the effective management of resources. Similarly, in our study, it was suggested that approaches to identify pre-frailty should focus on prioritising screening, ideally at opportunistic contact points with healthcare professionals e.g. while attending the emergency department [54], which can aid detailed assessment at later stages. Some participants also suggested that individual-level screening can be conducted by non-healthcare professionals e.g. family members, which can increase awareness and involvement of patients, informal caregivers and family members in the early identification of pre-frailty. This is particularly important for public health reasons [55], as preventing or slowing onset of frailty and subsequent functional decline can reduce costs [56] and improve quality of life [57] for older people. Recent consensus on frailty screening in primary care settings supports individual-level and opportunistic screening at point-of-care [50]; however, participants in that study noted that at present there is little evidence for the effectiveness of population-level screening, monitoring and surveillance of pre-frailty [58]. Considering recent events such as the COVID-19 pandemic and advancements in healthcare technology, innovative solutions including walking sensors [59], remote patient monitoring and telehealth [60] may represent the future of resource-efficient rapid screening for pre-frailty. Given their novelty, these new and potentially practical

solutions to screen pre-frailty need further investigation to understand their acceptability and benefits. However, these technological advancements are unlikely to influence the conceptual definition of pre-frailty. Further research is also required to specifically examine the 'real world' challenges related to screening and assessment in routine clinical practice, including in a variety of settings such as in emergency departments and with different patient groups including those with pre-existing complex medical conditions and or physical and cognitive impairments.

Prevention and management

Participants agreed that pre-frailty might be reversed or attenuated by tailored interventions. These include physical activity [21, 56], nutrition [21], participation to increase social capacity [54, 61] and the adoption of a healthy lifestyle [55]. Combined interventions also show potential to prevent pre-frailty by targeting multiple aspects of frailty with physical exercise conducted in groups, nutritional supplements and cognitive training found to be generally effective for reducing or delaying frailty [23, 55]. It is recommended that interventions that aim to reverse frailty or prevent further decline should be developed considering the needs and resources available for older adults in different care settings [53]. Despite this, participants highlighted that the evidence is as yet limited and there is a need for testing interventions focusing solely on pre-frail individuals rather than those with clinically established frailty [23]. Nevertheless, the identification of pre-frailty is increasingly recognised as a key step in actions that promote healthy ageing.

Limitations

This study has several limitations. The results represent the opinions of a limited number of participants, meaning that despite an attempt to include those with a broad range of expertise,

it is likely that some important perspectives were not included. The selection of participants was directed by the core team, who contacted experts within and outside their circle, potentially leading to bias. Some participants stated that despite having a quite strong opinion or preference for some statements, where the scientific evidence indicated otherwise or was lacking, they found it challenging to rate. This could be considered inherent to the Delphi consensus building process, which by its nature gathers the knowledge and experience of experts, which must be reconciled with the literature and evidence base. There are currently no standardised procedures for planning and conducting Delphi studies e.g. number of rounds or agreement thresholds. In our study, we decided to include statements if there was agreement of 70% (applying a cut-off of ≥4/5 on a Likert scale) but this threshold has varied widely from 50-97% between studies (median of 75%) [30]. A clearer approach to describe the level of agreement may have been to report the mean and standard deviations of the Likert scores as recommended by Greatorex and Dexter [62]. Also, we could not facilitate anonymous voting in the final consensus meeting due to technical issues, time constraints, constant discussions and time zone differences, limiting this to a refinement of the statements generated in the first two rounds of the e-Delphi. Although participants were encouraged to actively take part in the discussions, there was a risk of more senior panellists influencing less experienced participants' decisions, potentially leading to bias [27]. As participation in the consensus meeting was voluntary, this may explain the low number participating and might have led to over or under-representation of some perspectives. High attrition rate is an issue in Delphi studies, and our efforts, i.e., frequent communication and reminders [63], could not prevent it. On the other hand, this study gathered opinions from a diverse international group of renowned participants from a wide range of disciplines, which is a well-known strength of the Delphi methodology [27]. Although the COVID-19 pandemic has produced an unpredicted delay in the publication of the results of this consensus, it is

unlikely that it would affect the experts' views on the definition and concept of pre-frailty. In any case, all experts have reviewed the latest version of the manuscript and agreed that the consensus statement is not out of date.

Conclusions

This study presents the results of an e-Delphi process, which aimed to provide a better understanding of several aspects of pre-frailty including its concept, causes, and mechanisms, as well as approaches to assessment, prevention and management. This has produced a tentative consensus on the nature of pre-frailty supported by experts with relevant and complementary backgrounds from 12 countries across four continents. The findings suggest that pre-frailty is a multidimensional, multifactorial age-associated state that may precede the onset of frailty, and is associated with adverse health outcomes and reduced quality of life but which might be reversed or attenuated by targeted interventions. Brief, feasible and validated tools are recommended for opportunistic screening or case-finding followed by confirmation with multidimensional assessment. However, despite agreement on these key features, it was not possible to provide a compact definition that can be readily operationalised. Further real world research is now recommended to gather a better understanding of the operational definition of pre-frailty and the natural history of this complex prodromal state as people age. Indeed, currently, there is opportunity to research the pandemic of loneliness and deconditioning that is now shining a light on pre-frailty as a consequence of COVID-19 restrictions.

References

1. O'Caoimh R, Sezgin D, O'Donovan MR, Molloy DW, Clegg A, Rockwood K, Liew A. Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies. *Age and Ageing.* 2020; doi:10.1093/ageing/afaa219.

2. Le Cossec C, Perrine AL, Beltzer N, Fuhrman C, Carcaillon-Bentata L. Frailty, Frailty, and Multimorbidity: Prevalences and Associated Characteristics from Two French National Surveys. *J Nutr Health Aging*. 2016;20(8):860-69. doi: 10.1007/s12603-016-0802-2.

3. Kaiser MJ, Bandinelli S, Lunenfeld B. The nutritional pattern of frailty - Proceedings from the 5th Italian Congress of Endocrinology of Aging, Parma, Italy, 27-28 March 2009. *Aging Male*. 2009;12(4):87-94. doi: 10.3109/13685530903296706

4. Fairhall N, Kurrle SE, Sherrington C, et al. Effectiveness of a multifactorial intervention on preventing development of frailty in pre-frail older people: study protocol for a randomised controlled trial. *BMJ Open*. 2015;5(2):e007091. doi: 10.1136/bmjopen-2014-007091.

5. Liu LK, Lee WJ, Chen LY, et al. Association between Frailty, Osteoporosis, Falls and Hip Fractures among Community-Dwelling People Aged 50 Years and Older in Taiwan: Results from I-Lan Longitudinal Aging Study. *PLoS One*. 2015;10(9):e0136968. doi: 10.1371/journal.pone.0136968.

6. Morley JE, Vellas B, van Kan GA, 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.

7. Veronese N, Cereda E, Stubbs B, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results from a meta-analysis and exploratory meta-regression analysis. *Ageing Res Rev*. 2017;35:63-73. doi: 10.1016/j.arr.2017.01.003.

8. Vaes B, Depoortere D, Van Pottelbergh G, Mathei C, Neto J, Degryse J. Association between traditional cardiovascular risk factors and mortality in the oldest old: untangling the role of frailty. *BMC Geriatr*. 2017;17(1):234. doi: 10.1186/s12877-017-0626-x.

9. Sezgin D, Liew A, O'Donovan MR, O'Caoimh R. Pre-frailty as a multi-dimensional construct: A systematic review of definitions in the scientific literature. *Geriatr Nurs*. 2019; 0:1-8. doi: 10.1016/j.gerinurse.2019.08.004.

10. O'Caoimh R, Galluzzo L, Rodriguez-Laso A, et al. Transitions and trajectories in frailty states over time: a systematic review of the European Joint Action ADVANTAGE. *Ann Ist Super Sanita*. 2018;54(3):246-52. doi: 10.4415/ANN_18_03_12.

11. O'Caoimh R, Molloy DW, Fitzgerald C, et al. Healthcare recommendations from the personalised ICT supported service for independent living and active ageing (PERSSILAA) study. In *International Conference on Information and Communication Technologies for Ageing Well and e-Health*. 2017; 2:91-103. SCITEPRESS. doi: 10.5220/0006331800910103

12. Pujos-Guillot E, Petera M, Jacquemin J, et al. Identification of Pre-frailty Sub-Phenotypes in Elderly Using Metabolomics. *Front Physiol*. 2018;9:1903. doi.org/10.3389/fphys.2018.01903.

13. 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.

14. Santos-Eggimann B, Cuenoud 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.

15. 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*. 2018;8(3):e018195. doi: 10.1136/bmjopen-2017-018195.

16. Bandeen-Roche K, Seplaki CL, Huang J, Bet al. Frailty in Older Adults: A Nationally Representative Profile in the United States. *J Gerontol A Biol Sci Med Sci*. 2015;70(11):1427-34. doi: 10.1093/gerona/glv133.

17. Fried LP, Tangen CM, Walston J, et al. Frailty in Older Adults: Evidence for a Phenotype. *J Gerontol A Biol Sci Med Sci.* 2001;56(3):146-56. doi: 10.1093/gerona/56.3.m146.

18. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc*. 2010;58(4):681-7. doi: 10.1111/j.1532-5415.2010.02764.x.

19. Romero-Ortuno R. An alternative method for Frailty Index cut-off points to define frailty categories. *Eur Geriatr Med*. 2013;4(5). doi 10.1016/j.eurger.2013.06.005.

20. Mitnitski AB, Mogilner A, Rockwood K. Accumulation of deficits as a proxy measure of aging. *Scientific World Journal*. 2001;1:323-36. doi: 10.1100/tsw.2001.58.

21. Serra-Prat M, Sist X, Domenich R, 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 and Ageing*. 2017;46(3):401-7. doi: 10.1093/ageing/afw242.

22. Puts MTE, Toubasi S, Andrew MK, 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.

23. Apostolo J, Cooke R, Bobrowicz-Campos E, et al. Effectiveness of interventions to prevent pre-frailty and frailty progression in older adults: a systematic review. *JBI Database System Rev Implement Rep*. 2018;16(1):140-232. doi: 10.11124/JBISRIR-2017-003382.

24. Rodriguez-Manas L, Feart C, Mann G, et al. 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.

25. Soong JT, Poots AJ, Bell D. Finding consensus on frailty assessment in acute care through Delphi method. *BMJ Open*. 2016;6(10):e012904. doi: 10.1136/bmjopen-2016-012904.

26. Linstone HA, Turoff M. The Delphi Method: Techniques and Applications Newark 2002. Available from: https://web.njit.edu/~turoff/pubs/delphibook/delphibook.pdf [Last accessed 30/06/2020].

27. Hsu CC, Sandford BA. The Delphi technique: making sense of consensus. *Practical assessment, research & evaluation*. 2007;12(10):1-8. /doi.org/10.7275/pdz9-th90.

28. Giannarou L, Zervas E. Using Delphi technique to build consensus in practice. *Int Journal of Business Science and Applied Management*. 2014;9(2):65-82.

29. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. *Semin Arthritis Rheum*. 2011;41(2):95-105. doi: 10.1016/j.semarthrit.2010.12.001.

30. Diamond IR, Grant RC, Feldman BM, et al. Defining consensus: a systematic review recommends methodologic criteria for reporting of Delphi studies. *J Clin Epidemiol.* 2014;67(4):401-9. doi: 10.1016/j.jclinepi.2013.12.002.

31. McMillan SS, King M, Tully MP. How to use the nominal group and Delphi techniques. *Int J Clin Pharm.* 2016;38(3):655-62. doi: 10.1007/s11096-016-0257-x.

32. Xue QL. The frailty syndrome: definition and natural history. *Clin Geriatr Med*. 2011;27(1):1-15. doi: 10.1016/j.cger.2010.08.009.

33. Espinoza SE, Jung I, Hazuda H. Frailty transitions in the San Antonio Longitudinal Study of Aging. *J Am Geriatr Soc*. 2012;60(4):652-60. doi: 10.1111/j.1532-5415.2011.03882.x.

34. Chao CT, Wang J, Chien KL, and COhort of GEriatric Nephrology in NTUH (COGENT) study group. Both pre-frailty and frailty increase healthcare utilization and adverse health outcomes in patients with type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2018;17(1):130. doi.org/10.1186/s12933-018-0772-2

35. Jansen-Kosterink S, Van Velsen L, Frazer S, Dekker-van Weering M, O'Caoimh R, Vollenbroek-Hutten M. Identification of community-dwelling older adults at risk of frailty using the PERSSILAA screening pathway: a methodological guide and results of a large-scale deployment in the Netherlands. BMC public health. 2019 Dec;19(1):1-9..

36. Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *The Lancet Public Health*. 2018;3(7):e323-e32. doi: 10.1016/S2468-2667(18)30091-4.

37. Ng TP, Feng L, Nyunt MS, Feng L, Niti M, Tan BY, et al. Nutritional, Physical, Cognitive, and Combination Interventions and Frailty Reversal Among Older Adults: A Randomized Controlled Trial. *Am J Med*. 2015;128(11):1225-36 e1. doi: 10.1016/j.amjmed.2015.06.017.

38. Fernandez-Garrido J, Ruiz-Ros V, Buigues C, Navarro-Martinez R, Cauli O. Clinical features of prefrail older individuals and emerging peripheral biomarkers: a systematic review. *Arch Gerontol Geriatr*. 2014;59(1):7-17. doi: 10.1016/j.archger.2014.02.008.

39. Romero-Ortuno R, Scarlett S, O'Halloran AM, Kenny RA. Is phenotypical prefrailty all the same? A longitudinal investigation of two prefrailty subtypes in TILDA. *Age & Ageing*. 2019;49(1):39-45. doi: 10.1093/ageing/afz129.

40. Sezgin D, O'Donovan M, Cornally N, Liew A, O'Caoimh R. Defining frailty for healthcare practice and research: A qualitative systematic review with thematic analysis. *Int J Nurs Stud*. 2019;92:16-26. doi: 10.1016/j.ijnurstu.2018.12.014

41. Mulero J, Zafrilla P, Martinez-Cacha A. Oxidative stress, frailty and cognitive decline. *J Nutr Health Aging*. 2011;15(9):756-60. doi: 10.1007/s12603-011-0130-5.

42. Chen CY, Gan P, How CH. Approach to frailty in the elderly in primary care and the community. *Singapore Med J*. 2018;59(5):240-5. doi: 10.11622/smedj.2018052.

43. Makizako H, Shimada H, Tsutsumimoto K, et al. Social Frailty in Community-Dwelling Older Adults as a Risk Factor for Disability. *J Am Med Dir Assoc*. 2015;16(11):1003 e7-11. doi: 10.1016/j.jamda.2015.08.023.

44. Tsutsumimoto K, Doi T, Makizako H, et al. Association of Social Frailty With Both Cognitive and Physical Deficits Among Older People. *J Am Med Dir Assoc*. 2017;18(7):603-7. doi: 10.1016/j.jamda.2017.02.004.

45. Franse CB, van Grieken A, Qin L, Melis RJF, Rietjens JAC, Raat H. Socioeconomic inequalities in frailty and frailty components among community-dwelling older citizens. *PLoS One*. 2017;12(11):e0187946. doi: 10.1371/journal.pone.0187946.

46. Gale CR, Westbury L, Cooper C. Social isolation and loneliness as risk factors for the progression of frailty: the English Longitudinal Study of Ageing. *Age & Ageing*. 2018;47(3):392-7. doi: 10.1093/ageing/afx188

47. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging*. 2014;9:433-41. doi: 10.2147/CIA.S45300.

48. Qu T, Yang H, Walston JD, Fedarko NS, Leng SX. Upregulated monocytic expression of CXC chemokine ligand 10 (CXCL-10) and its relationship with serum interleukin-6 levels in the syndrome of frailty. *Cytokine*. 2009;46(3):319-24. doi: 10.1016/j.cyto.2009.02.015.

49. Li H, Manwani B, Leng SX. Frailty, Inflammation, and Immunity. *Aging and disease*. 2011;2(6):466-73. PMID: 22396895

50. Ruiz JG, Dent E, Morley JE, Merchant RA, Beilby J, Beard J, Tripathy C, Sorin M, Andrieu S, Aprahamian I, Arai H. Screening for and managing the person with frailty in primary care: ICFSR consensus guidelines. The journal of nutrition, health & aging. 2020;24(9):920-7.

51. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95

52. Abellan van Kan G, Rolland YM, Morley JE, Vellas B. Frailty: toward a clinical definition. J Am Med Dir Assoc. 2008;9(2):71–2.

53. Lee H, Lee E, Jang IY. Frailty and comprehensive geriatric assessment. Journal of Korean medical science. 2020;35(3).

54. O'Caoimh R, Costello M, Small C, Spooner L, Flannery A, O'Reilly L, et al. Comparison of Frailty Screening Instruments in the Emergency Department. *Int J Environ Res Public Health*. 2019;16(19). doi: 10.3390/ijerph16193626.

55. Walston J, Buta B, Xue QL. Frailty Screening and Interventions: Considerations for Clinical Practice. *Clin Geriatr Med*. 2018;34(1):25-38.

56. Yamada M, Arai H, Sonoda T, Aoyama T. Community-based exercise program is cost-effective by preventing care and disability in Japanese frail older adults. *J Am Med Dir Assoc*. 2012;13(6):507-11.

57. Masel MC, Graham JE, Reistetter TA, Markides KS, Ottenbacher KJ. Frailty and health related quality of life in older Mexican Americans. *Health Qual Life Outcomes*. 2009;7:70.

58. Rodriguez-Laso A, O'Caoimh R, Galluzzo L, Carcaillon-Bentata L, Beltzer N, Macijauskiene J, et al. Population screening, monitoring and surveillance for frailty: three systematic reviews and a grey literature review. *Ann Ist Super Sanita*. 2018;54(3):253-62.

59. Kumar DP, Toosizadeh N, Mohler J, Ehsani H, Mannier C, Laksari K. Sensor-based characterization of daily walking: a new paradigm in pre-frailty/frailty assessment. BMC geriatrics. 2020;20(1):1-1.

60. Kańtoch E, Kańtoch A. Cardiovascular and Pre-Frailty Risk Assessment during Shelter-In-Place Measures Based on Multimodal Biomarkers Collected from Smart Telemedical Wearables. Journal of Clinical Medicine. 2021;10(9):1997.

61. Fritz H, Tarraf W, Lysack C. Frailty prevention among older African Americans. Innov Aging. 2018;2(Suppl 1):644.

62. Greatorex J, Dexter T. An accessible analytical approach for investigating what happens between the rounds of a Delphi study. Journal of advanced nursing. 2000;32(4):1016-24.

63. Trevelyan EG, Robinson N. Delphi methodology in health research: how to do it?. European Journal of Integrative Medicine. 2015;7(4):423-28.

Conflict of Interest

The authors report no conflict of interest

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Tables & Figures

Table 1. Characteristics of the participants

Table 2. Final consensus statement towards a definition of pre-frailty

Figure 1. Methods flow chart

Figure 2. Summary results of Round 1 of the e-Delphi

Table 1. Characteristics of the participants

Characteristics	**n**	**%**
Gender		
Female	12	52.2
Male	11	47.8
Career stage*		
Early-Stage Career	6	26.0
Late-Stage Career	17	74.0
Area of expertise		
Geriatric medicine	12	52.2
Nursing	2	8.7
Acute medicine and geriatrics	1	4.3
Endocrinology and active ageing	1	4.3
Medical education and curriculum development	1	4.3
Physiotherapy and musculoskeletal health	1	4.3
Primary care	1	4.3
Psychology	1	4.3
Public health and statistics	1	4.3
Sociology	1	4.3
Telemedicine and e-health	1	4.3
Country		
Ireland	6	26.0
Spain	3	13.0
Australia	2	8.7
Italy	2	8.7
Portugal	2	8.7
Turkey	2	8.7
Austria	1	4.3

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Canada	1	4.3
Hong Kong	1	4.3
The Netherlands	1	4.3
United States of America	1	4.3
United Kingdom	1	4.3
Native English speaker		
Yes	11	47.8
No	12	52.2

* Early-Stage Career researcher = those still within a pre-specified period from the awarding of a PhD, professional qualification or academic appointment (10 years); Late is defined as those after at least 10 years

Table 2. Final consensus statement towards a definition of pre-frailty

Concept

Pre-frailty is a risk-state which predisposes to the development of frailty. Initially clinically silent, it may herald the onset of functional decline. It increases vulnerability to impairments, and is a risk factor for disability and adverse health and health-related quality of life outcomes if not detected early or managed poorly. Pre-frailty is hypothesized to be a dynamic nonlinear process that may be reversible, and where prevention may still be possible.

Multi-factorial aspects and causes

Pre-frailty is a multidimensional age-associated syndrome that may be caused by physical, cognitive, nutritional, socio-economic, and other factors. The relationship between pre-frailty and sarcopenia is hypothesized to be complex and bi-directional. Multi-morbidity and chronic diseases contribute to the onset of pre-frailty.

Mechanisms

Pre-frailty may involve alterations in multiple body systems associated with loss of physiological reserve and reduced ability to maintain homeostasis. Its impact is influenced by non-physical factors such as psychological and social capacity.

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Screening and assessment instruments supporting operational definitions and clinical assessment

It is recommended to undertake brief opportunistic screening for pre-frailty, preferably at routine contact points, for the earliest possible detection followed by confirmation using multidimensional assessment tools that are feasible and validated.

Prevention and management

Pre-frailty might be reversed or attenuated by targeted interventions including physical activity, nutritional interventions, healthy lifestyle and social participation, tailored to the individual.

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Figure 1. Methods flow chart

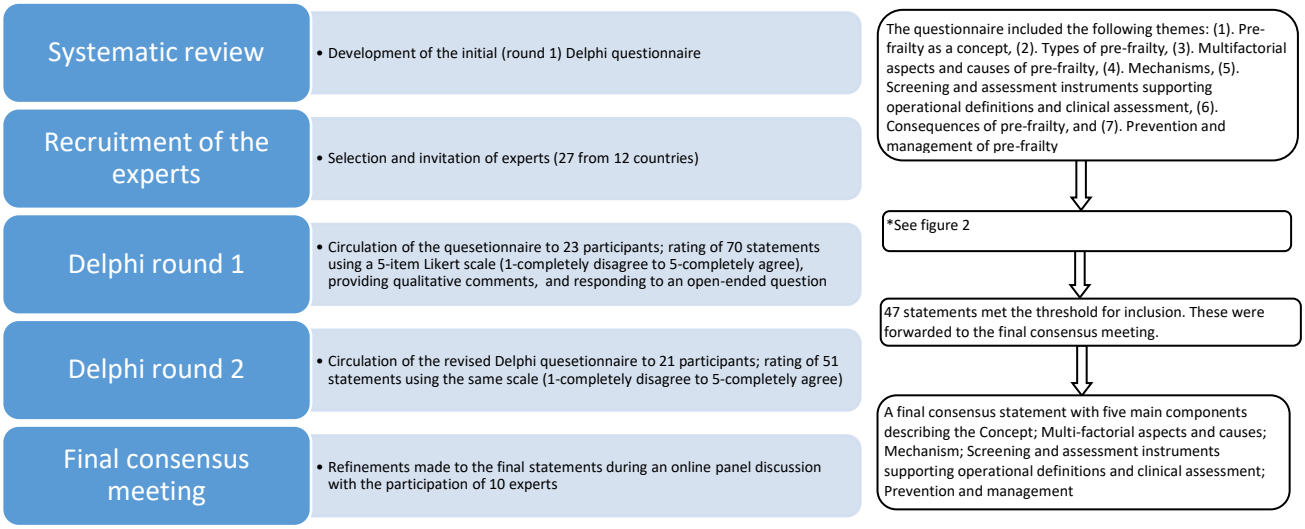

Figure 2. Summary results of Round 1 of the e-Delphi