
Article:
Thompson, M.Q., Theou, O., Ratcliffe, J. et al. (4 more authors) (2021) Frailty state utility and minimally important difference: findings from the North West Adelaide Health Study. Age and Ageing, 50 (2). pp. 565-569. ISSN 0002-0729

https://doi.org/10.1093/ageing/afaa166

OXFORD UNIVERSITY PRESS | Age And Ageing

Frailty State Utility and Minimally Important Difference: Findings from the North West Adelaide Health Study

Journal:	*Age and Ageing*
Manuscript ID	AA-20-0065.R1
Manuscript Category:	Short Report
Keywords:	Frailty, Utility, Minimally Important Difference, Older Adults, Quality of Life
Keypoints:	• Health state utilities and minimally important difference for frailty are yet to be examined in detail., • Frailty, for both the frailty phenotype and frailty index, was significantly associated with lower utility, MID estimates for frailty were identified for the frailty phenotype and frailty index, • These findings can be used to inform design of clinical trials and economic evaluations, Findings also provide useful clinical information on patient perspectives on frailty status

Frailty State Utility and Minimally Important Difference: Findings from the North West Adelaide Health Study

Abstract

Background: Frailty is a dynamic condition for which a range of interventions are available. Health state utilities are values that represent the strength of an individual's preference for specific health states, and are used in economic evaluation. This is a topic yet to be examined in detail for frailty. Likewise, little has been reported on minimally important difference (MID), the extent of change in frailty status that individuals consider to be important.

Objectives: to examine the relationship between frailty status, for both the frailty phenotype (FP) and frailty index (FI), and utility (preference-based health state), and to determine a MID for both frailty measures.

Design and Setting: Population-based cohort of community-dwelling Australians.

Participants: 874 adults aged ≥65 years (54% female), mean age 74.4 (6.2) years.

Measurements: Frailty was measured using the FP and FI. Utilities were calculated using the six-dimensional (SF-6D) Health Survey, with Australian and UK weighting applied. MID was calculated cross-sectionally.

Results: For both the FP and FI, frailty was significantly statistically associated ($p < .001$) with lower utility in an adjusted analysis using both Australian and UK weighting. Between person MID for the FP was identified as 0.59 (SD 0.31) (anchor-based) and 0.59 (distribution-based), while for the FI, MID was 0.11 (SD 0.05) (anchor-based) and 0.07 (distribution-based).

Conclusions: Frailty is significantly associated with lower preference-based health state utility. Frailty MID can be used to inform design of clinical trials and economic evaluations, as well as providing useful clinical information on frailty differences that patients consider important.

Key words

Frailty, Quality of Life, Utility, Minimally Important Difference, Older Adults

Introduction

Frailty is as a state of decreased functional reserve and resistance to stressors resulting from a cumulative decline in multiple physiological systems,[1] however, it is a dynamic and potentially modifiable condition [2, 3]. Frailty is common among older adults and is associated with a range of adverse outcomes,[1, 4] and has an inverse association with quality of life (QOL) [5, 6]. QOL can be reported as utilities, which are values that represent the strength of an individual's preference for specific health states [7], such as frailty. Utilities range between 1 (perfect health) and 0 (dead) and may be used in evaluating the comparative effectiveness of health interventions [7, 8]. Despite a range of studies describing the association between frailty and QOL at a population level [5, 6], to the best of our knowledge there have been no population level estimates of health-state utility.

A challenge exists in interpreting statistically significant changes in frailty status from the perspective of being clinically meaningful. Minimally Important Difference (MID) is the

smallest change in a treatment outcome which an individual would perceive as being important [9]. MID may be useful in providing a patient perspective that informs clinical decision making regarding the effectiveness of frailty interventions. To date, one other study has published MID estimates for frailty [10].

The aims of this study were to examine the relationship between frailty status, for both the frailty phenotype (FP) and frailty index (FI), and utility in a community-dwelling cohort, and to determine a MID for both frailty measures.

Methods

The North West Adelaide Health Study (NWAHS) is a longitudinal study of the North-West region of Adelaide, South Australia [11]. Participants aged ≥65 years attended a clinic for a biomedical examination and interview. Individuals unable to answer questions in English, or living in residential care facilities were excluded. Stage 2 (2004-06) data were used in this study, which was approved by the Queen Elizabeth Hospital Ethics Committee (HREC/15/TQEH/6)

Frailty Phenotype

This study used a modified FP where individuals with ≥3 characteristics out of five (weight loss, weakness, slowness, exhaustion, and low activity) were classified as frail, 1-2 characteristics as pre-frail, and no characteristics as non-frail [1]. (Supplementary Table S1). The FP used here has been described previously [12]. The FP is scaled on a 0-5 integer scale with 0 indicating no frailty characteristics present to a maximum of five characteristics.

Frailty Index

We developed a FI consisting of 34 variables [13]. (Supplementary Table S1). Variables were recoded to the interval 0–1, where 0= absence of deficit, and 1= full expression of deficit. Individual deficit scores were combined in an index, where 0= no deficit present, and 1= all 34 deficits present. The FI did not include any variables that were used to generate SF-6D values. Individuals with >0.21 proportion of deficits were classified as frail, 0.10-0.21 deficits as pre-frail, and <0.10 deficits non-frail. The FI used has been described previously [12].

Utility (preference-based health state)

Health state utility was captured by using the short-form (SF-36) health survey [14]. Data from the SF-36 were used to generate utilities for each participant by applying the SF-6D preference-based scoring algorithm [15]. We reported SF-6D values using both original UK [15], and Australian weightings (Model B) [16]. Utility scores of the UK SF-6D range from 0.29 to 1.00, compared to -0.363 to 1.00 for the Australian weighting. Certain Australian-weighted SF-6D states representing severe impairment are rated worse than being dead.

Minimally Important Difference

Two approaches, anchor-based and distribution-based methods, [17, 18], were used to identify a plausible MID range in this study.

Anchor-based methods to MID link changes in the outcome variable to another important 'anchor' variable [17]. Self-reported health is an anchor which provides information on an individual's global health status and is predictive of mortality [19]. We used question-1 from the SF-36: "In general, would you say your health is: excellent, very good, good, fair, poor."

in this study (which is not part of the SF-6D). We took a weighted average of the difference in both FP (range 0-5) and FI (range 0-1) continuous scores between each successive category of SF36-q1. The average was weighted by the number of observations contributing to each mean score. The use of cross-sectional data in this study allows for estimation of between-group and between-person MID, however, longitudinal data is required to report within-person estimates of minimally important change [18].

Distribution-based methods reflect the concept of using a distribution of observed scores in a sample as the basis for estimating MID [17]. The distribution method is considered to be a convenient proxy for MID, however, it has no external reference point to an anchor [18]. A ½ SD estimate has been suggested as an appropriate distribution based measurement of MID, and while not this is not necessarily ''minimal'', it is a useful conservative estimate for a clinically meaningful difference (i.e., it is obviously important) [17], and was the method used in this study.

Statistical Analyses

Statistical analyses were performed using SPSS version 23 (IBM Corporation. Armonk, NY). Cohort case weights were used in analysis, and reporting mean scores and percentages to ensure the sample was representative of the population [11]. Analysis of variance testing of statistical significance between frailty classification levels and QOL was measured using an alpha value of 0.05, and post hoc mean comparison was performed using Tukey's least significant difference. We performed a means comparison using complex samples general linear model to adjust for other covariates. Correlation analysis was performed between continuous frailty measures and the self-reported health anchor.

Results

In this cohort of community-dwelling adults (n=874, mean age 74.4 (SD 6.2) years, 54% female), 18.5% (146/874) of participants were classified as frail by the FP, and 48.8% (400/874) frail by the FI (Table 1).

Health state utility was significantly lower for both frail and pre-frail individuals compared to their non-frail counterparts for both frailty measures, using Australian and UK SF-6D weights. (Table 1) Tukey analyses demonstrated significant differences between all levels of frailty (non-frail, pre-frail, and frail) for both frailty measures in unadjusted analysis (all p<.001). Likewise, for each level of frailty classification in adjusted complex samples general linear regression models (all p<.001).

The self-reported health anchor was significantly correlated with both the FP (r=0.43, p<.001) and FI (r=0.69, p<.001). Using the anchor-based approach, 0.59 (SD 0.31) was the MID for the FP, while 0.11 (SD 0.05) was the MID for the FI (Table 2). Using a distribution-based approach of ½ SD of mean frailty scores, 0.59 was a MID for the FP, and 0.07 was the MID for the FI (Table 2). Findings were similar when analysis was stratified by sex.

Discussion

A novel finding of this study was that frailty and pre-frailty classification were significantly associated with lower health state utility for both frailty measures compared to their non-frail counterparts in community-dwelling older adults, for both the UK and Australian weightings of the SF-6D in adjusted analysis.

Our findings are consistent with other studies that have examined the relationship between frailty and lower QOL [5, 6], however, ours is the first to report QOL as a utility value, an important requirement for health economic cost-utility analysis. The adjusted SF-6D utility values (UK weighting) in our study (FP pre-frail: 0.75 and FP frail: 0.62) were similar to those reported in a model-based frailty economic evaluation (Pre-frail: 0.65, Frail: 0.57) [20]. Caution should be used in the generalisability of our findings to other populations, e.g. older people in residential care, and ideally, multiple data sources should be used to inform model-based economic evaluations.

Using cross-sectional anchor-based and distribution-based methods, 0.59 was an important MID for the FP. As 1 point is the smallest increment of the FP, it can be assumed that a change of this magnitude is minimally important. However, there may be variability in MID depending on which FP characteristics are present [21]. For the FI, MID ranged from 0.07 (distribution method) to 0.11 (anchor method). Our findings are similar to the conservative distribution-based within-person estimates for Korean older-adults ranging between 0.61-0.62 for the FP, and 0.06-0.08 for the FI as reported elsewhere [10].

The MID estimates in our study are specific to self-reported health and the ½ SD method. We caution against overinterpretation of these findings as our estimates represent a

'plausible range' of difference for frailty scores [18]. Additionally, our cross-sectional analysis does not allow us to report within-person estimates of minimally important change in frailty, which require change over time [18].

Limitations of this study included a modified FP due to a lack of aging-specific variables, the low socioeconomic status of the cohort, exclusion of individuals living in residential care, and 10-year age of data, limiting generalisability of findings. The cross-sectional estimation of MID is a further limitation, where minimally important change requires longitudinal data. This is an important topic for future research.

In conclusion, we identified that frailty was significantly associated with lower utility for both the FP and FI. Additionally, we identified between-person MIDs for both measures. These findings are relevant to the design of frailty RCTs, health economic evaluations of frailty interventions, and to clinicians for patient perspectives on important differences in frailty.

Acknowledgements

The authors would like to acknowledge the contribution of the North West Adelaide Health Study participants and clinic staff.

Declaration of Sources of Funding

This work was supported by a Resthaven G-TRAC travel grant to OT.

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Tables

Table 1. Baseline descriptive characteristic and frailty status (frailty phenotype and frailty index) and SF-6D utility scores (Australian and UK weighting)

		Frailty Phenotype n (%)			Frailty Index n (%)		
	n (%)	Non-frail	Pre-Frail	Frail	Non-frail	Pre-Frail	Frail
Total sample	874	281 (30.5)	447 (51.1)	146 (18.5)	204 (21.6)	270 (29.6)	400 (48.8)
Sex							
Male	437 (45.5)	160 (36.6)	219 (49.9)	58 (13.5)*	119 (26.9)	146 (34.0)	172 (39.1)*
Female	437 (54.5)	121 (25.3)	228 (52.0)	88 (22.7)	85 (17.2)	124 (25.9)	228 (56.9)
Age Groups							
65-74 years	531 (56.4)	198 (35.9)	279 (53.0)	54 (11.0)*	141 (26.0)	184 (34.0)	206 (40.0)*
≥75 years	343 (43.6)	83 (23.4)	168 (48.5)	92 (28.1)	63 (16.0)	86 (23.8)	194 (60.2)
Education Level [a]							
Up to secondary	545 (63.1)	157 (27.9)	289 (51.7)	99 (20.5)*	109 (18.7)	176 (31.6)	260 (49.8)*
Trade / Cert / Dip	280 (31.1)	110 (36.2)	130 (49.4)	40 (14.4)	82 (27.0)	79 (25.7)	119 (47.3)
≥Bachelor degree	24 (2.5)	13 (61.5)	10 (34.7)	1 (3.8)	10 (44.0)	10 (40.6)	4 (15.4)
Income Groups [a]							
Up to $20k	442 (46.2)	115 (23.7)	240 (55.2)	87 (21.1)*	79 (16.0)	136 (29.6)	227 (54.4)*
$20-$40k	274 (34.3)	114 (40.9)	125 (44.6)	35 (14.5)	85 (28.9)	90 (32.1)	99 (39.0)
$40-$60k	58 (6.8)	29 (45.5)	23 (42.9)	6 (11.6)	21 (34.5)	16 (27.5)	21 (38.1)
>$60k	25 (2.6)	12 (46.3)	12 (50.2)	1 (3.6)	10 (35.8)	10 (39.7)	5 (24.5)
SF-6D Utility Scores - Unadjusted							
Australian weighting (mean, SE)		0.72 (0.01)	0.60 (0.01)	0.32 (0.02)*	0.83 (0.01)	0.70 (0.01)	0.41 (0.01)*
UK weighting (mean, SE)		0.80 (0.01)	0.75 (0.01)	0.62 (0.01)*	0.86 (0.00)	0.79 (0.00)	0.66 (0.00)*
SF-6D Utility Scores – Adjusted [b]							
Australian weighting (mean, SE)		0.73 (0.02)	0.62 (0.02)	0.34 (0.03)*	0.83 (0.01)	0.70 (0.01)	0.40 (0.02)*
UK weighting (mean, SE)		0.81 (0.01)	0.76 (0.01)	0.63 (0.01)*	0.86 (0.01)	0.79 (0.01)	0.65 (0.01)*

n unweighted. % reported using cohort case weights. FP (number of characteristics): 0, non-frail; 1-2, pre-frail, ≥ 3, frail. FI (proportion of deficits): 0 to ≤.10, non-frail; >.10 to ≤.21, pre-frail; >.21, frail. SF-6D, short-form six-dimensional health survey. SE, Standard Error.
[a] missing nor included.
[b] Adjusted for age, sex, education, and income
* $p < 0.05$ (main effects reported)

Table 3. Minimally important difference (MID) for the frailty phenotype and frailty index.

	Total Sample		Male		Female	
	Anchor Method [a] Mean (SD)	Distribution Method [b] ½ SD	Anchor Method [a] Mean (SD)	Distribution Method [b] ½ SD	Anchor Method [a] Mean (SD)	Distribution Method [b] ½ SD
Frailty Phenotype	0.59 (0.31)	0.59	0.58 (0.38)	0.56	0.61 (0.29)	0.60
Frailty Index	0.11 (0.05)	0.07	0.11 (0.05)	0.07	0.12 (0.05)	0.08

Mean and SD reported using cohort case weights.
The FP is scaled on a 0 to 5 integer scale with a score of 0 indicating no frailty characteristics and a maximum of five characteristics.
The FI is scored on a 0 to 1 scale where 0 = no deficit present, and 1 = all 34 deficits present.
[a] Anchor method: a weighted average of the difference in both FP and FI continuous scores between each successive category of SF36 question 1. "In general, would you say your health is: excellent, very good, good, fair, poor".
[b] Distribution method, ½ standard deviation of mean continuous frailty measures.

Supplementary File

Table S1. Frailty Phenotype and Frailty Index Variables

Frailty Phenotype	Frailty Index (34-item)	
Weight Loss: > 10% weight loss over four years (clinic measurement)	Angina	Health limits lifting or carrying groceries
Weakness: original method	Heart attack	Health limits climbing several flights of stairs
Exhaustion: original method	Osteoporosis	Health limits climbing one flight of stairs
Slowness: Self-report 'a lot' to health limits walking 100m (SF36 q11)	Osteoarthritis	Health limits bending, kneeling or stooping
Low Activity Level: Australian Bureau of Statistics National Health Survey (< 100 METs per week)	Rheumatoid and any other arthritis	Health limits walking more than 1km
	Stroke or TIA	Health limits walking 100m
	Diabetes	Felt lonely
	Any mental health problem	Felt that could not get going
	Systolic blood pressure	Difficulty keeping mind on what you were doing
	Diastolic blood pressure	Felt everything was an effort
	10% weight loss over 4 years	Physical & emotional problems interfered with social activities
	FEV1/FVC post ratio	Felt full of life
	Weak grip strength	Felt calm and peaceful
	Falls	Felt worn out
	Hospital emergency admission	Felt tired
	Low activity level (<100 METs per week)	
	Healthy as anybody I know	
	Health is excellent	
	Self-reported health	

METs, metabolic equivalent of task; SF36, 36-Item Short Form Health Survey; TIA, transient ischaemic attack; FEV1/FVC, forced expiratory volume/forced vital capacity

Reviewer feedback and author response

Thank you for sending us your paper. Unfortunately our referees did not feel that it was suitable for Age and Ageing in its present form. I would, however, be happy to consider publishing it as a Short Report which incorporates the comments made by the reviewers. I would then send it out for further refereeing. Short Reports include an abstract and are still referenced and citable on repositories such as PubMed. Short Reports should be of no more than 1500 words, 2 tables or figures and 30 references. If you would please submit your revised paper and the revision sheet on ScholarOne, I would then send it out for further refereeing. The referees' comments can be found at the end of this email. I would be grateful if you would please resubmit your revised manuscript to me no more than four weeks after receiving this letter. If this is likely to pose a problem, I would be pleased to discuss a limited extension with you. Professor Rowan Harwood Editor **Associate Editor: Conroy, Simon** Thank you for submitting your paper to Age & Ageing; I have read your paper carefully and with interest. You have covered an important topic and I appreciate the time and effort that has gone into the study and preparing the paper. Unfortunately, I do not feel that we can give your paper adequate priority in Age & Ageing as a research paper, but would be happy to consider a revised, shortened version as a short report. The referees comments are available to you should you wish to pursue this avenue.	Thankyou for the opportunity to re-submit this paper as a short report. In order to do this, we have had to cut approximately 800 words from the original submission, without losing important content. Changes made throughout the manuscript in response to reviewer feedback and to reduce wordcount to brief report have been marked in blue text. In preparing the manuscript for re-submission we have cited a newly published paper on minimally important difference in frailty in the introduction and discussion sections. Jang, I.-Y., Jung, H.-W., Lee, H. Y., Park, H., Lee, E., & Kim, D. H. (2020). Evaluation of Clinically Meaningful Changes in Measures of Frailty. *The Journals of Gerontology: Series A*. doi:10.1093/gerona/glaa003 Changes to Manuscript: Introduction (p3, para 1): To date, one other study has published MID estimates for frailty [10]. Discussion (p7, para 3): Our findings are similar to the conservative distribution-based within-person estimates for Korean older-adults ranging between 0.61-0.62 for the FP, and 0.06-0.08 for the FI as reported elsewhere [9].
Referee: 1	
This paper is novel in that it attempts to identify MID in frailty index and phenotype. This could be important when frailty tools are used as outcomes in research and clinical studies.	Thank you for reviewing the paper and providing feedback.
I find two major limitations: 1.1. MID is not treated separately for men and women, where we know that characteristics and outcomes of frailty vary significantly by sex.	We have stratified Table 2 by sex (in addition to whole sample values) and have added a comment to the results section Changes to Manuscript: Results (p 6, para 3): Findings were similar when analysis was stratified by sex. Table 2: Sex stratified MID reported.
1.2. Frailty is understood (for both index and phenotype) as a homogenous state. There is still significant controversy about that and even a recent paper demonstrated heterogeneity in pre-frailty phenotype trajectories https://academic.oup.com/ageing/article/49/1/39/5618822	Thank you for raising these important points. We have briefly addressed this point in the discussion (however, were unable to elaborate in much detail due to reducing word count to a brief report).

The authors could perhaps consider sensitivity analysis by sex and also acknowledging in the discussion that MIC may be different in different individual scenarios given the heterogeneity behind frailty operationalisations.	Changes to Manuscript: Discussion (p7, para 3): As 1 point is the smallest increment of the FP, it can be assumed that a change of this magnitude is minimally important. However, there may be variability in MID depending on which FP characteristics are present [20].
Referee: 2	
Thank you for giving me the opportunity to review the manuscript Frailty State Utility and Minimally Important Difference: Findings from the North West Adelaide Health Study. This study aims to examine the relationship between frailty status, for both the frailty phenotype (FP) and frailty index (FI), and utility (preference-based health state), and to determine a minimally important difference (MID) for both frailty measures. Data from the North West Adelaide Health Study (NWAHS) were used (n=874 community dwelling older adults). FP and FI were significantly statistically associated with lower utility. Between person MID for the FP was identified as 0.59 (SD 0.31) (anchor-based) and 0.59 (distribution-based), while for the FI, MID was 0.11 (SD 0.05) (anchor-based) and 0.07 (distribution-based). The research question is relevant and interesting. The manuscript is well-written. I have made a few comments below that are solely intended to strengthen this already comprehensive work.	Thanks for reviewing the paper and providing feedback.
Major comments: 2.1 Utility (preference-based health state) is likely not a concept that is mastered by all clinicians. In the abstract, I would suggest presenting a clearer definition of this concept to facilitate the understanding of this study's background and the potential added value.	We agree that this term is not commonly understood. We have made changes to abstract and introduction. Changes to manuscript: Abstract (p1): Health state utilities are values that represent the strength of an individual's preference for specific health states, and are used in economic evaluation. Introduction (p2, para 3) QOL can be reported as utilities, which are values that represent the strength of an individual's preference for specific health states [7], such as frailty.
2.2 In the second paragraph of the results section, many analyses are presented but the data are not shown. As those analyses are relevant to the main objective of this study (explore the relationship between frailty status and utility), maybe consider presenting them in more depth.	As Tukey results between all frailty levels were $p < .001$ for both the FP and FI, we have included this p-value in the results section. Changes to Manuscript: Results (p6, para 2): Tukey analyses demonstrated significant differences between all levels of frailty (non-frail, pre-frail, and frail) for both frailty measures in unadjusted analysis (all p<.001). Likewise, for each level of frailty

	classification in adjusted complex samples general linear regression model (all p<.001).
2.3 Generalizability and applicability of the MID findings for the Frailty Phenotype (FP) is limited. FP was assessed using only 5 items (for 3 different frailty status) and the MID was 0.59. It is difficult to interpret.	The FP is a widely used frailty measure, and we have used a modified version as close to the original 5 item version as possible. We would agree that using a modified FP limits generalisability and we had mentioned this in the results section. We also had provided the following explanation of the FP MID in the discussion section: "Using cross-sectional anchor-based and distribution-based methods, 0.59 was an important MID for the FP. As 1 point is the smallest increment of the FP, it can be assumed that a change of this magnitude is minimally important." As the FI is known to be more sensitive that the FP in the measurement of frailty, and as both are commonly used, we saw that there was value in reporting utility values and MID for both forms of measurement in this paper.
2.4 The study design (cross sectional) rather than longitudinal is an important limitation. I do not believe we can conclude that these MID findings can be used to assess patient progress at this stage. The study design should also be presented in the abstract	We agree that this is an important point which we had raised in discussion, and have also now reflected this in the abstract. Changes to Manuscript: Abstract. Measurement (p1): MID was calculated cross-sectionally. Abstract. Conclusions (p1-2): Frailty MID can be used to inform design of clinical trials and economic evaluations, as well as providing useful clinical information on frailty differences that patients consider important.
Minor comments/suggestions: 2.5 ABSTRACT: a) The second sentence of the background (Health state utilities are based upon the preference that individuals place on health states and outcomes and form a critical component for economic evaluation.) might benefit to be simplified. b) Maybe consider presenting the association measure between the FP and FI with lower utility rather than just presenting the p value.	a) We have modified the utility sentence in the abstract (see response to 2.1) b) We have provided the p-value from ANOVAs in the abstract and discussed multiple comparison of the means in the results section. We don't see that there is value in adding ANOVA f-values to the abstract. Changes to Manuscript: Abstract (p1): Health state utilities are values that represent the strength of an individual's preference for specific health states, and are used in economic evaluation.
2.6 METHODS: - I know the main study has been published elsewhere but I believe more details would benefit the be presented with regards to the methods.	As we have changed this paper from a research report to a brief report at the recommendation of the editor, we have had to sacrifice some details across the entire paper. Unfortunately, we were unable add additional methodological detail.

2.7 LIMITATIONS: - I believe that the fact the study was conducted more than 10 years ago needs to be mentioned as a potential limitation.	We have now made mention of this in discussion. Changes to Manuscript: Discussion (p8, para 2): Limitations of this study included a modified FP due to a lack of aging-specific variables, the low socioeconomic status of the cohort, exclusion of individuals living in residential care, and 10-year age of data, limiting generalisability of findings
2.8 CONCLUSIONS: - Maybe consider calibrating the conclusions in light of the limitations such as the study design.	This is an important point. We have made changes to the conclusion section of the discussion as well as to the abstract Changes to Manuscript: Abstract. Conclusions (p1-2): Frailty is significantly associated with lower preference-based health state utility. Frailty MID can be used to inform design of clinical trials and economic evaluations, as well as providing useful clinical information on frailty differences that patients consider important. Discussion (p8, para 3): Additionally, we identified between-person MIDs for both measures.