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INVESTIGATING MUSCULOSKELETAL PAIN AND FRAILTY IN AN AGEING POPULATION

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy.

May 2025

DECLARATIONS

I hereby declare that this thesis is the result of original research. I have conducted it, and any assistance received is detailed below. It has not already been accepted for any degree, diploma, or other qualification. All authors and works to which reference has been made are fully acknowledged.

I primarily conducted study design, literature search, application for ethics approval, data collection, analysis, and thesis writing. Professors David Walsh (DAW), John Gladman (JRFG) and Dr Daniel McWilliams (DMcW) provided guidance and supervision in all aspects of the present work. In addition, Drs Daniel McWilliams and Afroditi Kouraki (AK) assisted with data collection for the inter-rater reliability studies. Dr Daniel McWilliams provided statistical advice for the analysis, particularly regarding cross-lagged pathway analysis. Professors David Walsh, John Gladman, and Dr Seyed Mohsen Shahtaheri (SS) assisted with the classification and coding of medications and morbidities. Mr Harrison Lewis helped classify painful and non-painful morbidities.

Study design for the Investigating Musculoskeletal Wellbeing and Health (IMW&H) study was conducted by Dr Bonnie Millar, Dr Daniel McWilliams, Professor Abhishek, Dr Kehinde Akin-Akinyosoye, Professors Dorothee Auer, Victoria Chapman, Michael Doherty, Eamonn Ferguson, John Gladman, Paul Greenhaff, Dr Joanne Stocks, Professors Ana Valdes, and David Walsh. The ethical application, data collection and general application for the Investigating Musculoskeletal Wellbeing and Health study was conducted by Dr Bonnie Millar and Professor David Walsh. I designed the methods protocol that utilised the IMW&H data under the supervision of Professors David Walsh and John Gladman, and Dr Daniel McWilliams. The ACHING study was designed, prepared, and submitted for ethical approval by me with the support of my supervisory team.

ACKNOWLEDGEMENTS

First and foremost, I would like to express my gratitude to my supervisors, Professor David Walsh, Professor John Gladman and Dr Dan McWilliams, for their support, guidance, and patience throughout this project. Through their invaluable feedback and suggestions, I have learned so much. Their knowledge has contributed to the quality of this project, and I am grateful to have the opportunity to collaborate with them.

I would also like to thank the members of 'Team Walsh' (Professor David Walsh, Dr Dan McWilliams, Dr Stephanie Smith, Dr Onosi Ifesemen, and Dr Vasileios Georgopoulos), who listened with patience and created a friendly and supportive environment in the department. I thank Dr Stephanie Smith for her wise advice and support throughout my PhD. I would like to thank Dr Mohsen Shahtaheri for helping me to develop the coding of analgesia and comorbidities. I extend my gratitude to those who helped me with my training in collecting clinical measures: Dr Dan McWilliams, Dr Vasileios Georgopoulos, and Dr Anthony Kelly.

I am grateful to Dr Julie Diette-Jones and Dr Amy Fuller for their friendship and support in difficult times. I am also thankful to my friends Dave and Pansie Clarke, Jackie and Robin Williams, Jenny, Chris and Sam Hawke, who made my transition to Nottingham much easier and supported me throughout my PhD project and the pandemic.

I would like to take this opportunity to thank the PPI members who met with me and provided information and feedback to help develop the ACHING study. I am also grateful to those students and staff who volunteered to participate in my practice of techniques.

I would also like to thank the NIHR Nottingham Biomedical Research Centre and the University of Nottingham for funding and hosting my PhD.

I would like to thank my parents and my children, Gina and Chris, for their support and understanding of my many absences while I completed my PhD.

Lastly, I would like to express my gratitude and sincere thanks to my friends Gini Dellow and Dr Afroditi Kouraki for their unwavering support and friendship throughout my PhD project.

COVID IMPACT STATEMENT

I commenced my PhD studies in October 2019, and the COVID pandemic started in early 2020, resulting in national lockdowns. This meant that I worked from home for most of that year. I was able to work on the IMH&W data that had already been made available. I met regularly online with my supervisors via Microsoft Teams. In-person clinical research was suspended.

I was isolated from family, friends, and other students during this period. At the start of lockdown, I was a first-year PhD student in an office with many final-year students. However, when we returned to the offices, I was now the senior PhD student, which meant no other students could point me in the right direction. I think this delayed progress on the ethics procedures.

When research processes reopened after the national lockdowns, there were delays, partly caused by the volume of studies but also hindered by restrictions that meant some people still worked from home or only two people were allowed to be present in some rooms.

The ACHING study received a favourable ethical opinion from the Health Research Authority in the last month of my PhD. Subsequently, I was unable to collect the data without additional funding. In consultation with my supervisors, I decided to conduct the reliability study in preparation. Then, investigate opportunities to apply for a grant for the ACHING study. To prepare, I have attended several courses to develop grant application skills. This included a three-day NIHR training camp in which, working in groups, we designed a study and made a mock grant application, including addressing an interview panel.

LIST OF PUBLICATIONS AND PRESENTATIONS

Journal articles based on PhD work.

Chapters 3 and 4 include materials published in the following:

The bidirectional relationship between chronic joint pain and frailty: data from the Investigating Musculoskeletal Health and Wellbeing cohort. *BMC Geriatrics* 23, 273 (2023). https://doi.org/10.1186/s12877-023-03949-4
W.J. Chaplin, D.F. McWilliams, B.S. Millar, J.R.F. Gladman, D.A. Walsh

Chapter 5 includes material published in the following:

The association of painful and non-painful morbidities with frailty: a cross-sectional analysis of a cohort of community-dwelling older people in England. BMC Geriatrics 24, 158 (2024). https://doi.org/10.1186/s12877-023-04602-w

W.J. Chaplin, H.R. Lewis, S.M. Shahtaheri, B.S. Millar, D.F. McWilliams, J.R.F. Gladman, D.A. Walsh

Presentations at conferences

- Osteoarthritis Research Society (OARSI) (*poster, video, and rapid-fire oral presentation*). 30th April 2021. The association of knee pain with frailty: the Investigating Musculoskeletal Health and Wellbeing cohort study.
  W.J. Chaplin, D.F. McWilliams, B.S. Millar, J.R.F. Gladman, D.A. Walsh
  DOI:10.1016/j.joca.2021.02.369
- UK RiME 2nd September 2021 – (*oral presentation and poster*).
  The association of knee pain with frailty: the Investigating Musculoskeletal Health and Wellbeing cohort study.
  W.J. Chaplin, D.F. McWilliams, B.S. Millar, J.R.F. Gladman, D.A. Walsh
- European Alliance of Associations for Rheumatology (EULAR) 2022 – *(abstract)* The association of painful and non-painful comorbidities with central mechanisms of knee pain.
  H.R. Lewis; W.J. Chaplin; D.F. McWilliams; B.S. Millar; S. Shahtaheri; J.R.F. Gladman, D.A. Walsh
  DOI: 10.1136/annrheumdis-2022-eular.1586

- UK RiME 1st September 2022 – (*oral presentation and poster*). The association of chronic pain and comorbidities with frailty
  W.J. Chaplin; H.R. Lewis; S. Shahtaheri; B.S. Millar; D.F. McWilliams; J.R.F. Gladman; D.A. Walsh.
- Pain Centre Versus Arthritis External Scientific Meeting 14th October 2022 – *(oral presentation)*. The association of chronic pain and comorbidities with frailty.
  W.J. Chaplin; H.R. Lewis; S. Shahtaheri; B.S. Millar; D.F. McWilliams; J.R.F. Gladman; D.A. Walsh.
- British Geriatrics Society Autumn Meeting 18 November 2022. (The association of painful and non-painful comorbidities with frailty.
  W.J. Chaplin; H.R. Lewis; S. Shahtaheri; B.S. Millar; D.F. McWilliams; J.R.F. Gladman; D.A. Walsh.
  DOI:10.1093/ageing/afac322.017

Other posters and publications from the period of this thesis

1. 2023 Conference Poster P073: Comparative effectiveness of different exercise interventions on central sensitisation indices in humans: A systematic review and network meta-analysis.
   Aya A Abd Elkhabir; Daniel F McWilliams; Stephanie Smith; Wendy Chaplin; Mitra Salimian; Vasileios Georgopoulos; Afroditi Kouraki; David A Walsh
   DOI: 10.1093/rheumatology/kead104.114
2. EULAR Conference Poster AB1432: Lewis HR, Chaplin WJ, McWilliams DF, Miller BS, Shahtaheri S, Gladman JRF, Walsh DA. AB1432 The association of painful and non-painful comorbidities with central mechanisms of knee pain. *Annals of the Rheumatic Diseases* 2022;81:1822
3. 2023 Conference abstract: Effects of Exercise on Indices of Central Sensitisation in Humans: A Systematic Review and Network Meta-Analysis
   A. Abd Elkhabir; D.F. McWilliams; S. Smith; W. Chaplin; M. Salimian; V.

Georgopoulos; A. Kouraki; D.A. Walsh
DOI: 10.1016/j.joca.2023.01.427

4. Conference Abstract: Central pain mechanisms predict physical inactivity at 1-year in individuals with knee pain
   M.U. Habib, S.L. Smith, W.J. Chaplin, B. Millar, D.F. McWilliams, D.A. Walsh
   DOI: 10.1016/j.joca.2022.02.511
5. Development of a Motivation Communication Training to Aid Diabetes-Specialist Podiatrists with Adherence Discussions. *Health Education & Behavior*, p.10901981231216744.
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6. The Web-Based Pain-at-Work Toolkit with Telephone Support for Employees with Chronic or Persistent Pain: Protocol for a Cluster Randomized Feasibility Trial. *JMIR Research Protocols, 12*(1), e51474.
   Blake, H., Chaplin, W.J., Wainwright, E., Taylor, G., McNamee, P., McWilliams, D., Abbott-Fleming, V., Holmes, J., Fecowycz, A., Walsh, D.A. and Walker-Bone, K., 2023.
7. Alcohol Prevention in Urgent and Emergency Care (APUEC): development and evaluation of workforce digital training on screening, brief intervention, and referral for treatment. *International journal of environmental research and public health, 20*(22), p.7028.
   Blake, H., Adams, E.J., Chaplin, W.J., Morris, L., Mahmood, I., Taylor, M.G., Langmack, G., Jones, L., Miller, P. and Coffey, F., 2023.
8. Motivation communication training programme for healthcare professionals to support adherence in patients with diabetic foot ulcers: proof of concept study. *Plos one, 19*(2), e0295180.
   Hancox, J.E., Chaplin, W.J., Hilton, C., Vadaszy, N., Gray, K., Game, F. and Vedhara, K.,
9. Comparative effectiveness of various exercise interventions on central sensitisation indices: A systematic review and network meta-

analysis. *Annals of Physical and Rehabilitation Medicine*, *68*(4), p.101894.

Ibrahim, A.A.E., McWilliams, D.F., Smith, S.L., Chaplin, W.J., Salimian, M., Georgopoulos, V., Kouraki, A. and Walsh, D.A., 2025.

ABSTRACT

Background: Frailty is defined as a vulnerability state with decreased physiological reserve observed in older people. Frailty may be characterised by a loss of homeostatic resilience due to multi-organ, age-associated decline. People with frailty have an elevated susceptibility to stressors and/or disproportionate response to challenges; this leads to a significant functional decline and increased risk of adverse health outcomes.

Chronic pain is long-term or persistent pain which lasts for an extended period, typically beyond the normal healing time of an injury or illness; it is generally defined as pain that remains unresolved for three months.

While previous studies have touched upon the association of pain and frailty, my research delves deeper into this relationship, offering insight into this under-recognised association. This thesis proposes that chronic pain might make the transitions from non-frail to frail states more likely or less likely. Moreover, the presence of frailty might hinder the improvement of pain. The current evidence implies a potential bidirectional relationship between pain and frailty, but most of the previous research has examined each direction separately.

Pain is not usually accounted for in frailty classification; however, it is important to consider why pain is linked to frailty. People who are classified as frail may have more painful morbidities than those classified as non-frail. Additionally, it is possible that central aspects of pain could be evidence of a dysfunctional central nervous system. Such dysfunction may result in an overall increase in pain sensitivity. Central aspects of pain factor (CAPf) are considered to be associated with increased pain hypersensitivity and have been shown to predict future knee pain. Each of the 8 characteristics associated with the underlying CAP factor (anxiety, depression, catastrophising, pain distribution, neuropathic-like pain, cognitive impact, sleep, and fatigue) have been associated with frailty. Central pain

mechanisms may explain the association of pain and frailty, but other sources of pain and pain mechanisms should also be investigated.

Understanding the association between these two common conditions. Furthermore, increasing awareness of this relationship may allow the implementation of actions to reduce the burden on health services and individuals.

Aims:

[1] to examine cross-sectional and longitudinal associations of pain with frailty in a cohort study. To investigate whether there is a unidirectional or bidirectional relationship between pain and frailty.

[2] to examine the extent to which the association of chronic pain with frailty might be attributed to morbidities.

[3] to investigate whether Central Aspects of Pain explain the association between chronic pain and frailty.

[4] to design the ACHING study, which aims to measure and assess the association of frailty with central pain mechanisms, alongside other potential causes of pain and pain severity in individuals with knee pain. This included preparation and training to collect some of the main physiological measures.

Methods:

Data were drawn from Investigating Musculoskeletal Health and Wellbeing, a UK-based cohort (n=2185). Participants were aged 60 years and over and either had or were at risk of musculoskeletal problems or frailty.

The main variables for this thesis were frailty, classified as present/absent using the FRAIL questionnaire, and average joint pain severity over the previous month was assessed using an 11-point numerical rating scale (NRS pain).

To confirm the association between pain and frailty, baseline and 1-year data were used for cross-sectional analysis and regression. Subsequently, this led

to assessing directionality using longitudinal data and employing cross-lagged path analysis.

To assess chronic pain related to morbidities, pain from any source was reported using the McGill Pain Rating Index (PRI). Morbidities were classified as painful/non-painful using the International Association for the Study of Pain criteria. A modified FRAIL was employed in which the 'illness item' was omitted to remove the overlap with morbidity. These cross-sectional analyses used standardised variables in regression and Z-tests to assess the degrees of the association of pain (McGill Pain Rating Index), painful and non-painful morbidity counts with frailty (modified FRAIL).

Analyses of pain mechanism data were conducted in a subgroup of people with knee pain (NRS≥1) (n=639). This used the Central Aspects of Pain in the Knee questionnaire to calculate a modified Central Aspects of Pain score in which the 'fatigue item' was omitted to remove the overlap with the 'fatigue item' in FRAIL.

The ACHING study planned to recruit 122 participants to a case-control study. Participants classified as frail would be age- and sex-matched with people classified as robust. Measures were selected to explore multiple causes of pain, including peripheral indices and central aspects of pain. Additionally, selecting measures to explore multiple possible causes of frailty. The reliability of some of the main physiological measures was established in a group of healthy volunteers (n=20).

A statistical plan was devised for the ACHING study. The reliability between raters was assessed using Bland-Altman plots, calculating intraclass correlation coefficients and concordance correlation coefficients.

Results:

The cross-sectional data were drawn from 2,185 participants from the Investigating Musculoskeletal Health and Wellbeing cohort. Of those, 55% were female, with a median age of 74 (range 60 to 96) years. FRAIL classified 438 (20%) of participants as frail. Mean (SD) NRS pain was 5.5 (2.5). NRS pain

was associated with frailty at baseline (aOR1.68, (95%CI 1.57 to 1.79), p<0.001).

Longitudinal data were from 1,179 participants who completed both baseline and 1-year measures. At baseline, 176 (15%) participants were classified as frail, and the mean (SD) NRS pain score was 5.2 (2.5). In logistic regression, NRS pain was associated with frailty at baseline (aOR 1.72, (95%CI 1.56 to 1.92), p<0.001). Additionally, NRS pain at baseline was associated with 1-year frailty (aOR 1.28, (95%CI 1.15 to 1.43), p<0.001). In cross-lagged path analysis, higher baseline pain strongly predicted 1-year frailty [β =0.25, (95%CI 0.14 to 0.36), p<0.001] and baseline frailty predicted higher 1-year pain [β =0.06, (95%CI 0.003 to 0.11), p=0.040].

When the influence of morbidities on pain and frailty was examined, PRI pain (aOR 2.07, (95%CI 1.83 to 2.33) and 'any' morbidity (aOR 1.74, (95%CI 1.54 to 1.97) were both significantly associated with frailty. When morbidity was subclassified, painful (aOR 1.48, (95%CI 1.30 to 1.68) and non-painful (aOR 1.39, (95%CI 1.24 to 1.56) morbidities each were associated with frailty, and PRI pain also remained associated (aOR 2.07, (95%CI 1.83 to 2.34), p<0.001).

In the subgroup of people with knee pain at baseline (n=639), 26% of participants were classified as frail, and the mean (SD) NRS pain was 6.0 (2.1). At 1-year, there were data from 343 participants with a mean (SD) NRS pain of 5.5 (2.3). A higher modified Central Aspects of Pain factor was associated with frailty (aOR 1.53, (95%CI 1.41 to 1.66), p<0.001) at baseline. When both modified Central Aspects of Pain factor (aOR 1.37, (95%CI 1.26 to 1.50) and NRS pain (aOR 1.54, (95%CI 1.33 to 1.78) were included in the same model, they were both significantly associated with frailty classification, (p<0.001). At 1-year, the modified Central Aspects of Pain factor did not predict future frailty, but NRS pain at baseline did predict 1-year frailty (aOR 1.33, (95%CI 1.05 to 3.79), p =0.016).

The ACHING study protocol was developed and prepared. An ethics application was submitted and received ethical approval from the Health

Research Authority. The training and collection of the main physiological measures showed acceptable reliability.

Conclusion:

There is a bidirectional relationship between chronic pain and frailty. This could lead to a vicious cycle in which each accelerates the other's progression. Pain could be the key driver of this association, as implied by its stronger coefficient from the analyses performed. Focusing on pain management as an intervention pathway could mitigate the effect of chronic pain upon frailty. Future studies might focus on comprehensive assessments of pain mechanisms to determine which causes of pain might be most important as future treatment targets. Given the ageing population in many countries, it is increasingly important to address frailty which disproportionately affects older individuals and to ensure that we manage chronic pain.

ABBREVIATIONS

ACR	American College of Rheumatology
ADL	Activities of Daily Living
AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrome
ALSWH	Australian Longitudinal Study on Women's Health
aOR	adjusted odds ratio.
AUC	Area Under the Curve
AWGS	Asian Working Group for Sarcopenia
BIA	Bio Impedance Analysis
BMI	Body Mass Index
BR	Brachialis Radialis
BRAFs	Bristol Rheumatoid Arthritis Fatigue scale
BRC	Biomedical Research Centre
CAP score	Central Aspects of Pain score.
CAPf	Central Aspects of Pain factor
CAP-Knee	Central Aspects of Pain in Knee
CBT	Cognitive Behaviour Therapy
CCC	Concordance Correlation Coefficient
CCI	Charleson Comorbidity Index
CDI	Charleson-Deyo Index
CES-D	Center for Epidemiologic Studies Depression Scale
CHAMP	Concord Health and Ageing in Men Project
CHF	Chronic Heart Failure
CI	Confidence interval
CLPA	Cross-lagged path (or panel) analysis
CMT	Central Mechanism Trait
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease.
CPM	Conditioned pain modulation
CRF	Case Report Form
CS	Central sensitisation
CSB	Clinical Sciences Building
CSV	Comma-separated values
CV	cardiovascular
CWP	Chronic Widespread Pain
DALY	Disability-Adjusted Life Years
DEXA	Dual-energy X-ray Absorptiometry
DHEA	dehydroepiandrosterone
eCRF	electronic Case Report Form
ED-5D-3L	Euro 5 Dimension 3 Level (HRQoL)
eFI	electronic Frailty Index
ELSA	English Longitudinal Study of Ageing
EPS	Elixhauser Point Score
ETS	Elixhauser Total Score
EWGSOP	The European Workgroup for Sarcopenia

FCI	Functional Comorbidity Index
FFQ	Food Frequency Questionnaire
FiND	Frail in Non-Disabled
FP	Fried Phenotype
FRAIL	FRAIL scale
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
GDPR	Data Protection Regulation
GI	gastrointestinal
GMS	General Medical Services
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale – Anxiety
HADS-D	Hospital Anxiety and Depression Scale – Depression
HALE	Healthy Average Life Expectancy
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRA	Health Research Authority
HRQoL	Health-Related Quality of Life
hs-CRP	High sensitivity C-Reactive Protein Test
IADL	Independent Activities of Daily Living
ICC	Interclass Correlation Coefficient
ICF	Informed Consent Form
ICFSR	International Conference on Frailty and Sarcopenia Research
ICOAP	Intermittent and Constant Osteoarthritis Pain Questionnaire
IMD	Indices of Multiple Deprivation
IMH&W	Investigating Musculoskeletal Health and Wellbeing
IRAS	Integrated Research Application System
JSN	Joint Space Narrowing
KOOS	Knee injury and Osteoarthritis Outcome Score
KPIC	Knee Pain in the Community study
LoA	Limit of Agreement
MAR	Missing At Random
MBSR	Mindfulness-Based Stress Reduction (MBSR)
mCAPf	modified Central Aspects of Pain factor
MCAR	Missing Completely At Random
mFiND	modified FiND.
mFRAIL	modified FRAIL (with 4 items)
MI	myocardial infarction
ML	Medial joint Line
mPDQ	modified Pain Detect Questionnaire
MPQ	McGill Pain Questionnaire
MSK	musculoskeletal
NHS	National Health Service
NIHR	National Institute for Health Research
NIS-LL	Neuropathy Impairment Score in Lower Limbs
NKP	Neuropathic Knee Pain

NLDA	Nottingham Line Drawing Atlas
NRS	Numerical Rating Scale
NSAIDs	Nonsteroidal anti-inflammatory drugs
NWC	Number of Words Chosen (McGill)
OA	Osteoarthritis
OR	odds ratio (unadjusted)
PA	Physical Activity
PCS	Pain Catastrophising Scale
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
PPT	Pain Pressure Threshold
PRI	Pain Rating Index (McGill)
PROMs	Patient Reported Outcome Measures
PSQI	Pittsburgh Sleep Quality Index
PVD	peripheral vascular disease
QST	Quantitative Sensory Testing
R&D	Research and Development department
RA	Rheumatoid Arthritis
RCT	Randomised Control Trial
RDCI	Rheumatic Disease Comorbidity Index
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
RMSEA	Root mean square error of approximation.
ROA	Radiographic Osteoarthritis
ROC	Receiver Operating Characteristic Curve
RR	Relative Risk
SAE	Serious Adverse Event
SARC-F	'Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls'
SD	Standard Deviation
SE	Standard Error
SF-12	Short Form Health Survey (12 items)
SF-36	Short Form Health Survey (36 items)
SHARE	The Survey of Health, Ageing and Retirement in Europe
SMD	Standardised mean difference.
SOA	Symptomatic Osteoarthritis
SOF	Study of Osteoporotic Fractures Index
SPPB	Short Physical Performance Battery
TA	Tibialis Anterior
TENS	Transcutaneous electrical nerve stimulation
TJR	Total Joint Replacement
TRAcP5b	Tartrate resistant acid phosphatase 5b
TS	Temporal Summation
UK	United Kingdom
UoN	University of Nottingham
USA	United States of America

VAS	Visual Analogue Scale
WHR	Waist Hip Measurement
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

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CHAPTER 1 INTRODUCTION AND LITERATURE REVIEW

1.1 Frailty

1.1.1 Definition and concept

Frailty is defined as a vulnerability state with decreased physiological reserve observed in older people (Clegg et al., 2013, Dent et al., 2016). Frailty may be characterised by a loss of homeostatic resilience due to multi-organ, age-associated decline (Clegg et al., 2013). People with frailty have an elevated susceptibility to stressors and/or disproportionate response to challenges; this leads to a significant functional decline and increased risk of adverse health outcomes (Dent et al., 2019a).

Although frailty has been viewed as a continuum from robust to frail (Rockwood et al., 2004, Rockwood et al., 2011); it can also be classified into identifiable stages, including robust, pre-frail, and frail, as shown in Figure 1-1 (Morley et al., 2012, Fried et al., 2001). Nevertheless, recent studies show that frailty is a more dynamic condition than previously thought, with numerous frailty state transitions occurring over time (Romero-Ortuno et al., 2021). This suggests that frailty is not inevitable and that measures can be taken to mitigate risk factors.

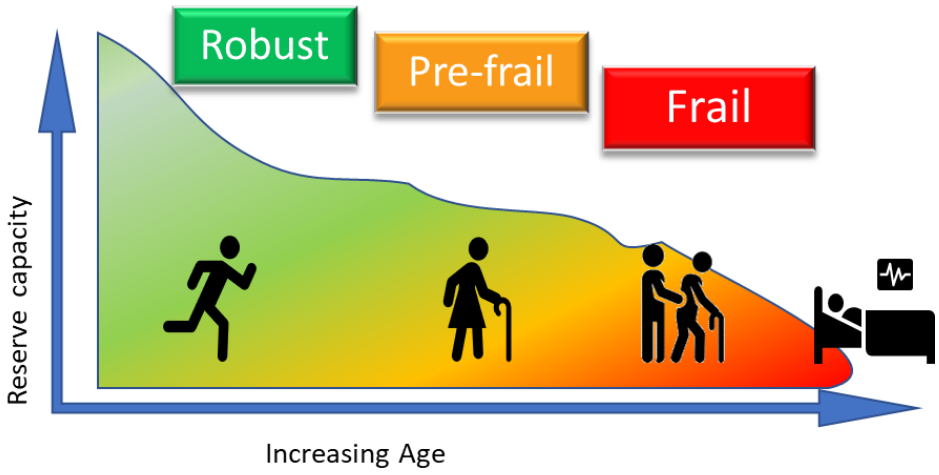


Figure 1-1 Frailty stages: loss of reserve capacity results in loss of independence.

People with frailty have higher mortality and hospitalisation rates and are more disabled than those who are robust (Chang et al., 2018,

Ravindrarajah et al., 2013, Rockwood et al., 2006, Clegg et al., 2013, Fried et al., 2001, Hoogendijk et al., 2019). Frailty, disability and morbidities have overlapping albeit distinct concepts that are not interchangeable (Fried et al., 2001, Cesari et al., 2014); the key distinguishing feature of frailty is the catastrophic response to stressors (Figure 1-2).

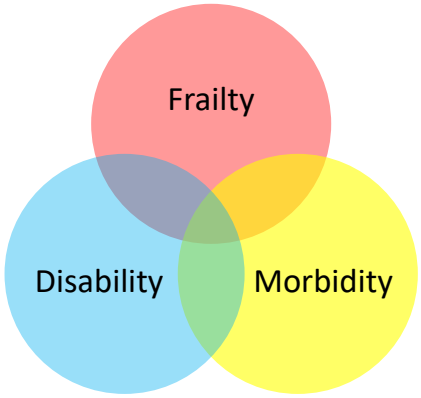


Figure 1-2 Frailty, disability, and morbidity are overlapping concepts.

The concept of frailty is complex and multi-dimensional, influenced by various biological, psychological, and social factors (Pilotto et al., 2020). As people age, they expect to experience a gradual decline in physiological reserve, which can manifest as a loss of strength, speed, and stamina. However, the rate at which this occurs can vary widely depending on several factors. Frailty occurs when there is a rapid decline in homeostatic mechanisms, resulting in reduced reserve capacity (as shown in Figure 1-1) (Clegg et al., 2013).

1.1.2 Epidemiology and prevalence.

As the proportion of older adults in the population rises, so does the need to understand frailty. Frailty is of epidemiological interest to medical services, social services and policymakers (Hoogendijk et al., 2019). Epidemiology is defined as the "study of distribution and determinants of health-related states among specified populations and the application of that study to the control of health problems" (Porta, 2014). Prevalence, which refers to the number of those diagnosed with a condition, is also an important concern in frailty (Porta, 2014).

A meta-analysis of community-based studies estimated the European frailty prevalence at 12% (O'Caoimh et al., 2018). In comparison, the global weighted rate for community-dwelling adults aged 65 years is 10.7%. In the UK, the estimated prevalence of frailty in people 65 years and over is 15% (Reeves et al., 2018), while non-community-based studies suggest a prevalence rate of 45%. In adults aged 80 years and over, the prevalence is estimated to be 50% (O'Caoimh et al., 2018).

1.1.3 Frailty: the cost to UK healthcare

Frailty is associated with increased healthcare costs (Hoogendijk et al., 2019). People who are frail have an increased risk of falls, hospitalisation and admission to long-term care (Hoogendijk et al., 2019).

Individuals with frailty may also experience other health conditions, which can further increase their healthcare burden (Fried et al., 2009). This often means that they need to see multiple specialist care teams and take multiple medications. While the United Kingdom's (UK) National Health Service (NHS) provides free medical treatment, it may be inconsistent across all geographical regions and lengthy waiting lists for specific treatments. Additionally, healthcare services tend to work independently in healthcare silos without sharing information, leading to repeated tests and investigations (McCartney, 2016). Patients may feel overwhelmed and confused by conflicting advice.

Clear communication between medical and social care services is also necessary. Although medical care is free in the UK, social care is assessed based on an individual's financial status, which can cause delays in receiving help. For example, people with dementia may need social care, which is not fully funded by the government, resulting in delays in being discharged from hospitals and other medical facilities (Scott and Hawkins, 2008). This delay can complicate recovery, causing a loss of independence.

The healthcare system requires more integration and collaboration, which may not happen in the near future (Pepler et al., 2018).

1.1.3.1 Individual consequences of frailty

Individuals living with frailty experience a significant burden, including impaired quality of life and loneliness, both in the UK and other parts of the world (Kojima et al., 2016a, Hoogendijk et al., 2016, Gale et al., 2018, Sha et al., 2020, Kojima et al., 2016b). Physical symptoms of frailty may result in dependency on others due to a lack of mobility, strength, and fatigue (O'Donovan et al., 2019). The disability-adjusted life years (DALY) is a critical measure of the burden of disease. It is calculated by combining the time lost to disease-related quality of life through years lived with disability and time lost due to premature mortality through years of life lost (O'Donovan et al., 2019). Their results showed a significant association between frailty and DALY.

Fatigue is frequently associated with frailty and is incorporated in nearly half of frailty assessment tools (Knoop et al., 2019). Various frailty scales account for fatigue, with it being one of the five components in each of Fried Phenotype and FRAIL. Moderate to severe fatigue is common in older people, affecting between 27-50% of community-dwelling adults, with higher proportions in those living in care facilities (Yu et al., 2010). Fatigue in older adults has many possible origins, including anaemia, endocrine disorders, sleep apnoea, polypharmacy, depression, and nutritional status, and it may be associated with particular health conditions, for example, depression or cancer (Uslu and Canbolat, 2021, Morley et al., 2014).

Fatigue unrelieved by rest is classified as physical, emotional, and cognitive aspects, affecting quality of life, physical capacity, and the ability to overcome challenges (Uslu and Canbolat, 2021). There is some evidence that fatigue is the least responsive item in attempts to mitigate frailty, but this may be due to the heterogeneity between different

frailty instruments and the multidimensional aspects of fatigue (Knoop et al., 2019).

Physical frailty is associated with decreased social networks and perceived social support, which makes individuals more socially vulnerable (Penninx et al., 1999, Berkman et al., 2000, Bowling et al., 2002, Woo et al., 2005). It is unclear whether low social support leads to frailty or vice versa (Woo et al., 2005). Factors that mitigate low social support include the number of contacts with relatives and neighbours, and the frequency of helping others (Woo et al., 2005). However, older adults who experience both frailty and loneliness are at higher risk of mortality (Hoogendijk et al., 2020).

Research suggests that social isolation could contribute to the onset or progression of frailty. However, there is limited evidence on manipulating these factors at a population level or conducting trials to examine if interventions to increase social support can reduce the risk of frailty.

It is not only the individual who faces the consequences of frailty but also their spouse and/or family. Low reserve capacity may require extra care to be taken; this became particularly prominent during the COVID pandemic when people had to shield those particularly vulnerable to the infection and its consequences (Maltese et al., 2020).

1.1.4 Frailty risk factors

Frailty comprises multiple risk factors that incur a risk of a catastrophic response to insult. These include biological factors, including age-related physiological changes, chronic health conditions, and genetic predispositions. Psychological factors such as cognitive impairment, depression, and decreased motivation can all play a role. Social factors encompassing social isolation, limited social support, and socioeconomic position can also contribute to frailty. It is important to note that some risk factors can be modified through lifestyle changes, while others, such

as age, gender, and genetics, are non-modifiable. However, lifestyle changes depend on the individual's agency and other environmental factors.

1.1.4.1 Biological risk factors

There is some evidence of pathophysiology involving cellular changes, system deregulation and impairments, including those of the musculoskeletal system, which lead to multi-system decline (Waldon, 2018). However, what underpins frailty remains to be understood. Frailty is best understood as age-associated damage across multiple organs and tissues; it may manifest as traditional disease states, and others are recognised only through their effect on function. Many processes are likely at play, to different degrees in different individuals, interacting with different genomes (Clegg et al., 2013).

1.1.4.2 Chronic health conditions

Interrelated physiological systems are often affected simultaneously due to comorbidity or new pathologies (Clegg et al., 2013). When multiple body systems are affected at one time, this is likely to have a more significant impact on the individual and is likely to reduce their physiological and psychological reserves, sometimes referred to as their reserve capacity (Figure 1-1) (Guerriero and Reid, 2020, Clegg et al., 2013, Karp et al., 2008). For example, someone diagnosed with diabetes mellitus is more likely to experience retinopathy, neuropathy, and nephropathy as the disease progresses, as well as concomitant cardiovascular disease leading to myocardial infarction and stroke (Forbes and Cooper, 2013, Keenan et al., 2010). Diabetes is associated with a higher frailty risk (Aguayo et al., 2019); it is estimated that over 5 million people in the UK are living with diabetes (Diabetes UK, 2023). Once people are diagnosed with morbidities, many remain not fully resolved even after treatment; this results in an accumulation of conditions with age. Frailty is associated with a higher risk of cardiovascular disease (Veronese et al., 2017a, Newman et al., 2001).

Fried and colleagues (2009) reported that people with impairment in three or more physiological systems were more likely to be frail (OR 11) compared with people with one or two impaired systems (OR 4.8). Moreover, those with >3 impaired systems showed a further increased risk of frailty (OR 26).

Evidence shows that different comorbidities have differing associations with the risk of frailty. For example, angina (aOR 2.51, (95%CI 1.88 to 3.35) p<0.001), congestive heart failure (aOR 7.51, (95%CI 4.66 to 12.12), p<0.001), (Newman et al., 2001). However, there is evidence that other impairments, such as hearing dysfunction, also increase the Relative Risk (RR) of frailty (RR 1.90, (95%CI 1.38 to 2.61), p<0.001) (Wang et al., 2022, Tian et al., 2021). This indicates that psychological and social aspects may also play a role in increasing frailty risk, as hearing loss can reduce social support, increase isolation, and impact psychological well-being. There is evidence to support a bidirectional effect between hearing loss and frailty (Liu et al., 2022).

1.1.4.3 Polypharmacy

Polypharmacy is defined as prescribing five or more medications concurrently (Cesari, 2020, Viktil et al., 2007). As people age, they are more likely to experience multiple morbidities, which may result in taking multiple medications (Morley, 2016). Medication has many benefits, but it also has risks, adverse reactions, and side effects. When multiple medications are taken, they may interact and increase the risk of other issues, e.g., increased fall risk (Dhalwani et al., 2017), incident frailty (Shmuel et al., 2019, Palmer et al., 2018), hospitalisation (Oscanoa et al., 2017). Reductions in polypharmacy are possible when a healthcare practitioner reviews the medication prescribed. Medication requires careful review, as any change may result in instability in an already vulnerable individual. The patient may often visit separate hospital specialists with competing priorities.

A systematic review and meta-analysis found that taking a higher number of medications was associated with frailty (RR 1.72, (95%CI 1.17 to 2.28, p<.001) (3 trials I^2 = 90%, p<0.001); and polypharmacy (≥5 medications) (RR 1.49, (95%CI 1.39 to 1.60), p<.001) (8 trials I^2 = 93% p<0.001) (Wang et al., 2022). There is evidence that this may also be a bidirectional relationship, and thus causal, utilising the Frailty Index (Gutierrez-Valencia et al., 2018). As such, reducing polypharmacy could offer a potential way to manage or prevent future frailty. Also, very ill people may be taking more medications, so there is a possibility that this association may be due to confounding. Similar findings were observed using the Fried Phenotype, with a pooled OR = 2.62 (95%CI 1.81 to 3.79), p<0.001, I^2 = 84.8% in people classified as frail (Palmer et al., 2019). Individuals with pain are frequently prescribed multiple analgesic medications (Macfarlane et al., 2017). Long-term exposure to opioids has been shown to increase pain perception (opioid-induced hyperalgesia) and promote dysfunctional pain mechanisms (Brush, 2012). There is a need to examine the mechanisms involved, which are complex and difficult to assess.

1.1.4.4 Low muscle mass

The age-related accelerated loss of muscle mass with the resultant loss of function is referred to as sarcopenia (Dent et al., 2021, Narici and Maffulli, 2010, Rosenberg, 2011). Sarcopenia shares many of the features of frailty, and some individuals living with frailty may have sarcopenia but only focus on a single aspect. Sarcopenia has been proposed as an early stage of frailty (Morley et al., 2014), so there is some overlap in their assessments. The risk factors for sarcopenia and frailty have some similarities, including physical inactivity (Steffl et al., 2017), malnutrition (Sieber, 2019), morbidities (Lee et al., 2021), and polypharmacy (König et al., 2018). However, sarcopenia only focuses on the loss of muscle mass and does not fully explain the increased vulnerability that accompanies frailty.

Sarcopenia is the outcome of reduced muscle-building capacity (anabolism) and increased breakdown of muscles (catabolism) within the body (Narici and Maffulli, 2010). Usually, there is a balance between these processes, but as individuals age, these systems may become unbalanced, resulting in an overall decline in muscle mass. Cohort studies have found a gradual decline in muscle mass from 20 years to 80 years, equivalent to 18% in males and 27% in females (Janssen et al., 2004). These changes become more apparent from 45 years onwards and are particularly apparent in the lower limbs (~15%) compared with the upper limbs (~10%). This is important as leg strength is measured in items such as the ability to walk, climb stairs or gait speed in the frailty and sarcopenia classification tool. Losing leg strength will also result in losing independence and a higher risk of falls. Additionally, studies have indicated that muscle loss is not the only factor; but there are changes in muscle quality (Narici and Maffulli, 2010). Fat can infiltrate the muscle tissue, resulting in myosteatosis and decreased muscle strength and efficiency (Narici and Maffulli, 2010). Myosteatosis is a condition of concern for older individuals with sarcopenic obesity, a combination of sarcopenia and obesity. Fat infiltration of skeletal muscle sustains sarcopenia through inflammation. Sarcopenic obesity is associated with a high risk of diseases and mortality. The loss of muscle mass promotes insulin resistance, which sets up a vicious circle between sarcopenic obesity and sarcopenia, ultimately resulting in low energy levels and the loss of muscle mass (Narici and Maffulli, 2010).

A systematic review and meta-analysis highlighted that biomarkers are shared by sarcopenia and frailty (Picca et al., 2022). Picca and colleagues (2022) found that two inflammatory molecules were significantly associated with both conditions, namely Interleukin 6 (IL) in people aged <75 years and tumour necrosis factor alpha (TNF-α). Further investigations of this type may identify whether there are biomarkers that can be used to indicate and clarify the pathway of these conditions.

There are different classification tools for identifying sarcopenia; one commonly used is the European Working Group for Sarcopenia (EWGSOP) and its revised version, EWGSOP-2. Sarcopenia is estimated to have a worldwide prevalence of approximately 13% of adults over 60 years (Mayhew et al., 2019) and over half of individuals aged over 75 years (Berger and Doherty, 2010).

The clinical diagnosis of sarcopenia, using the EWGSOP-2 (Cruz-Jentoft et al., 2010, Cruz-Jentoft et al., 2019), involves the assessment of the following:

- muscle mass: using Dual-energy X-ray Absorptiometry scan (DEXA), or Bioelectrical Impedance Analysis (BIA), or anthropometric measurement.
- muscle strength: using grip strength.
- physical performance: using either gait speed, or the Short Physical Performance Battery (SPPB) or the Timed-Up-and-Go test.

The EWGSOP-2 tool has been shown to predict hospitalisation and the incidence of falls (Yang et al., 2019). However, it is not the only classification system for sarcopenia. The Asian Working Group for Sarcopenia (AWGS) defines sarcopenia as “age-related loss of muscle mass, plus low muscle strength, and/or low physical performance”(Chen et al., 2020). The assessment shares similarities with the EWGSOP-2 but is specifically tailored for use with a Southeast Asian population. The AWGS-2 uses the following assessment criteria:

- muscle mass: using DEXA scan or BIA.
- muscle strength: using hand grip strength.
- physical performance: using either gait speed, the SPPB, or the 5 x chair-stand test.
- calf circumference measure, or the ‘Strength, Assistance walking, Rise from a chair, Climb stairs, and Falls’ (SARC-F) questionnaire (Malmstrom and Morley, 2013).

It is not possible to assess sarcopenia using a questionnaire, so my future clinical studies should include sarcopenia assessment criteria. This would allow comparison between participants classified as frail and those with sarcopenia; it may be that the pain is more strongly related to frailty than sarcopenia or vice versa. This could improve understanding of the underlying mechanisms in the pain-frailty association.

1.1.4.5 Loss of weight and nutritional status

Frailty classification tools frequently include an item related to unexpected weight loss. There are multiple reasons that older people might experience weight loss. These include, but are not limited to, malabsorption or loss of appetite due to medications or underlying morbidities (Morley, 2016), alongside difficulty preparing food, changes in food preferences, poor dentition, and food insecurity (Volpi et al., 2013). Additionally, there may be an association with declining levels of hormones, particularly testosterone (Morley et al., 2005). Furthermore, low Vitamin D levels are associated with ageing (Berridge, 2017), falls (Murad et al., 2011), functional deterioration (Kotlarczyk et al., 2017), and frailty (Clegg et al., 2013).

Sometimes, this is referred to as 'anorexia of ageing', defined as a loss of appetite and reduced food intake (Martone et al., 2013). Muscle atrophy, previously mentioned, is also associated with weight loss (Morley, 2016). Poor nutrition can result in low energy levels, which may further reduce activity levels and result in loss of muscle mass.

Weight loss is associated with adverse clinical outcomes in older patients, such as decreased physical functions and increased mortality (Lim et al., 2012, Wilson et al., 2019). Malnutrition is prevalent in hospitalised older people (Hong et al., 2019). A systematic review and meta-analysis found that malnutrition and lower Vitamin D levels were cross-sectionally associated with frailty in a meta-analysis of 13 studies with a standardised mean difference (SMD) = -1.31 (95%CI -2.47 to -

0.15), p=0.0271 in people classified as frail by the Fried Phenotype (Marcos-Pérez et al., 2020). This study found high heterogeneity even after removing one study, I^2=96.05%.

1.1.4.6 Systemic risk factors

1.1.4.6.1 Age

Although frailty is more common in people aged over 80 years, it is not synonymous with ageing. Ageing is a heterogeneous process influenced by individual characteristics (Fogg et al., 2022). The onset of frailty may vary depending on geographic location; life expectancy varies between regions and genders. In the Global North, the average male life expectancy is 75 years, and 82 in females; in less developed countries, 69 and 73, respectively; and in the least developed countries, 62 and 67, respectively (Dyvik, 2022). However, life expectancy in individual countries varies widely.

Increasingly, there is interest in healthy average life expectancy (HALE); frailty is associated with increased mortality and morbidity. In England, a male born between 2018 and 2020 is expected to have 63.1 healthy years and for a female, 63.9 years (Office for National Statistics, 2022a). There is considerable regional disparity; the lowest is the North East (males 59.1, females 59.7), and the highest is South East (males 65.5, females 65.9) (Office for National Statistics, 2022a)Other regions of the UK, Scotland, Wales, and Northern Ireland, all have lower HALEs than England. Delaying or reversing frailty could potentially increase HALEs.

Different parts of the world have explored different age cut-offs for frailty research based on the life expectancy in the region. Even in the Global North, there are various ages used. Generally, research in the Global South uses a younger age cut-off. Healthy ageing depends on many factors, from occupation to food security and natural hazards (for example, extreme weather, causing flooding or drought). There is some

evidence that frailty is also present in the middle-aged population (Swain and Chandra Mishra, 2019, Spiers et al., 2021).

1.1.4.6.2 Sex

Studies report a higher prevalence of frailty in females (8.8 %) than in males (5.4%) (Zhang et al., 2018); and females (5%) and males (2%) (Fried et al., 2001); and females (22.4%) and males (10.8%) (Jung et al., 2016). A meta-analysis in China found higher frailty in females (11%) compared to males (8%) (He et al., 2019). These confirm findings from an earlier global systematic review (Mello et al., 2014). Many frailty studies focus on single-sex cohorts, for example (Susanto et al., 2018), which makes it harder to draw generalisable findings. Several reasons are proposed, such as females having less muscle mass than men, so muscle atrophy reaches a critical loss earlier.

Additionally, some studies report that men with frailty have a higher mortality rate, with the leading cause of death being cardiovascular; this may result in a disproportionate percentage of females living with or 'tolerating' frailty (Park and Ko, 2021, Gordon et al., 2017). This survival effect (fewer men surviving to over 80 years) can distort samples. Still, Gordon and colleagues' systemic review and meta-analysis (2017) indicated that the oldest women had the highest frailty index values and had more comorbidities and poor health indicators than age-matched men.

1.1.4.6.3 Genetics

There is some evidence of genetic risk factors and the development of frailty (Inglés et al., 2019, Pansarasa et al., 2019). Alterations to the immune system may increase frailty through increasing inflammation, which could result from the interplay between genetic and nutritional factors, such as the gut biome (Pansarasa et al., 2019).

1.1.4.6.4 Obesity and underweight

Frailty is frequently associated with weight loss, and frailty classification tools measure the 'unexpected loss of weight' as a frailty indicator (Fried et al., 2001, Morley et al., 2012). Additionally, low weight is associated with frailty (Wang et al., 2022). However, others have also demonstrated a U-shaped association between BMI and frailty, which indicates that those with either low or high BMI are more likely to be frail (Hubbard et al., 2010, Crow et al., 2019). They suggest obesity in older people may be due to low physical activity, increased metabolic instability, increased inflammation, and low antioxidant capacity. Obesity measured using waist circumference was shown to be a better indicator than BMI in predicting frailty. (Crow et al., 2019). This is because central obesity is associated with increased morbidity and mortality (Gale et al., 2013). A measure of waist circumference should be included in my clinical observations.

1.1.4.7 Psychological factors

Various studies have associated frailty with a higher risk of depression (Soysal et al., 2017b, Chu et al., 2019, Mhaolain et al., 2012, Lakey et al., 2012, Pegorari and Tavares, 2014, Mezuk et al., 2012, Wang et al., 2022)*;* increased anxiety (Mhaolain et al., 2012); reduced quality of life (Kojima et al., 2016a, Kojima et al., 2016b); and cognitive impairment (Li et al., 2020a, Wang et al., 2022). These factors may be causative rather than solely consequences; some studies found a bidirectional association with frailty and these factors (Mezuk et al., 2012).

A systematic review and meta-analysis conducted by Wang and colleagues (2022) found that individuals with cognitive impairment, poor sleep, and depression were at a higher risk of frailty when compared to those without frailty. The study reported that the risk of frailty in individuals with cognitive impairment (RR 2.32, (95%CI 2.10 to 2.56), p<0.001) (7 studies I^2 = 88%, Z=16.38, p<0.001), poor sleep (RR 1.71 (95%CI 1.55 to 1.89), p<0.001) (7 studies I^2 = 84%, Z= 10.90

p<0.001) and depression (RR 3.47, (95%CI 3.06 to 3.95), p<0.001) (8 studies I^2 = 82%, Z= 19.09 p<0.001). A further meta-analysis observed frailty was significantly associated with geriatric cognitive disorders (pooled OR 1.80 (95%CI 1.11 to 2.92), p=0.02 (6 studies I^2 =79%) (Borges et al., 2019).

1.1.4.8 Lifestyle factors

One of the primary lifestyle risk factors for frailty is low activity levels (Wang et al., 2022, Woo et al., 2005, Fried et al., 2001). This is measured directly and indirectly, but it is hard to know the direction of causation, whether frailty causes inactivity or vice versa; they may be bidirectional.

There are several lifestyle factors associated with frailty, smoking (Kojima et al., 2015, Ng et al., 2014, Wang et al., 2022, Feng et al., 2017); alcohol intake and excess (Kojima et al., 2018, Wang et al., 2022, Feng et al., 2017). There is mixed evidence of the effect of dietary patterns, but some suggest that adherence to a Mediterranean-style diet may be beneficial (Feng et al., 2017).

1.1.4.9 Socioeconomic determinants

Evidence indicates that social determinants such as low social support and stressors associated with high economic burden are associated with increased risk of frailty (Peek et al., 2012, Hajek et al., 2018). Lower education was associated with frailty (Stolz et al., 2017, Ng et al., 2014). Often, those in disadvantaged groups are also at higher risk for other morbidities, such as cardiovascular disease (Mannoh et al., 2021) and diabetes (Tatulashvili et al., 2020). The long-term impact of any socioeconomic disadvantage is complex, and it is harder to distinguish individual factors, particularly frailty, as these are viewed over a lifetime of exposure. There is evidence of opposing factors acting as protective factors for frailty development, for example, higher education (Peek et al., 2012, Chen et al., 2015), cultural engagement (Rogers and Fancourt, 2020), social support (Peek et al., 2012, Chen et al., 2015), and higher

wealth (Marshall et al., 2015). The ability to examine socioeconomic effects is observed in cohort studies, but mitigating these risks is problematic and likely to require complex societal interventions.

There is emerging evidence that loneliness and living alone are associated with frailty (Wang et al., 2022, Ng et al., 2014). A systematic review and meta-analysis demonstrated a SMD between frail and robust of 0.77 (95%CI 0.57 to 0.96), p<0.001 (6 studies I^2 = 69%, p<0.001) (Kojima et al., 2022).

Older people may be isolated by family moving away, partner bereavement or disability, and their lack of mobility. Men may be particularly vulnerable if they have retired and lost a partner; women may have more developed social networks (Freer and Wallington, 2019). Some suggest that isolation leads to more isolation due to the loss of social and cognitive cues (Freer and Wallington, 2019).

Living alone and with frailty may increase the environmental challenges. If there are other factors, such as low income and old housing stock, tasks such as the independent activities of daily living, are likely to take more time and energy, resulting in a less safe environment (Freer and Wallington, 2019). Some home improvements and adaptations can mitigate these environmental challenges.

1.1.5 Classification of frailty

Frailty is conceptualised in different ways. Frailty may be defined as a phenotype that groups clinical characteristics, such as the Frailty Phenotype (Fried et al., 2001). Another approach uses an accumulated deficit model such as the Frailty Index (Rockwood and Mitnitski, 2007). Alternatively, the hybrid FRAIL (Morley et al., 2012) can be utilised.

A comparison of these classification tools using data from the European Male Ageing Study (Ravindrarajah et al., 2013) found that all three models significantly predicted mortality. A cohort of 3,369 male participants aged 40-79 years from eight European centres. At baseline,

71 (2.5%) FRAIL and 70 (2.6%) Fried Phenotype were classified as frail. The 39-item Frailty Index was a continuous variable (range 0 to 0.68). At follow-up (mean 4.3 years SD 1.3), Cox regression models showed each unitary increase (0.1 unit) in baseline Frailty Index predicted mortality at follow-up which was reported using Hazard Ratios (HR) 1.49, (95%CI 1.33 to 1.67)); and those people classified frail compared to robust using FRAIL (HR 3.87, (95%CI 2.25 to 6.66)) and Frailty Phenotype (HR 3.84, (95%CI 2.24 to 6.60)) all p<0.001,

Lim and colleagues suggest that the Fried Phenotype, FRAIL and Frailty Index capture distinct but intersecting constructs and, therefore, are not interchangeable (Lim et al., 2020). Each classification tool has advantages and disadvantages.

Bouillon and colleagues (2013) reviewed 2166 papers about frailty research and described 27 different frailty scales. There was heterogeneity in the number of items, types of items (e.g., subjective or objective), reliability, and validity; this is problematic as it is difficult to assess results without universal classification tools.

1.1.5.1 Fried Phenotype frailty classification

The Fried Phenotype (sometimes referred to as the Cardiovascular Health Study) is one of the most widely adopted frailty classification tools. Fried Phenotype is operationalised by five variables described below (Fried et al., 2001). The disadvantages of this tool are that it requires some skill to administer and utilises specialist equipment (e.g., hand dynamometer) alongside clinical support and may be challenging to perform in non-clinical settings such as nursing homes (e.g., gait speed). This tool is frequently adapted or modified, which reduces the generalisability (Bouillon et al., 2013).

- Shrinking: weight loss, unintentional, of ≥ 10 pounds in the prior year or, at follow-up, of ≥ 5% of body weight in the prior year (by direct weight measurement).

- The exhaustion item is measured using an item from the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977). The following statements are read. A) I felt that everything I did was an effort; B) I could not get going. The question is asked, “How often in the last week did you feel this way?” 0 = rarely or none of the time (<1 day). 1= some or a little of the time (1-2 days), 2= a moderate amount of time (3 – 4 days), or 3= most of the time. Subjects answering “2” or “3” to either of these questions are categorised as frail by the exhaustion criterion.”
- Weakness: grip strength in the lowest 20% at baseline, adjusted for gender and body mass index.
- Slowness: The slowest 20% of the population was defined at baseline based on the time it takes to walk 15 feet, adjusting for gender and standing height.
- Low physical activity level: A weighted score of kilocalories expended per week was calculated at baseline, based on each participant’s report from The Minnesota Leisure Time Activity Questionnaire (Taylor et al., 1978), completed over a two-week period. The lowest quintile of physical activity was identified for each gender.

The Fried Phenotype categorises individuals as non-frail (robust) if no criteria are met, pre-frailty (vulnerable) when 1 or 2 criteria are met, and frail when 3 or more of the 5 criteria are present.

1.1.5.2 Frailty Index frailty classification

Frailty indices are based on accumulated deficit models (Rockwood and Mitnitski, 2007)The Frailty Index proposes that a count of health deficits represents an individual’s frailty index score and is thus indicative of an individual's likelihood of frailty.

Frailty indices recognise the multifactorial effect on multiple physiological systems. However, some criticise indices for overfocusing

on morbidities and disabilities rather than frailty per se (Morley et al., 2012). The inclusion of more deficits in an index leads to greater precision in indicating frailty, but collecting a large number of items may be problematic. Items may be collected via the 40-item Comprehensive Geriatric Assessment or medical records (e.g., hypertension), while others are subjective, for example, “How would you rate your health?” Some items require tests such as the Mini-Mental State Examination (Folstein et al., 1975).

Frailty indices are based on similar principles but vary in the number of items. Rockwood and colleagues propose that any index list of at least 40 deficits would produce comparable results (Rockwood et al., 2006). The disadvantage is that measuring deficits requires significant resources regarding clinic time and personnel to deliver and record. Additionally, the number and type of deficits vary between indices, making it difficult to compare studies. Furthermore, this measure has shown age sensitivity (Ravindrarajah et al., 2013), perhaps due to the accumulation of deficits (they are less likely to be resolved).

1.1.5.3 FRAIL frailty classification

This thesis employs the FRAIL frailty classification tool, which is a combination of the Fried Phenotype and Frailty Index. FRAIL has certain advantages over each of the other methods. The Geriatric Advisory Panel of the International Academy of Nutrition and Aging identified a need for a simple, rapid, standardised screening tool that could be used in various settings to identify individuals at risk of frailty (van Kan et al., 2008). Although the Fried Phenotype and Frailty Index are widely used, their methods are frequently modified and require face-to-face examination, leading to non-standardised results. Therefore, the panel recognised the need for a standardised tool and proposed five domains. Employing a standardised quick and straightforward tool was considered necessary to screen before further individual assessment. Furthermore, it allows the identification of the complex physiopathological pathways

leading to frailty (van Kan et al., 2008). Subsequently, the FRAIL scale questionnaire was developed and validated in an African-American cohort (Morley et al., 2012). It offers a simplified self-report questionnaire and removes the need for direct clinical observations or access to medical records.

The FRAIL and the cumulative deficit models share the belief that accumulated comorbidities are part of frailty, reflecting a decline in multiple physiological systems and a reduced capacity to respond to acute challenges such as falls or infection (Clegg et al., 2013).

FRAIL includes five items: **F**atigue, **R**esistance, **A**mbulation, **I**llnesses and **L**oss of weight. Full details of the criteria appear in Chapter 2. FRAIL is similar to the Fried Phenotype, classifying individuals as robust, pre-frail or frail based on the number of criteria met. However, there are also some differences between the two.

FRAIL has been shown to identify those who are frail (Morley et al., 2012). It has been validated in eight European countries (Susanto et al., 2018) and also worldwide for people aged over 40 years (Ravindrarajah et al., 2013). This suggests that FRAIL is more sensitive to identifying people with frailty at an earlier stage or younger age than other frailty classification tools without ADL deficits (Morley et al., 2012). Early identification of prefrailty or frailty may increase the chances of successful intervention.

The African American Health cohort demonstrated a cross-sectional baseline association between frailty classification using FRAIL with IADL difficulties, SPPB, hand-grip strength, and single-leg stand among participants without baseline ADL difficulties (N=703) and those outcomes plus gait speed in those without baseline ADL dependencies (N=883). Longitudinally:(N=423 without baseline ADL difficulties or N=528 without baseline ADL dependencies), and adjusted for the baseline value for each outcome, being pre-frail at baseline significantly predicted future ADL difficulties, worse single-leg stand scores and

mortality in both groups, plus IADL difficulties in the dependence-excluded group (Morley et al., 2012).

The Australian Longitudinal Study on Women's Health was the first to validate FRAIL in a predominately white, older population (Gardiner et al., 2015) and a middle-aged population (Susanto et al., 2018). The original FRAIL was developed with people from the middle-aged African-American community (Morley et al., 2012). The FRAIL with a cut-off of 3 was correlated with Activities of Daily Living r_s=0.46, (95%C 0.44-0.48) and Independent Activities of Daily Living r_s=0.56, (95%C 0.54-0.58) (Gardiner et al., 2015); they propose that responsiveness suggests the FRAIL scale is may be useful in intervention trials to observe change in frailty classification. In people classified as frail, there was an association with ADL (95%CI 0.44 to 0.48) and IADL aOR 4.90, (95%C3.67 to 6.54) compared with those considered robust (Lopez et al., 2012). FRAIL predicted mortality HR 2.01, (95%C 1.40 to2.87) and was significantly associated with disability OR 6.87, (95%C 4.84 to 9.77) and depression OR 2.77, (95%C 2.12 to-3.63) (Susanto et al., 2018).

FRAIL has been shown to perform comparably with the other frailty classification tools (Papachristou et al., 2017, Aprahamian et al., 2017, Ravindrarajah et al., 2013, Jung et al., 2016).

1.1.5.4 Advantages and disadvantages of FRAIL

In this section, I will briefly describe the advantages and disadvantages of using FRAIL rather than the more established Fried Phenotype. FRAIL has the advantage of using self-assessment, which is time-efficient and cost-effective to administer. It has the potential to identify those at risk and offer the development of an intervention pathway. FRAIL relies on participant recall and self-reporting, it can be completed remotely by questionnaire or telephone, which permits more frequent assessment intervals.

The FRAIL asks practical questions about function. The resistance measure in FRAIL asks people whether they can climb a flight of stairs unaided and the ability to walk several hundred meters unaided. Most individuals will know the answer to these questions; however, the Fried Phenotype assesses hand grip strength and gait speed, which require clinical observation. Factors such as OA rather than strength alone will likely affect these classifications. These items may assess different aspects of physical vulnerability.

A disadvantage of the Fried Phenotype is that it focuses on physical activity over two weeks. Whilst this may be a useful measure, it is also entirely subjective. It may result in individuals who participate in formal exercise overestimating their activity levels, and those who do not participate in formal exercise, such as carers, may underestimate their activity levels.

The fatigue item in FRAIL and the exhaustion item in the Fried Phenotype potentially measure similar aspects of frailty, but the degree to which they overlap is unclear. There is some evidence of differentiation in this measure (p=0.015) (Aprahamian et al., 2017).

Fried Phenotype and FRAIL assess 'loss of weight,' but the FRAIL asks patients to recall their weight from a year ago and their current weight. This may be challenging for some people who do not weigh themselves regularly or remember measurements. In contrast, the Fried Phenotype uses clinical records, which require at least two face-to-face visits a year apart. However, a study comparing this item showed no significant difference (p=0.335) between the two frailty tools (Aprahamian et al., 2017).

1.1.5.5 Other frailty classification tools

The Frail in Non-Disabled Questionnaire (FiND) (Cesari et al., 2014) aims to identify people at risk of frailty but without a disability; it shares many features and demonstrates substantial agreement with the Fried

phenotype. There are numerous other frailty classification tools. Some, such as the Study of Osteoporotic Fractures, the Frailty Instrument for Primary Care, and the Survey of Healthy Ageing and Retirement in Europe (SHARE-FI), are all similar to the physical phenotype of frailty (Romero-Ortuno et al., 2010, Ensrud et al., 2009, Romero-Ortuno and Soraghan, 2014). Frailty is defined as present if there were 2 of 3 criteria: weight-loss≥ 5%; the inability to rise from a chair 5 times without using the arms; and poor energy identified by an answer of 'no' to the question ''Do you feel full of energy?'' on the Geriatric Depression Scale. This has 71% concordance with the Fried Phenotype.

Others include psychosocial items such as the Tilburg Frailty Indices and Groningen (Gobbens et al., 2017, Peters et al., 2012). The Kihon Checklist was developed as a self-report screening tool to identify people vulnerable to becoming frail in Japan (Nemoto et al., 2012). It comprises 25 items, including: physical strength, nutrition, eating, socialisation, memory, mood, and lifestyle.

In the United Kingdom, the General Medical Services (GMS) contract mandates routine frailty screening of people aged ≥65 years using the electronic Frailty Index (eFI) or another such tool (Clegg et al., 2016, Travers et al., 2019). The eFI is used to identify patients living with moderate to severe frailty using medical information collected and held by the General Practitioner (GP). However, it does not seek to classify frailty but to identify individuals who need further investigative tests (NHS England, 2022b). The eFI contains a list of 36 deficits, consisting of comorbidities, symptoms, activity/ mobility restrictions, social vulnerability, and care requirements, but does not include pain directly (Clegg et al., 2015). Patients identified by their GP practice as living with severe frailty receive an annual review, which assesses medications and fall history and explores opportunities for clinically relevant interventions (Travers et al., 2019). The eFI screening tool only applies

to individuals aged 65 years or above, and its implementation may vary across GP practices.

1.1.6 Management of Frailty

Several interventions have been shown to have a weak effect on preventing or reversing frailty, such as physical activity, including resistance training, nutritional supplementation, and hormone-based treatments. Also, exploring the reduction of pharmacological treatment load, many older people are on large amounts of medication, some of which may cause side effects and increase patient burden (Dent et al., 2019b, Travers et al., 2019). The International Conference on Frailty and Sarcopenia Research (ICFSR) agreed that these treatments required a better evidence base and more high-quality research. Currently, there is only a relatively small number of Randomised Controlled Trials (RCTs) (considered the gold-standard method of producing evidence) (Dent et al., 2019b).

Travers and colleagues (2019) systematic review of primary care interventions found "a significant improvement of frailty status was demonstrated in 71% (n = 10) of studies and of frailty indicators in 69% (n=22) of studies where measured" and that the most effective intervention to delay or reverse frailty was strength training combined with protein supplementation. An advantage of these is that they are relatively easy to implement compared to other interventions, such as home visits or one-to-one care.

A further systematic review and network meta-analysis of RCTs supports the findings of the Travers and colleagues' study (Negm et al., 2019). Physical activity interventions were most associated with reduced frailty and were likely more effective when combined with nutritional supplementation. There was no significant heterogeneity (0.37, p=.665). The network meta-analysis showed that only one treatment option (physical activity intervention vs placebo and standard care) was statistically significant (3.6%). The eight interventions that used this

treatment were associated with a decrease in frailty (SMD=0.92, (95%CI 1.55 to 0.29) (Negm et al., 2019).

1.1.6.1 Exercise interventions.

The ease of implementing an intervention has important implications for its acceptability by both GP practices and patients. Exercise interventions, for example, are often delivered in groups to keep costs low and provide social stimulation, sometimes referred to as relatedness (Ryan and Deci, 2000). Exercise programmes that promote autonomy, competence and relatedness and align with the patient's motivation are more likely to be successful (Kirkland et al., 2011).

Whilst Travers and colleagues' (2018) systematic review reported a significant improvement in frailty status (71%) and frailty indicators (69%) with muscle strength and nutrition supplements. Studies which used other types of exercise, such as walking (Cesari et al., 2015) and tai-chi (Wolf et al., 1997), were also effective. However, they may only be suitable for those who are not too frail. Exercise such as chair yoga or chair exercise can safely increase the amount of possible physical activity. However, it may be more important in terms of reducing sedentary behaviour. Meta-analysis of mixed RCT interventions showed significant effect estimates on measures of mobility (SMD 0.75, (95%CI 0.40 to 1.10), ADLs (SMD 0.64, (95%CI 0.004 to 1.27), cognitive function (SMD 0.62, (95%CI 0.12 to 1.11), quality of life (SMD 0.68, (95%CI 0.16 to 1.21) and frailty (SMD –1.57, (95%CI –2.57 to –0.57); RR 0.72, (95%CI 0.63 to 0.83). These effects were large for frailty, with moderate certainty of evidence; medium for mobility, cognitive function and quality of life, with moderate certainty of evidence; and medium for ADLs, with low certainty of evidence (Racey et al., 2021).

Physical activity affects every cell in the body. Increased physical activity is associated with an improvement in many conditions: coronary heart disease, diabetes, hypertension, stroke, cancer, osteoporosis, depression and dementia (Academy of Medical Royal Colleges, 2015).

While there is agreement that increased physical activity is beneficial, it is multidimensional; there is no single measure. In studies which sought to decrease sedentary behaviour, two minutes of activity per 20 minutes of the waking day showed a change in glucose and insulin concentrations (Chen et al., 2018, Healy et al., 2007). A meta-analysis of physical activity interventions in adults with frailty found significant effects for mobility, SMD= 0.60, (95%CI 0.37 to 0.83), Activities of Daily Living (SMD= 0.50, (95%CI 0.15 to 0.84), cognitive function (SMD= 0.35, (95%CI 0.09 to 0.61), quality of life (SMD= 0.60, (95%CI 0.13 to 1.07) and frailty (SMD= –1.29, (95% CI –2.22 to -0.36); RR 0.58, (95%CI 0.36 to 0.93), with moderate certainty of evidence (Racey et al., 2021).

Exercise may be perceived as 'too difficult' for people who are frail. Instead, reducing sedentary behaviour may be more achievable and safer (Harvey et al., 2018, Skelton, 2023). Doing something is better than doing nothing. Also, measuring sedentary behaviour is more straightforward and allows for randomised controlled trials to test the effects of reminders to move around. The SITLESS project, conducted in several European countries, is an RCT to promote activity (Giné-Garriga et al., 2017). Early results have highlighted the acceptability of these interventions to older people and in Ireland, that a whole hospital focus can enhance results by promoting self-efficacy (Giné-Garriga et al., 2020, Blackburn et al., 2021).

1.1.6.2 Nutritional interventions

Some nutritional interventions aim to increase the levels of essential vitamins and proteins. In a randomised controlled trial (RCT) (Teh et al., 2022), a group-based nutrition program was combined with physical activity to target pre-frail older adults. Participants who identified as pre-frail were randomly assigned to one of three programs: nutrition, low-intensity exercise, or a combination of both. The participants' Fried frailty was assessed at 6, 12, and 24 months. However, this RCT showed

no significant differences between the intervention and control groups after 24 months.

1.1.6.3 Other interventions

Other interventions involved health education, home visits, hormone supplementation, and counselling.

Hormone supplementation using testosterone in men, in a 12-month RCT, strength and function remained unchanged, although there was an improvement in fat mass and lean tissue in those receiving the intervention; in those receiving strength training simultaneously with supplementation, there was an increase in strength (Hildreth et al., 2013). Another RCT involving testosterone supplementation found no differences in frailty scores over 6 and 12 months in under-nourished older people (Theou et al., 2016). An RCT using supplementation of dehydroepiandrosterone (DHEA) and atamestane with men living in the community did not show improvement in any physical frailty items (Muller et al., 2006). However, a Dutch RCT was conducted with older frail women to study the effects of raloxifene and tibolone supplementation. The trial found an increase in body mass but no improvement in strength. Additionally, the study revealed that raloxifene impacted the participants' health status and verbal memory (Jacobsen et al., 2012).

A non-randomised control trial used life goal-setting techniques with frail people in Japan (Yuri et al., 2016). This combined exercise with oral and nutritional education, and the intervention group also received life goal-setting support. They found that the intervention group improved significantly at 3 and 6 months, using the Kihon Checklist for frailty and quality of life at 3 months. In this method, the participant reflects on their life activities and set life goals that align with their individual values (Yuri et al., 2016).

Other studies include health education (Salem et al., 2017, Behm et al., 2016, Chan et al., 2017b) and involved behavioural change, which targeted improvements in fatigue (Liu et al., 2019), and a study used acupressure to treat frailty (Chan et al., 2017a). It is common for interventions to include more than one element; for example, combining exercises with health education may be more successful than either one applied alone. However, more complex interventions are more challenging to assess which elements are effective.

Frailty summary

- Frailty is a state of vulnerability seen in older people due to the age-associated decline of multiple organs. It is characterised by the failure of the body's ability to maintain balance in response to challenges or stressors.
- Tools for classifying frailty have limitations, as there are no direct measures of vulnerability to challenge.
- FRAIL was selected as suitable for a self-report survey such as the IMH&W.
- Frailty classification tools do not incorporate a pain measure.
- Many frailty risk factors are complex and interconnected; they include physiological, psychological, and social factors. Complex interventions may hold the greatest potential for benefit, as they work on different aspects of frailty.

1.2 Pain

1.2.1 Definition and prevalence

Pain is defined as “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” (Raja et al., 2020, International Association for the Study of Pain, 2019). Pain is frequently categorised chronologically as either acute or chronic, with unresolved pain after 3 months being referred to as chronic (Fayaz et al., 2016).

1.2.2 Nociceptive pain

Acute pain is frequently viewed as a protective or functional response, warning and promoting avoidance of actual or potential tissue damage (Nikolenko et al., 2022, Moseley and Butler, 2015).

Traditionally, pain has been thought of in terms of nociception, in which tissue damage triggers pain sensation in a bottom-up process. Noxious stimuli, such as thermal, mechanical, and chemical stimuli, are detected as present by afferent neurons (nociceptors) (Nikolenko et al., 2022). The brain subsequently interprets this neuronal activation as signalling damage. Nociceptors are strongly linked to MSK pain as they are located within joints, periosteum, subchondral bone, muscles, ligaments, and menisci (O'Neill and Felson, 2018). There are several types of receptors on nociceptors which transduce noxious stimuli to neural impulses; the resultant action potential is transmitted through unmyelinated C nerve fibre (group III) and fast-conducting myelinated Aδ fibre (group IV) that project to the superficial laminae of the spinal cord dorsal horn (Grau et al., 2017, O'Neill and Felson, 2018). The nerves convey signals from the spinal cord to the brain in an ascending pathway. However, the brain regulates the nociceptive signals using descending fibres via efferent neurons and opioid and non-opioid processes (Grau et al., 2017).

Pain is perceived when the incoming nerve signals trigger parts of the thalamus and somatosensory cortex into high activity levels (O'Neill and Felson, 2018). How pain is interpreted may be modulated by various mechanisms that amplify or dampen the signal. These depend on several things, and there are individual variances. This top-down processing can offer some explanation as to why individuals experience pain differently; impairments in inhibitory control may also explain some conditions, such as fibromyalgia (International Association for the Study of Pain, 2017). Psychological factors such as attribution, experience, depression, emotion and stress can influence the level and the meaning people attach to pain, which in turn can influence the severity, frequency or distribution of pain experienced (Toates, 2007). Individual differences in pain sensitivity and severity have been observed in distinct phenotypes with links to genetics (Fillingim et al., 2016) and biopsychosocial elements (O'Neill and Felson, 2018, Moseley and Butler, 2015). The dynamic interplay of signals in the CNS is sometimes termed the neuromatrix, referring to multiple areas of the central nervous system working together (Institute for Chronic Pain, 2019).

1.2.3 Pain mechanisms

In the past, it was assumed that the pain mechanism was hard-wired. However, research has indicated a high degree of plasticity. Prolonged exposure to chronic pain can result in central sensitisation (Arendt-Nielsen et al., 2018b), defined as “increased responsiveness of nociceptive neurons in the Central Nervous System to their normal or subthreshold afferent input” (International Association for the Study of Pain, 2019). This results in pain, which is disproportionate to the injury or pathology and may serve to maintain chronic pain (Woolf, 2011, Smart et al., 2012). Similarly, increased responsiveness to stimuli may occur at a peripheral or local site, resulting in peripheral sensitisation.

These neuroplastic changes to the nociceptive pathways may reflect altered pain processing mechanisms during the transition from acute to chronic pain and result in the receptive neurons amplifying neural signalling, resulting in pain hypersensitivity (Arendt-Nielsen et al., 2018b). Central and peripheral sensitisation have been shown to contribute to several clinical syndromes, for example, osteoarthritis and rheumatoid arthritis (Woolf, 2011). Research has found a strong association with maladaptive psychosocial factors, including catastrophising and fear (Smart et al., 2012). These neuroplastic changes can lead to persistent pain after the initial injury or pathology has healed.

1.2.4 Nociplastic pain

Chronic pain can arise from various underlying conditions or causes, including inflammatory disorders, nerve damage or dysfunction, musculoskeletal conditions, neuropathic pain syndromes, or chronic illnesses such as fibromyalgia, arthritis, or cancer-related pain. It can also develop without an identifiable cause.

Nociplastic pain is defined as “pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage, causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain” (International Association for the Study of Pain, 2019).

1.2.5 Neuropathic pain

Neuropathic pain refers to a type of chronic pain that originates from damage or dysfunction of the nervous system. It occurs when the nerves themselves are affected and send abnormal pain signals to the brain, leading to persistent or recurring pain sensations. Unlike acute pain, which serves as a protective response, neuropathic pain is often described as a dysfunctional pain system.

Neuropathic pain is defined by the International Association for the Study of Pain (2019) as “pain caused by a lesion or disease of the somatosensory nervous system”.

Neuropathic pain can arise from various causes, including:

- Nerve injuries: Traumatic injuries, such as accidents or surgeries, can damage nerves and result in neuropathic pain.
- Diseases and conditions: Certain diseases and medical conditions, such as diabetes, multiple sclerosis, shingles (herpes zoster), HIV/AIDS, and certain types of cancer, can cause nerve damage and trigger neuropathic pain.
- Compression or entrapment: Nerves may be compressed or trapped by surrounding structures, such as herniated discs, tumours, or inflamed tissues, leading to neuropathic pain.
- Neurological disorders: Conditions like peripheral neuropathy, trigeminal neuralgia, and post-stroke pain syndrome involve abnormalities in the nervous system and often manifest as neuropathic pain.

Neuropathic pain is characterised by features, including:

- Shooting or burning pain: Patients often describe the pain as shooting, burning, stabbing, or electric shock-like sensations.
- Hyperalgesia: There may be an increased sensitivity to pain, where normally non-painful stimuli elicit an intense pain response.
- Allodynia: Patients may experience pain in response to normally non-painful stimuli, such as light touch or temperature changes.
- Chronicity: Neuropathic pain is typically chronic, persisting beyond the expected healing time of an initial injury.

1.2.6 Chronic pain

Chronic pain is long-term or persistent pain which lasts for an extended period, typically beyond the normal healing time of an injury or illness. It is generally defined as pain that remains unresolved for

three months (Treede et al., 2019, International Association for the Study of Pain, 2021).

Unlike acute pain, which serves as a protective response to tissue damage and typically resolves as the underlying cause heals, chronic pain often persists or recurs over an extended period. It can result from various underlying conditions or causes, such as injury, inflammation, nerve damage, musculoskeletal disorders, or chronic illnesses like fibromyalgia, arthritis, or neuropathy.

Chronic pain can significantly impact a person's physical and emotional well-being. It can lead to functional limitations, reduced mobility, sleep disturbances, fatigue, mood changes, and decreased quality of life.

Chronic pain is common, affecting between a third and half of the UK population (Fayaz et al., 2016, Versus Arthritis, 2021, Versus Arthritis, 2023). The British Pain Society reported that 43% of the population in 2016 in the UK were living with chronic pain and that 14.3% regard their pain as disabling. The Health Survey for England 2017 (NHS Digital) suggests that 34% of adults experience chronic pain, with more women (38%) reporting pain than men (30%). Additionally, it reported that over half of 75-year-olds experience chronic pain and a higher prevalence of pain in disadvantaged groups (NHS Digital, Versus Arthritis, 2021).

1.2.6.1 Musculoskeletal chronic pain

Whilst there are many sources of chronic pain, such as cancer, visceral, headache including migraines, and gynaecological conditions. Musculoskeletal (MSK) pain is regarded as the leading cause of pain and physical disability globally (World Health Organization, 2022).

MSK pain arises or feels as though it arises from muscles, bones, joints or related soft tissues as a symptom of specific conditions, for example, osteoarthritis, inflammatory conditions, fibromyalgia or because of trauma or frequent overuse. MSK conditions are a prevalent

cause of chronic pain, affecting over a third of the UK population. For example, an estimated 11 million people in the UK have back pain (Versus Arthritis, 2023). MSK conditions are often age-associated, progressing with age.

MSK pain may be characterised by diffuse aching pain and referred pain to distant somatic structures, but may include severe, localised, or transient pain. People with pain use many different descriptors to describe their experience. Exposure to chronic pain reduces pain detection thresholds (International Association for the Study of Pain, 2017).

1.2.7 Risk factors.

The risk factors for the incidence of MSK pain conditions vary, although many have a genetic component (Hocking et al., 2012, Diatchenko et al., 2013). Evidence suggests that increased age may be associated with decreased pain sensitivity (Brown et al., 2015), but there is also evidence which supports this, with lower Pain Pressure Thresholds being observed in older age groups (Bartley et al., 2016). The risk factors for OA and back pain risk increase with age, female sex, smoking, obesity, malnutrition, physical injury, previous joint illnesses, or injury (Versus Arthritis, 2021, Chin et al., 2020, Mills et al., 2019). Chronic pain has a higher prevalence with female sex (Greenspan et al., 2007); smokers (Weingarten et al., 2008); obesity (Okifuji and Hare, 2015); malnutrition (Bauer et al., 2021) multi-morbidity (Barnett et al., 2012, Schneider et al., 2021); acute injury (Elliott et al., 2002).

An increase in chronic pain is associated with depression (Zigmond and Snaith, 1983), anxiety (Zigmond and Snaith, 1983), catastrophising (Sullivan et al., 1995), neuropathic-like pain (Hochman et al., 2011), cognitive impairment (Ferguson and Daniel, 1995); social deprivation and educational attainment (Kouraki et al., 2021).

1.2.8 Pain burden

1.2.8.1 Individual costs

Chronic pain affects the patient in terms of sensory and emotional problems (Dueñas et al., 2016). Pain is associated with low mood, sleep disturbance, fatigue, cognitive ability, catastrophising, anxiety and other psychological factors (Akin-Akinyosoye et al., 2020) and reduced quality of life (Versus Arthritis, 2021, Beaudart et al., 2018). Chronic pain affects the patient's family, social network, and employment status (Dueñas et al., 2016, Ojeda et al., 2014, Kouraki et al., 2022). Additionally, it reduces the opportunity to participate in leisure activities and social interaction, which may improve those psychological factors, with a subsequent reduction in well-being (Ojeda et al., 2014, Dueñas et al., 2016). Pain is associated with increased stiffness, loss of dexterity, reduced mobility and increased disability (Versus Arthritis, 2021, Versus Arthritis, 2023).

1.2.8.2 Socioeconomic costs

Chronic pain is viewed as a major health problem, producing a significant economic and social burden. Chronic pain affects 43% (28 million adults) in the UK (Fayaz et al., 2016). In the working population, sickness, absence, and reduced productivity cost the UK economy £100 billion annually (Versus Arthritis, 2021, Versus Arthritis, 2023). However, this accounts for only those of working age. Chronic pain is more prevalent in older adults, 49% of adults aged 65-74 years and 53% of those >75 years (Versus Arthritis, 2023). The percentage of older people in the population is rising, and many health conditions are associated with ageing; thus, the proportion of the population with chronic pain is likely to increase (Fayaz et al., 2016). Pain is responsible for a high percentage of primary care visits (20%). As such, it uses significant time and resources for the health service (Treede et al., 2015). MSK conditions are estimated to cost the NHS £5 billion in 2013-14, although this is likely to have increased (Versus Arthritis, 2021). It is clear that

chronic pain affects large numbers of people in this country and globally, which is estimated at 20% (Treede et al., 2015).

1.2.8.3 Osteoarthritis

Osteoarthritis (OA) is the most prevalent chronic joint disease, and its most predominant symptom is pain. It is estimated in the UK that 10-11 million people are affected (Versus Arthritis, 2023). The most common cause of knee pain in older people is OA, estimated at 5.4 million in the UK (Versus Arthritis, 2023). The disease has a gradual progression but is a leading cause of disability in older people (O'Neill and Felson, 2018). Pain may worsen when the joint is active, increasing frequency and intensity as the disease progresses. Although radiological joint changes may be observable, there is a relatively poor correlation between the severity of the disease observed and the symptoms of pain intensity (O'Neill and Felson, 2018, Hannan et al., 2000, Lawrence et al., 1966).

1.2.9 Measurement of chronic pain

Pain is a private, subjective experience that cannot be measured directly. Participant-reported outcome measures (PROMS) ask people to evaluate their pain level. The level of pain reported can be altered by mood and other factors, such as previous experience. Different methods are used depending on what is required. Ultimately, pain is whatever the individual says it is and wherever they say it is (McCaffery and Pasero, 1999).

1.2.10 Pain intensity and Impact

Pain intensity is the severity of pain experienced by an individual. Whilst eliminating pain is the goal in pain treatment, with chronic pain, there are often complex needs and unclear underlying mechanisms, which means that management of the levels of pain intensity and impact is common. Some pain medications, such as opioids, are linked with abuse, overdose, mortality, and they might induce hyperalgesia (Ballantyne and Shin, 2008, Eriksen et al., 2006). Careful monitoring during long-term use is required. Prescribing decisions are often not based on evidence related to the underlying mechanisms, which is a possible reason for their limited efficacy. The intensity of pain affects quality of life and the type, disability and causes stress (Hootman and Helmick, 2006). Thus, a reduction in pain intensity may result in pain being present but at an 'acceptable' level, which depends on the individual (Kvien et al., 2007). Pain at a lower intensity may be easier to manage with less impact on quality of life, and the patient may consider themselves well (Tubach et al., 2005, Georgopoulos et al., 2021).

Pain intensity is measured using scales such as the Numeric Rating Scale (NRS) or Visual Analogue Scale (VAS). This measurement is important as qualitative research indicates that people with MSK pain want to get their lives back (Larsen et al., 2013). So, when pain intensity is reduced, they become more active. Therefore, pain intensity largely determines pain impact

In summary, while pain intensity provides a measurable aspect of pain. Addressing pain impact is highly important for the individual, but impact is highly influenced by pain intensity. This thesis focuses on pain intensity, which has several validated measurement scales, for example,

the numerical rating scale, allowing for robust quantitative analysis, and many of its effects determine the impact upon each person.

1.2.10.1 Numerical rating scale

Numerical rating scales (NRS) are a widely used clinically to assess self-reported pain intensity. NRS is not a single measure; it depends specifically on the anchors and questions. Participants are asked to indicate which number on a segmented scale corresponds with their pain experience (McCaffery and Pasero, 1999)(Herr and Garand, 2001) When used as a pain scale, the rating can be from 0 to 10 (or 20 or 100). This is usually related to a specified period, such as the last 24 hours. The NRS 11-point scale was found to have the most sensitivity and stability compared with 4 commonly used scales (Visual Analogue Scale, 6-point Verbal Rating Scale and Face Pain Scale -Revised) (Euasobhon et al., 2022).

The advantages of utilising the NRS scale are that it is a quick and simple measure that can be used either verbally or in writing on paper or electronically. The NRS has been found to be reliable and suitable for rating pain intensity, and with older adults (Wood et al., 2010, Herr and Garand, 2001). NRS can be routinely used in clinical and research settings to monitor change (Williamson and Hoggart, 2005). The scale may be challenging to use if there are large fluctuations in pain over the period monitored, so care needs to be taken when setting the appropriate question. In clinical trials that assess the efficacy of pain treatments, it is usual to report the reduction in pain intensity by comparing to pre-trial values (Dworkin et al., 2005). It is reported that a reduction of 1 to 2 points or 30% in the NRS represents a clinically important difference (Farrar et al., 2001, Dworkin et al., 2008).

1.2.10.2 The McGill Pain Rating Index

Patients describe pain with different qualities (Fillingim et al., 2016). These aspects are captured in some scales, such as the McGill Pain

Questionnaire (Melzack, 1975). This index represents pain of any type or source; for example, acute or chronic pain (Melzack, 1975). This instrument comprises 78 pain descriptors in 20 sets of words. These descriptors categorise pain into a common intensity dimension, in which a higher score indicates greater pain. Only one word may be ticked per set. The descriptor rank value is based on the word position within each set.

Although a systematic review criticised the index for its lack of clinometric testing, it has been translated into many languages, and questions are raised about its validity in these new forms, and more research is required (Costa et al., 2009). This index takes considerably longer to complete than the NRS pain and uses word descriptors that may be too difficult for some participants to understand; for example, the original instrument uses American descriptors. The word lists are unequal in length, and the four domains have different numbers of word sets; this may result in many combinations of words adding up to the same pain rating index. The large number of response values results in the scale being more responsive to change, which may be easier to observe on the newer short-form version of the scale (Strand et al., 2008).

1.2.11 Pain mechanism measures

Pain mechanisms can be assessed using Quantitative Sensory Testing (QST), which aims to assess the contributions of somatosensory and pain modulatory function to pain by measuring the response to stimuli, but is used for research purposes rather than clinical assessment (Treede, 2019).

The Central Aspects of Pain in Knee (CAP-Knee) questionnaire (Akin-Akinyosoye et al., 2021, Akin-Akinyosoye et al., 2020). The CAP scores have been shown to have a shared factor referred to as CAP factor (CAPf); previously, this was referred to as the Central Mechanism Trait (CMT) (Akin-Akinyosoye et al., 2020). CAPf has a stronger association

with Pain Pressure Threshold (PPT) (which is believed to be an index of central pain hypersensitivity) than any of the individual characteristics. This suggests that a high CAP score may be indicative of a dysfunctional pain system.

1.2.12 Pain management

Managing chronic pain often requires a multidisciplinary approach involving healthcare professionals such as doctors, pain specialists, physical therapists, psychologists, and other complementary therapies.

Although a reduction of pain is positive, it should be recognised that chronic pain may still be present. Research has suggested that people experiencing chronic pain would find a numerical rating score of <4 acceptable for the remainder of their lives (Georgopoulos et al., 2021).

Treatment strategies for chronic pain may involve a combination of pharmacological interventions (such as pain medications), physical therapies, psychological interventions (such as cognitive-behavioural therapy), lifestyle modifications, and alternative therapies. Some examples of pain management are shown below.

1.2.12.1 Pharmacological

1.2.12.2 Medications:

The following analgesics are used to treat pain,

- Nonsteroidal anti-inflammatory drugs (NSAIDs): These over-the-counter medications such as ibuprofen, or prescription medications, such as naproxen, help reduce inflammation and relieve mild to moderate pain. For example, in people with osteoarthritis there was a relative change (RC) 34.3% (95%CI 32.6 to 36.0), using the visual analogue scale from 9 studies (n=1132) mean age 60.5 years (Stewart et al., 2018). The drugs studied in this example were naproxen, ibuprofen and diclofenac. The heterogeneity analysis

yielded non-significant results for all drug categories. The amount of variance due to heterogeneity was I^2=0% (Stewart et al., 2018).

- Opioids: Strong prescription medications, like morphine or oxycodone, are used for severe pain when other treatments are ineffective. Weak opioids can be purchased over the counter. For example, in people with osteoarthritis there was RC = 35.4% (95%CI 33.6 to 37.2), using the visual analogue scale from 4 studies with 11 treatment arms (n=1878) mean age 59.5 years (Stewart et al., 2018). The drugs studied were tramadol and oxycodone. The heterogeneity analysis yielded non-significant results for all drug categories. The amount of variance due to heterogeneity was I^2=0% (Stewart et al., 2018).
- Antidepressants: Certain antidepressant medications, such as amitriptyline or duloxetine, can help relieve neuropathic pain. A meta-analysis for duloxetine including 5 RCTS (n=1713) showed moderate benefits on pain function and quality of life in knee OA patients for up to 13 weeks (Osani and Bannuru, 2019). Results indicated an SMD=-0.38 (95%CI -0.46 to -0.24) there were minimal heterogeneity for all included studies (I^2= 5%). A meta-analysis of amitriptyline use in MSK pain found in 7 studies, one study with a low risk of bias indicated that amitriptyline reduced pain by 3.9 points on a VAS (0-10)when used to treat chronic low back pain in (n=200) mean age 41.5 ranging from 21 65 years(van den Driest et al., 2017).
- Anticonvulsants: Medications commonly used for focal seizures, such as gabapentin or pregabalin, can be effective in treating neuropathic pain (Joint Formulary Committee, 2020). Pregabalin showed superior results when compared with gabapentin using the VAS at intervals up to 14 weeks SMD= -0.47 (95%CI -0.74 to -0.19) in 9 studies (n=1848) I^2=87%, age range 32-61.9 years (Mayoral et al., 2025). Whilst the gabapentin group age range was 36-61.9 years. At 12 months, there were significant differences in favour of pregabalin

(SMD −1.44, 95% CI −2.82 to −0.07; participants = 141; studies = 1. I^2= 92%)(Mayoral et al., 2025).

- Nerve Blocks: Local anaesthetics or anti-inflammatory medications are injected near specific nerves to block pain signals and provide temporary relief. In a meta-analysis of basivertebral nerve ablation for chronic low back pain, 27 studies I^2=97.86%, showed a significant improvement in VAS at 6months = -3.37 (95%CI -4.11 to -2.63); 12 months = -3.27 (95%CI -4.28 to –2.26) and 24 months -3.82 (95%CI 4.31 to -3.34) (Mekhail et al., 2023)
- Epidural Steroid Injections: Steroids are injected into the space around the spinal cord to reduce inflammation and alleviate pain in conditions like herniated discs or spinal stenosis. A meta-analysis of epidural steroid injections in adults with low back pain showed a decrease in VAS mean difference (MD) = -1.16 (95%CI -2.04 to -0.28) using parasagittal intralaminar for short-term <6months. In the long term transforaminal MD =-0.37 (95%CI -1.14 to -0.32) was significant. Pooled studies showed I^2= 16.4% p=0.2876 (Helm Ii et al., 2021).
- Radiofrequency Ablation: A procedure in which heat generated by radiofrequency waves is used to selectively damage the axons of nerves that transmit pain signals, providing long-lasting pain relief. In a meta-analysis of 19 RCTs a MD -1.53 (95%CI -2.62 to 0.45) in short-term pain relief treatment to the sacroiliac joint and intervertebral discs MD=-0.98 (95%CI -1.84 to 0.12) I^2= 59%, but the placebo effect is large and effect size is small < 1, on a VAS 0-10 (Chappell et al., 2020).

Pharmacological treatment is the most common way that healthcare professionals treat pain, including over-the-counter medications and prescribed medications. The pain ladder system published by the World Health Organisation (WHO) has guided treatment, by indicating a graduated stepwise increase in pain treatment corresponding with

analgesic class (Ventafridda and Stjernsward, 1996). The pain ladder assumes that all pain has the same cause and that it can be treated with reference to underlying mechanisms.

The pain ladder has subsequently been simplified but encourages treatment of pain at the lowest effect step of the ladder, step 1 is non-opioid medications such as NSAIDs, step 2 is weak opioids, step 3 is minimal invasive intervention, and step 4 is strong opioids. The early overuse of opioids has been associated with poorer outcomes in low back pain (Lin et al., 2020a) and should be used with caution for a short duration (Kreiner et al., 2020). Despite the widespread use of opioids for people with chronic low back pain, there is doubt about their efficacy, possibly due to the lack of mechanistic information informing treatment (Shaheed et al., 2016). In a meta-analysis of 20 RCTS with 7925 participants only found moderate evidence of short-term (<3 months) pain relief (mean difference (MD) =-10.1 (95%CI -12.8 to -7.4) but the effect is not likely to be clinically important within guideline-recommended doses (Shaheed et al., 2016). Clinically meaningful pain relief was described as >20 points on at 0-100 pain rating scale (Dworkin et al., 2008). There was moderate evidence for medium-term (>3-12 months) pain relief (MD= -11.9 (95%CI -19.3 to -4.4)(Shaheed et al., 2016). However, there were no long-term (>12 month) outcome data (Shaheed et al., 2016, Chou et al., 2015).

The risks associated with pharmacological treatments has led to a proliferation of non-pharmacological methods, these take many forms.

1.2.12.3 Non-pharmacological

- Transcutaneous electrical nerve stimulation (TENS), a non-invasive low-voltage electrical current, temporarily relieves pain by interrupting nociceptive signals. This differs from the above interventional techniques in that it can be self-administered and thus controlled by the patient. There is some evidence supporting

the efficacy of TENS for both acute and chronic pain, although the level of effect is uncertain due to the low quality of the evidence

1.2.12.3.1 Physical therapy

- Exercise and or physical activity: Specific exercises and stretches can help improve strength, flexibility, and mobility, reducing pain in conditions like OA or MSK disorders and often represent the first line of therapeutic treatment for chronic pain. Pain may be reduced or eliminated following exercise interventions: chronic low back pain (Searle et al., 2015) and knee pain (Gohir et al., 2021). A meta-analysis and systematic review of 75 studies, including a wide range of modes of exercise (aerobic and strength), reported a significantly positive correlation between the analgesic effect of exercise and both duration (p=0.0059) and frequency (p=0.0053) (Polaski et al., 2019). The model developed estimated a significant pain effect of 0.743 standardised effect size. Of the 75 studies reviewed, all but six demonstrated a positive effect. There was a high risk of bias in over three-quarters of the studies due to a lack of blinding of the participants and researchers for self-assessment outcomes (Polaski et al., 2019). In these types of studies, it is difficult to quantify the exercise and its dosage, but in the systematic review, the available data indicated a positive effect from exercise.

  In a network analysis meta-analysis, comparing the effectiveness of exercise interventions showed the effects of exercise on pain mechanisms (Ibrahim et al., 2025). A reduction of post-exercise central sensitisation was observed SMD= -0.81 (95%CI -0.93 to -0.70). In combined exercises including stretching and strengthening, there was a reduction in central sensitisation of (SMD - −1.67, (95 % Credible Interval −2.41 to −0.97) and when combined with aerobic components this was SMD= -1.61, 95 % Credible Interval −2.74 to −0.56). This indicates that exercise can be used to reduce pain sensitivity.

- Manual Therapy: Techniques such as massage, joint mobilisation, or manipulation performed by a physical therapist can help alleviate pain, improve tissue mobility, and promote relaxation in knee pain (Pollard et al., 2008). Manual therapy covers a wide range of modalities from physiotherapy to massage. It has been shown to have some beneficial effects, but it is very difficult to quantify the dose because individual therapies are very variable. In a systematic review of the effects of manual therapy on MSK pain reported on 13 RCTs, a significant effect on pain pressure threshold (PPT) was found in 10 studies (Voogt et al., 2015). This review included 450 participants. Most researchers and participants were unblinded to the condition being studied. There was moderate evidence that manual therapy reduced PPT in participants with MSK pain immediately after treatment (Voogt et al., 2015). In eight studies, PPTs increased by >15%, which was regarded as a clinically important change. In three studies, there were no significant effects. Individual studies were contradictory, and no overall effect size was calculated. In one of the included studies, knee joint mobilisation for OA for 9 minutes (Moss et al., 2007). Moss and colleagues reported an increased mean PPT of 27.3% (95%CI 20.9 to 33.7), compared with manual contact 6.4% (95%CI 0.4 to 12.4) and no contact (-9.6% (95%CI -20.7 to 1.6), p=0.008. There was also an increase in a PPT measure taken at the distal non-painful heel (Moss et al., 2007). This showed that joint mobilisation may be effective in reducing OA pain.
- Heat or Cold Therapy: Applying heat packs or ice packs may provide temporary pain relief in back pain (French et al., 2006), and osteoarthritis (Jorge et al., 2017).

1.2.12.3.2 Alternative or complementary therapies

- Acupuncture: Thin needles are inserted at specific points on the body to stimulate nerves and relieve pain; back pain (Li et al., 2020b) Knee OA (Li et al., 2019). A systematic review and meta-analysis

showed 8 studies showed that when compared to a sham method such as TENS, a small to moderate effect size (Hopton and MacPherson, 2010). Pooled results showed a SMD= 0.13 (95%CI 0.01 to 0.24) for a knee pain review to 0.61 (95%CI 0.21 to 1.01) for a back pain review (Hopton and MacPherson, 2010). These effects appeared to be effective in the longer term (6-12 months). The reviews showed very low heterogeneity.

- Mind-Body Techniques: Practices like meditation, deep breathing exercises, or relaxation techniques can help reduce stress, manage pain perception, and improve overall well-being (Garland et al., 2020). A systematic review of 21 RCTs observed significant improvement of chronic pain (Vambheim et al., 2021). The large number of modes of treatment resulted in high heterogeneity and resulted in no overall conclusion regarding the effectiveness of treatment.
- Herbal Remedies and Topical Treatments: Some herbal supplements, such as turmeric, ginger, or capsaicin cream, may have pain-relieving properties (Gagnier et al., 2007). Some of these treatments are topical. Capsaicin (licensed version) was found to be effective for pain relief in OA effect size 0.32 (95%CI 0.24 to 0.39) when compared with placebo (Persson et al., 2018). A Cochrane review found that there was poor evidence in trials reporting on the effectiveness of herbal remedies on pain management (Gagnier et al., 2016). There were 14 RCTs with 2050 participants included in the review. They reported on capsaicin, white willow bark, Brazilian arnica, devil's claw and lavender essential oil and found they all seem to reduce pain more than a placebo.

1.2.12.3.3 Weight management

Obesity is associated with pain in many MSK conditions; therefore, frequent advice is given to patients to lose weight, which may reduce but not always eliminate pain. A meta-analysis of 3602 participants

indicated there was very low credibility evidence for a moderate effect of weight-loss interventions on pain intensity (10 trials, n = 1806; SMD, -0.54, (95%CI –0.86 to –0.22), I^2 = 87%, p<0.001 and a small effect on disability (11 trials, n = 1821; SMD, –0.32, (95%CI –0.49 to –0.14); I^2 = 58%, p<.001 compared to minimal care in people with OA. In knee OA there was low- to moderate-credibility evidence that weight-loss interventions were not more effective than exercise only for pain intensity and disability, respectively (4 trials, n = 673; SMD –0.13, (95%CI –0.40 to 0.14), I^2 = 55%; 5 trials, n = 737; SMD –0.20, (95%CI –0.41 to 0.00), I^2 = 32%) (Robson et al., 2020). Approximately 70% of adults with a long-term MSK condition are overweight or obese (Versus Arthritis, 2021). There is evidence that people who are obese have lower pain detection thresholds (McKendall and Haier, 1983). There are many factors associated with obesity, including nutrition, genetics, disability, eating behaviours, physical activity, sleep disorders, fear of pain, psychological conditions, socioeconomic position, medications and morbidities (Chin et al., 2020). Pain and obesity are complex conditions with overlapping aspects; they may have a reciprocal relationship (Chin et al., 2020). This complexity indicates that a multifaceted biopsychosocial approach might be required to tackle these conditions. Weight loss may be challenging for people with disabilities or low mobility due to chronic pain. The amount of support for people to lose weight can be variable, and the individual may struggle to find success.

1.2.12.3.4 Psychological approaches

There are different psychological approaches to managing pain; they are often grouped as CBT (Moseley and Butler, 2015). CBT interventions attempt to change the patients' cognitive beliefs about their pain, challenging negative thoughts and behaviours associated with pain, promoting healthier coping mechanisms, and reducing pain perception.

- CBT is frequently based on acceptance and rationalisation of the biological processes combined with understanding how an individual

can ‘take control.’ An example of a strategy is pacing, whereby an activity is broken into time chunks; thus, a task which may be impossible to complete becomes achievable (Jamieson-Lega et al., 2013, Stewart, 2018).

- Mindfulness-Based Stress Reduction (MBSR): Techniques that focus on being present in the moment, accepting pain without judgment, and reducing the emotional impact of pain.

A systematic review and meta-analysis of the association between psychological interventions and chronic pain outcomes in older adults included 22 studies with a total of 2608 participants (mean [SD] age 71.9 [7.1] of whom 1799 (69%) were women (Niknejad et al., 2018). They found modest heterogeneity, I^2 = 25.9% to 27.6%. The different ways of measuring and reporting pain change reduced the generation of an overarching effect, but they observed several outcomes: pain intensity was reduced by -0.181, p=0.006; catastrophising beliefs by 0.184, p=0.046; and self-efficacy for managing pain was increased by 0.193, p=0.02. A reduction in pain intensity was observed for up to 6 months. The results are encouraging, and more research is required to assess which components are important and for whom these treatments are most beneficial. The use of medications may be detrimental to the long-term health of individuals, whereas psychological therapies report few serious adverse events (Niknejad et al., 2018). The use of psychological therapies may make other treatments or pain management techniques more likely to be successful by encouraging the patient to adopt a positive mindset and reduce external stressors. A multimodal and multidisciplinary approach is likely to treat different aspects of pain and so may be more effective.

1.2.12.4 Surgical

Those with severe joint disease, such as OA, may receive total joint replacement (TJR) or arthroplasty, particularly for weight-bearing joints such as the knee and hip. TJR will resolve pain in some patients, but this

is not always the case (Larsen et al., 2021, Wylde et al., 2011). In 2021, the number of recorded joint replacements in England, Wales and Northern Ireland were as follows: hip 84,998 (90% OA, 5% trauma); knee 77,830 (97% OA); ankle 710 (92% OA, 7% Inflammatory conditions); shoulder 5,529 (61% OA, 15% trauma); elbow 760 (National Joint Registry, 2022).

1.2.13 Recommended clinical practice guidelines for managing MSK pain.

A systematic review of best practice for MSK pain identified 11 consistent recommendations for best practice from clinical practice guidelines (Lin et al., 2020a). Lin and colleagues (2020) recommend patient-centred care; screening of patients to identify serious pathologies; assessment of psychosocial factors; a reduction in unnecessary radiological imaging; a physical examination that may include neurological screening, assessments of mobility and muscle strength; evaluation of patients progress and outcome measures; providing patients with information and involving them in pain management; addressing physical activity guidelines; provide manual therapy only as an adjunct to other evidence-based treatments; offer evidence-informed non-surgical care pre-surgery; and continuation or resumption of employment.

1.2.14 Chronic Pain Management in Long-term Care

A Cochrane-style review of pain management in care homes found 42 trials that consisted of 26 non-pharmacological treatments, 8 educational interventions, 7 system modifications, 3 non-analgesic drug treatments, 2 analgesic treatments, and 9 combined interventions (Knopp-Sihota et al., 2022). The pooled results demonstrated that, except for non-analgesic drugs and health system modification interventions, all the interventions were at least moderately effective in reducing pain. Analgesic drugs were the most effective with an SMD

= -0.80 (95%CI -1.47 to -0.12), p=0.02 followed by non-drug alternative treatments such as exercise and acupressure SMD= -0.70 (95%CI -0.95 to -0.45), p<0.001, combined interventions SMD= -0.37 (95%CI -0.60 to -0.13), p=0.002, and educational interventions SMD= -0.31 (95%CI -0.48 to -0.15), p<0.001. In this, 0.2 represents a small effect, 0.5 represents a moderate effect, and 0.8 represents a large effect. The overall heterogeneity was I^2 = 60%, p<0.001, but there was a low to moderate effect of bias.

These findings indicate that there are a number of options available for pain management in older adults. Although pharmacological treatments were the most effective, other treatments were also effective when combined or alone. This suggests that effective pain management may adopt a number of modalities.

1.2.15 Pain summary

Overall, chronic pain is a complex and multi-faceted phenomenon that extends beyond the traditional understanding of pain as a simple response to noxious stimuli, and it is important to understand both its mechanisms and how these are moderated.

There is evidence suggesting that central sensitisation may maintain pain in patients, which is disproportionate to their pathology, and this may go some way to explain the chronic nature of MSK pain. This has implications for treating pain and understanding how this may relate to other conditions. Older people may experience more MSK pain due to central sensitisation following a lifetime of exposure (Bartley et al., 2016); this has implications for wellbeing and quality of life.

- Musculoskeletal conditions are common causes of chronic pain, affecting over a third of the UK population.
- Pain management involves intricate interactions between biological, psychological, and social factors, requiring a comprehensive and interdisciplinary approach to its study and management.

- The goal of chronic pain management is to improve pain control, enhance functioning, and enhance the overall quality of life for individuals with chronic pain. Whilst pain elimination is desirable, for many people, pain reduction might be acceptable.

1.3 Pain and frailty review

1.3.1 The association of pain with frailty

Several studies have identified an association between pain with frailty in populations from many countries using different frailty classification tools (Bindawas et al., 2018, Veronese et al., 2017b, Megale et al., 2018, Blyth et al., 2008, Rodríguez-Sánchez et al., 2019, Sodhi et al., 2019, Wade et al., 2017, Shega et al., 2012, İlhan et al., 2019, Misra et al., 2015).

Some studies have been conducted in specific patient populations, for example, rheumatoid arthritis (Salaffi et al., 2019); chronic widespread pain (CWP) (Wade et al., 2016, Livshits et al., 2018b); and HIV (Derry-Vick et al., 2022). Selected examples are shown below. I will first outline the findings from those who used a single frailty classification method. Then, outline those which employed multiple methods of frailty classification. It will then focus on OA-related pain.

1.3.1.1 Association of pain with Frailty Index

A UK cohort of people aged over 50 years (The English Longitudinal Study of Ageing) (ELSA) started recruiting in 2001 and has reported nine waves. Different waves have added topics, but the questionnaire is supported by a health visit in waves 2, 4, 6, 8, 9 and 11. The health visit permitted the collection of participant data such as body weight and height. The study used pain categorised as absent or present: mild, moderate, or severe, with a validated frailty index composed of 51 deficits (Rockwood et al., 2006). Data from waves 2 and 6 reported an association between pain and frailty severity in 5,316 participants. No pain was used as the reference, and in a fully adjusted model, they showed a significant longitudinal association of moderate pain with frailty (aOR 2.96, (95%CI 2.17 to 4.03), $p<0.001$) and severe pain with frailty (aOR 3.72, (95%CI 2.44 to 5.67), $p<0.001$) (Wade et al., 2017). Additionally, the same model showed an association of frailty with age,

depressive symptoms, physical activity, smoking, and socioeconomically disadvantaged groups. A strength of this study was that it included both sexes and a large cohort; many other studies are single-sex studies, which limits generalisability.

1.3.1.2 Association of pain with the Fried Phenotype

The Concord Health and Ageing in Men Project (CHAMP), an Australian cohort study, investigated the longitudinal relationship between pain and the Fried Phenotype (Megale et al., 2018). Chronic pain was indicated if present for ≥3 months, then the following question was used to assess whether pain intruded on their life, using the Short Form health questionnaire (SF-12) (Ware et al., 1996): 'During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?' At baseline, 1,705 participants were included; this fell to 1,332 at 2 years and 940 at 5 years. Loss to follow-up was mainly due to mortality. Results demonstrated that being pre-frail or frail did not significantly predict future chronic pain (Pre-frail: aOR 1.07, (95%CI 0.80 to 1.44), p = 0.649; Frail: aOR 0.82, (95%CI 0.38 to 1.79). p= 0.618 or intrusive pain (Pre-frail: OR 0.91, (95%CI 0.67 to 1.23), p = 0.551; Frail: OR 1.38, (95%CI 0.70 to 2.74), p = 0.356) at follow-up, compared to individuals classified as robust (Megale et al., 2018). However, they did show that chronic pain was associated with future frailty (aOR 1.60, (95%CI 1.02 to 2.51), p=0.039) but that intrusive pain was not associated with future frailty (aOR 1.64, (95%CI 0.97 to 2.78), p=0.063).

In earlier work with the same CHAMP cohort using cross-sectional baseline data (n=1705), utilising Fried Phenotype frailty classification. Blyth (2008) and colleagues found that intrusive pain was associated with frailty adjusted for age, comorbidity, qualifications, arthritis and depressed mood (Pre-frail: aOR 1.3, (95%CI 1.0 to1.8), p=0.038; Frail aOR 1.7, (95%CI 1.1 to 2.7), p=0.0149). The finding that adjusting for depressed mood, but not a history of arthritis, diminished the

association between frailty and intrusive pain indicated a key role for central mechanisms. The CHAMP is a single-sex cohort, which limits generalisability.

Lohman and colleagues describe pain as a marker of vulnerability and propose it as an additional criterion in frailty phenotyping (Lohman et al., 2017). The Health and Retirement Study cohort from the United States of America (USA) with 3,652 participants (56.5% female); frailty was classified using Fried Phenotype. Persistent pain was assessed based on frequency and intensity. Those recording moderate or severe pain 'most of the time' were classified as experiencing persistent pain. Lohman and colleagues compared a five-factor frailty phenotype with a six-factor frailty model that included pain as an extra factor. This was tested using latent class models with a two-class (frail/ non-frail model) and a three-class model (frail/prefrail/robust). Findings indicated that including pain in the model led to greater differentiation of frailty classification and improved prediction of incident adverse outcomes in the three-class model. Adverse outcomes included mortality, falls, hospitalisation, nursing home entry, and severe Activities of Daily Living (ADL) or Independent Activities of Daily Living (IADL) disability. This indicated that including the importance of recognising the pain and frailty relationship.

These studies use a categorical pain classification; using a continuous pain measure may provide evidence of a dose-response relationship between pain and frailty. If a dose-response relationship exists, then pain management in which pain is reduced may considerably reduce frailty risk. Whilst elimination of pain might be desirable, a reduction in pain may be acceptable (Georgopoulos et al., 2021).

Both the Fried Phenotype and Frailty Index were used in a Spanish prospective cohort of 1,505 (50% female) participants alongside a constructed pain scale which included pain frequency, intensity, number of sites and location (Rodríguez-Sánchez et al., 2019). At 3-year follow-

up, 67 individuals developed frailty using the Fried Phenotype and 141 using the Frailty Index. Pain was assessed using the Survey on Chronic Pain instrument and combined scores based on frequency, intensity, interference, and distribution. Pain intensity was measured on an NRS 0-10 ('no pain' to a pain 'I cannot imagine bearing'. The resultant scores were classified as follows: lowest (score 0), middle (score 1 to 4) and highest (score 5 to 6)

The association between pain status at baseline and risk of frailty classification (Fried Phenotype) at 3 years of follow-up aOR 1.24 (95%CI 0.56 to 2.75) in the middle range and aOR 2.39 (95%CI 1.34 to 4.27; P-trend <0.01) in the highest score. Contrastingly, the association between pain status at baseline and risk of frailty (Frailty Index) at 3 years of follow-up was aOR 1.39 (95%CI 0.80 to 2.42) and aOR 2.77 (95%CI 1.81 to 4.24; P-trend <0.01). A higher pain score was linked to a higher risk of exhaustion and low physical activity (two out of five Fried criteria) and to a worse score in all FI domains. Comparing two frailty classification tools within the same cohort provides valuable information to support findings. The IMH&W has two pain measures, the NRS and the McGill Pain Rating Index; they may provide support and increase confidence in my findings.

1.3.1.3 Association of FRAIL with pain

There is less evidence of the association frailty classified using FRAIL with pain. A Turkish cross-sectional study assessed 1,441 participants (67% female); the measures were administered at face-to-face medical outpatient appointments (İlhan et al., 2019). The dependent variable, pain intensity, was measured using an NRS 0-10 scale. Participants were asked to rate their pain intensity on a numeric scale between 0 (no pain) and 10 (unbearable pain). A secondary analysis showed that two variables, FRAIL and female sex, were associated with chronic pain (aOR 0.39, (95%CI 0.29 to 0.53), p<0.001) (aOR 0.41, (95%CI 0.30 to 0.57), p<0.001).

A study with 178 residents of nursing homes in Hong Kong assessed frailty using FRAIL and pain using an NRS 0-10 pain measure (in which 0 refers to no pain and 10 refers to the worst pain imaginable) (Tse et al., 2016). Findings showed no significant difference between the prevalence of pain and pain level with frailty status.

A further study by Yang and colleagues (2019) was reported in a systematic review (Lin et al., 2020b). This Chinese study is not reported in English; it used FRAIL with pain evaluation using Comprehensive Geriatric Assessment. This may use an NRS pain scale (0-10) or similar. Yang et.al reported an increased likelihood of frailty in people with chronic pain (aOR 1.57, (95%CI 1.03 to 2.40), p<0.001).

Utilising FRAIL in a self-report survey has benefits in scale and economy; research is required to identify if the pain-frailty association is observed in a UK cohort using this classification tool.

1.3.1.4 The association of OA-related pain with frailty.

Osteoarthritis is a very painful musculoskeletal condition, as described in Section 1.2.6.1. Pain is the main OA symptom, so several studies have investigated the association between OA and/or OA-related pain and frailty. A large American study focused on knee pain (Misra et al., 2015). Frailty was defined using The Study of Osteoporotic Fractures Index (SOF) (Ensrud et al., 2009) described in Section 1.1.5.5. Radiographic Osteoarthritis (ROA) was defined using a Kellgren and Lawrence radiographic score of ≥2 (Kellgren and Lawrence, 1957) Symptomatic Osteoarthritis (SOA) was defined as ROA and pain in at least one knee. This study included 3,707 participants (61% female), comparing those with OA and those without OA. Cross-sectional analyses demonstrated frailty was more prevalent among participants with ROA (4.39% vs 2.77%; Prevalence Ratio (PR) 1.60, (95%CI 1.07, 2.39) and SOA (5.88% vs 2.79%; PR 1.92, (95%CI 1. 35, 2.74)) compared with those without ROA or SOA, respectively. Longitudinal analyses indicated the risk of developing frailty was greater among those with ROA (4.73% vs 2.50%;

RR 1.45, (95%CI 0.91, 2.30)) and SOA (6.30% vs 2.83%; RR 1.66, (95%CI 1.11, 2.48)) than those without ROA or SOA, respectively. Knee pain and OA were associated with greater prevalence and incidence of frailty.

An Italian cohort study supported the findings of Misra and colleagues. Their study explored whether people with OA-related pain had an increased risk of becoming frail (Veronese et al., 2017b). The study included 1,775 participants (66% female), utilising the Fried Phenotype frailty classification and pain classified as present/absent. Medical professionals interviewed and examined participants, reviewing their medical history and radiograms. A rheumatologist confirmed OA diagnosis using a standardised algorithm. This study aimed to compare the incidence of frailty onset in participants with OA with pain and those with OA who did not report pain. In contrast to many frailty studies, Veronese and colleagues found a stronger association of OA-related pain with frailty in males (aOR = 2.65, (95%CI 1.94 to 3.61), p<0.001. In females, OA-related pain was not significantly associated with frailty.

In a fully adjusted cross-sectional model at baseline, they found OA-related pain at the following joints was associated with frailty: hand (aOR 1.86, (95%CI 1.65 to 2.09), p<0.001); hip (aOR 1.62, (95%CI 1.44 to 1.83), p<0.001) OA); and knee (aOR 1.42, (95%CI 1.26 to 1.60) p<0.001).

Longitudinal analyses (4.4 years) found that people classified as non-frail with lower limb OA pain were more likely to develop frailty than those with OA and without pain, independent of covariables.

OA is a common source of chronic pain, so finding an association with frailty is unsurprising. Some understanding of the mechanisms of knee pain exists (Section 1.2.11); therefore, it is possible that this knowledge can shed insight into the mechanisms underlying the pain-frailty association.

A longitudinal design from the USA studied 3,053 non-frail participants (55% female) and the association with OA knee pain (Bindawas et al.,

2018). Participants were grouped into no knee pain, unilateral and bilateral knee pain. Frailty was assessed over six years using the Fried Phenotype. Unilateral knee pain was associated with pre-frailty (aOR 1.14, (95%CI 1.01 to 1.27)) and frailty (aOR 2.21, 95% CI 1.63 to 3.01)) when compared to people with no knee pain.

1.3.1.5 Pain and frailty and bidirectionality

Evidence from individual studies suggests a bidirectional pain-frailty association This was analysed in the aforementioned CHAMP study (Megale et al., 2018). They did not observe a bidirectional association. However, they implemented a categorical pain classification, which may have reduced sensitivity. Employing a continuous pain scale with a large sample size may increase the understanding of the pain-frailty relationship.

1.3.1.6 Systematic reviews of the relationship between pain and frailty

Several systematic reviews have synthesised information across multiple studies to examine the pain-frailty association in the community. It should be noted that some individual studies are included in all the following systematic reviews.

According to one systematic review, the presence of chronic pain predicts frailty (Otones-Reyes et al., 2019). The review highlighted that chronic widespread pain, pain intensity, and pain interference are all contributing factors. This review included 23 studies, two of which did not find a pain-frailty association (Morais et al., 2017, Miguel et al., 2014).

Another systematic review and meta-analysis of prospective longitudinal studies identified that people with persistent pain were twice as likely to become frail during follow-up compared to people without pain (pooled RR 2.22, (95%CI 1.14 to 4.29), $p< 0.001$ (5 studies $I^2= 82.6\%$. This suggests that chronic pain may play a causal role in the development of frailty (Saraiva et al., 2018).

A systematic review and meta-analysis in 2020 aimed to estimate the prevalence of frailty and pre-frailty among older adults with chronic pain and review the longitudinal association between frailty status and chronic pain (Lin et al., 2020b). This included 24 studies (12 longitudinal). People with chronic pain were predicted to have an increased likelihood of developing frailty (OR 1.85, (95%CI 1.49 to 2.28) I^2=93.2%, p<0.001) after a mean follow-up time of 5.8 years.

In summary, the systematic reviews indicate a consensus that there is a positive association between chronic pain and frailty in cross-sectional and longitudinal studies using different measures of pain and frailty classification tools.

1.3.2 Interventions aimed at reducing pain in a frail population.

Three RCTs demonstrated a reduction in pain in a frail population. An 8-week non-pharmacological pain intervention trial. There were 2 arms, chair yoga, and a health education program. Participants were older women with lower limb OA (n=112) (Park et al., 2020). Pain was measured using the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Index, pain and pain interference, and frailty (measured using an 82-variable frailty index). The findings showed that each 0.01 increment of the Frailty Index was associated with higher WOMAC pain (β=0.28 SE=0.06, p<0.001) and pain interference (β=0.51, SE=0.12, p<0.001) at baseline.

There was no significantly greater decline in frailty for the chair yoga group compared to the health education group (between-group difference − 0.01; p = 0.509) and no significant trend changes in frailty (p for interaction = 0.605). Park and colleagues (2020) found a slight decrease in WOMAC pain in both groups and no substantial difference in rates of decrease. However, at a higher level of baseline frailty (baseline FI = 0.57 [P100]), they observed slight decreases in WOMAC pain in the yoga group but rapid increases in the health education

group, exhibiting obviously different changing patterns. There were similar findings for pain interference.

One Belgian study employed a patient-centred activity and community-orientated intervention delivered by Occupational Therapists (De Vriendt et al., 2016). Participants were aged ≥65 years, single, receiving healthcare support, Dutch speaking and having 1 of more functional problems in basic ADL operationalised by the BEL-profile scale. The latter is mandatory in the Flanders region and is used to identify frail older adults. The study utilised goal setting, a therapy plan, and the intervention aligning with the patient's perceived needs, including health education. Results demonstrated a statistically significant improvement in the basic ADL index (p=0.013) and the 'physical pain subscale' (p=0.049) in the intervention group. Nevertheless, these results are encouraging as the participants regarded as frail and had at least one indication of functional impairment. However, this study did not explore any improvement in frailty.

An earlier study in Finland examined the effect of an 8-month network-based rehabilitation intervention (Hinkka et al., 2007). Participants in the intervention group received three inpatient periods (21 days) and a home visit; controls received usual care. There were no differences in symptoms at one year between the intervention and control groups, but there was a subjective health improvement. Pain was measured using a VAS 0-100mm (Huskisson, 1974). At one year, there were no differences in symptoms between the groups (p=0.64). Subjective health was improved in the intervention group and impaired in the control group ($p < 0.01$). Mean (SD) pain in the intervention group was 42mm (27) at baseline and 38 (29), p=0.046. There was also a reduction in mean (SD) pain in the control group, but this was not statistically significant (p=0.21).

These studies varied in their effect on pain. However, all the studies indicate that pain reduction is possible in a frail population using non-

pharmacological interventions. The mechanisms involved in this intervention may address mechanisms that link pain and frailty. To date, no interventions have sought to reduce frailty by improving pain management.

1.3.3 Pain and frailty

Evidence suggests that there is an important and complicated relationship between pain and frailty. Therefore, it is crucial to understand the direction of possible causality to develop effective interventions.

Different stages of frailty may call for different approaches. For instance, while exercise can effectively enhance the functioning of individuals with frailty, it may not be suitable for those with severe frailty. If people with chronic pain are at a higher risk of frailty, it's crucial for healthcare providers, clinicians, and individuals to be aware of the risks and take necessary measures to reduce the chances of developing frailty. It may be more feasible to prevent frailty rather than reverse it. Therefore, early identification of individuals at risk of frailty and the implementation of interventions such as improved pain management could have a greater impact on long-term health.

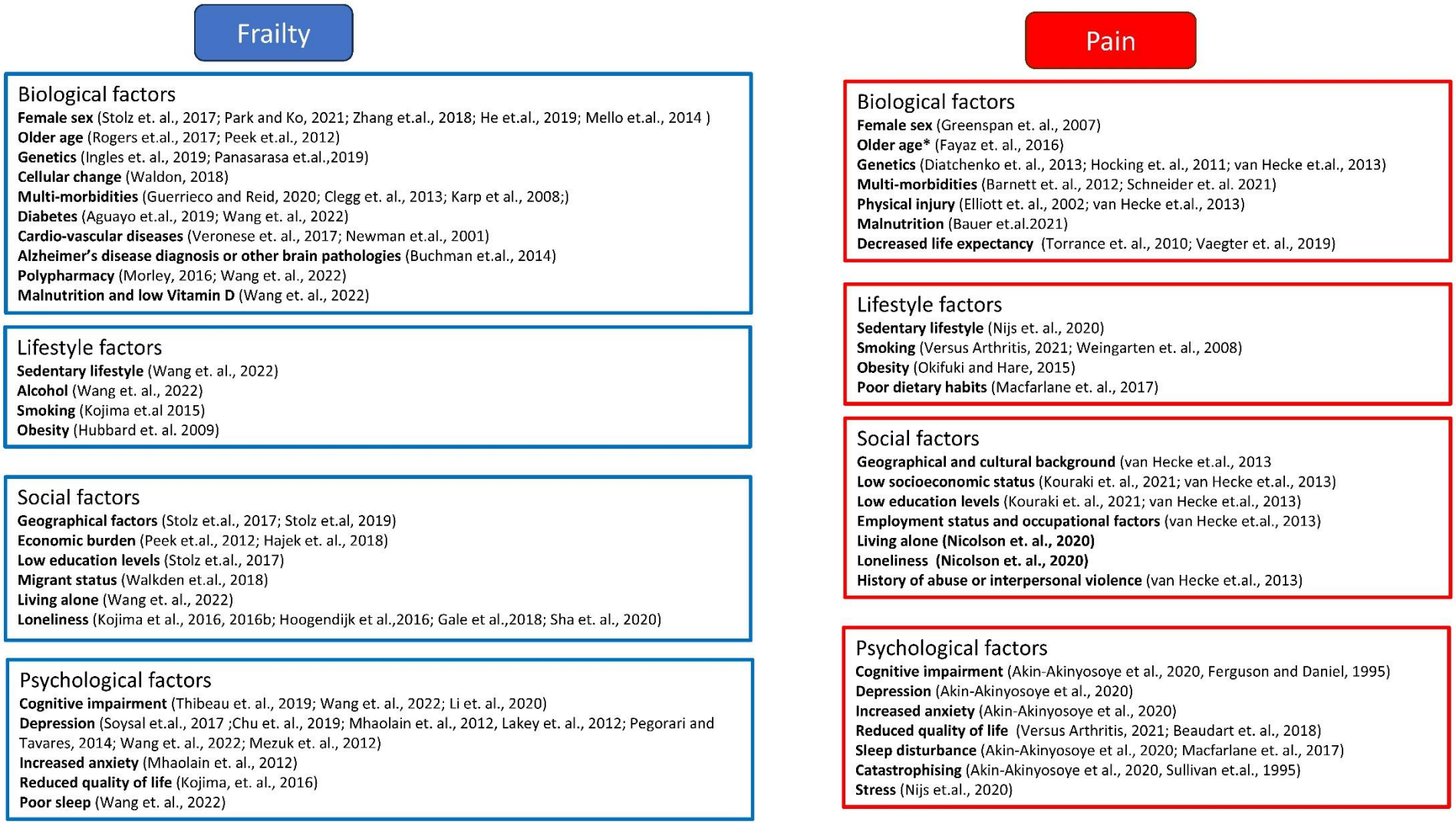
Physical activity is often limited or reduced in people who experience chronic pain (Ambrose and Golightly, 2015). Paradoxically, physical activity can improve pain management and reduce pain symptoms. This connection is relevant to frailty, as reduced physical activity can impact items directly measured in frailty assessments: FRAIL: resistance and ambulation; Fried Phenotype: gait speed and physical activity.

Regular physical activity is viewed as a significant tool for primary and secondary prevention of chronic health conditions, with the ability to mitigate symptoms and delay or prevent disease progression (Durstine et al., 2013, Centers for Disease Control and Prevention, 2023). This may

be related to morbidity and accumulated deficit items from the FRAIL and Frailty Index, respectively.

Fatigue is independently associated with chronic pain and frailty (Knoop et al., 2019, Ifesemen et al., 2022). It could be that fatigue explains the association between pain and frailty. All frailty classification tools include an element of fatigue or exhaustion. Fatigue has both physiological and psychological aspects. Pain and/or frailty may affect these aspects of fatigue. Understanding the complex relationship between pain and frailty is key to understanding the underlying mechanisms that explain this relationship.

There is evidence that pain can be altered and amplified by nociplastic mechanisms (Arendt-Nielsen et al., 2018b), which may be particularly important in people classified as frail (Brown et al., 2015). Traits associated with nociplastic pain are also factors that are associated with frailty, for example, depression (Soysal et al., 2017b, Chu et al., 2019, Mhaolain et al., 2012, Lakey et al., 2012, Pegorari and Tavares, 2014, Mezuk et al., 2012, Wang et al., 2022); increased anxiety (Mhaolain et al., 2012); and cognitive impairment (Li et al., 2020a, Wang et al., 2022). Mechanisms that make someone more vulnerable to homeostatic challenges in the form of frailty may be the same as those which increase their pain sensitivity. Understanding the mechanisms involved is important for understanding how future interventions, classification, or diagnostic tools could be utilised. Arguably, the interventions described previously (1.3.2) addressed factors that might be included in an intervention to reduce traits associated with nociplastic pain, which is promising as they are suitable for people with severe frailty.



N.B. There are some factors which will have effects across more than one category of risk factor

Figure 1-3 Risk factors associated with frailty classification or chronic pain.

1.3.4 Summary

- Chronic pain is associated with frailty, regardless of the frailty classification tool.
- Osteoarthritis (OA), a painful MSK condition, is associated with frailty.
- Systematic reviews and meta-analyses show that there is an increased risk of frailty in people living with chronic pain.
- There is limited evidence of interventions that target both pain and frailty.

1.4 Rationale/ justification for thesis

The relationship between chronic pain and frailty is complex. Chronic pain might make the transitions from non-frail to frail states more likely or make the transitions from frail to non-frail states less likely. Additionally, the presence of frailty may reduce the likelihood of pain improving. The current evidence implies that there could be a bidirectional relationship between pain and frailty, but most of the previous research has examined each direction separately. Statistical tools, such as cross-lagged path analysis, are available to address this question in the most efficient manner, accounting for multiple relationships within a single model.

Instruments for the classification of frailty, such as FRAIL, include a morbidity count and central aspects of pain. These items are also associated with chronic pain. Therefore, the association between pain with frailty might be attributable to morbidities or pain mechanisms. Furthermore, the CAP-knee questionnaire comprises eight single-question items that assess fatigue, anxiety, depression, sleep disturbance, neuropathic-like pain, cognitive impairment, catastrophising, and pain distribution. A high score from these items may indicate a dysfunctional pain system leading to pain sensitivity. Investigating whether there is an association between the CAP factor and frailty may provide insight into the relationship between pain and frailty. Other researchers have explored the association of the characteristics that are associated with CAP factor items individually, such as depression with frailty. However, it may be that examining the CAP factor (the combined score of all 8 items) may also reveal a dysfunctional response to stressors.

Unravelling the association between chronic pain and frailty would be helpful, for example, to justify whether improved pain management could prevent or delay the development of frailty. Conversely, to manage frailty and reduce pain. Understanding the association between these two common conditions may help develop interventions that help both conditions. This could save money if one intervention could have a dual effect. Preventing or delaying frailty may reduce the burden on health services and individuals.

Identifying modifiable items or factors involved in the association of pain with frailty is key to planning future interventions.

1.5 Aims and Objectives

The aims of this thesis are:

1. To examine cross-sectional and longitudinal associations of pain with frailty in a cohort study. To investigate whether there is a unidirectional or bidirectional relationship between pain and frailty.
2. To examine the extent to which the association of chronic pain with frailty might be attributed to morbidities.
3. To investigate whether Central Aspects of Pain explain the association between chronic pain and frailty.
4. To design the ACHING study, which aims to measure and assess the association of frailty with central pain mechanisms, alongside other potential causes of pain and pain severity in individuals with knee pain. This included preparation and training to collect some of the main physiological measures.

CHAPTER 2 GENERAL METHODS

In this chapter, I will describe the methods used to prepare and analyse the data used in this thesis.

2.1 Introduction to methods

The study data were obtained from the longitudinal self-report questionnaire using the Investigating Musculoskeletal Health and Wellbeing (IMH&W) cohort; protocol details are described elsewhere (Millar et al., 2020). Although I was not involved in the study's design or data acquisition, the IMH&W study team gave me access to the raw data from baseline and one year. This IMH&W fulfils the criteria for an observational study.

The IMH&W is a prospective questionnaire survey that collected self-report data from adults based in the East Midlands, UK. The survey was developed under the musculoskeletal theme of the National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre (BRC). It is designed to collect data about musculoskeletal pain, frailty, and disability to identify subgroups and their associations. The design and ethics permitted nested studies, which could use data already collected without the need for further ethical approval. Data collection started in May 2018, and baseline data for this thesis were extracted in July 2020.

The IMH&W applied and received a favourable ethical opinion from the Central London Research Ethics Committee (REC ref. 18/LO/0870) and the Health Research Authority (HRA) approval. All procedures were performed in accordance with the Declaration of Helsinki and followed the principles of Good Clinical Practice and the UK Policy Framework for Health and Social Care Research, 2018 (NHS Health Research Authority, 2020). The NIHR Biomedical Research Centre, Academic Rheumatology, University of Nottingham, maintains the IMH&W study database.

The IMH&W study team consisted of Mohammad Bashir, Louise Borg, Rhianne Bostock, Rebecca Boulton, Lauren Buchanan, Philip Buckley, Debra Campion, Rachel Chandler, Melanie Chrystal, Max Cook, Heather Cripps,

Eleanor Day, Alexander Dean, Helen Dobson, Natalie Draper, Catherine Dupont, Nadia Firth, Deri Fitzpatrick, Eoin Gormley, Tom Gray, Marya Habib, Alexander Howson, Nitasha Jumbu, Debbie Lee, Thomas Lott, Sean Mcloughlin, Bonnie Millar, Fozia Naushahi, Dilan Ozdemir, Megan Ridley, Jennifer Taylor, Nadezhda Velkova, David Walsh, and Naomi Watson. The individuals had various roles, including inputting the questionnaire, auditing, and managing the IMH&W.

This chapter describes how I conducted data cleaning, extraction, and analyses to build the database for subsequent studies. Any deviations from the methods in this chapter will be detailed within the individual chapters. Unless otherwise stated, my analyses were conducted using Stata software (Stata Statistical Software: Release 16, College Station, TX: StataCorp LP).

2.1.1 IMH&W Participants and recruitment

The study was conducted with data from adults who either had musculoskeletal problems or were at risk of developing them. The participants were recruited from primary and secondary healthcare sources, as well as those who had previously participated in Pain Centre studies and who agreed to be contacted for future research. To enrich the study, patients with frailty were invited via their General Practitioners (GPs); those with an electronic Frailty Index (eFI) score of ≥0.12 (considered the threshold for mild frailty) (Clegg et al., 2016).

Since 2017, GP practices have been required to use an appropriate tool, such as eFI, to help identify people over 65 years who may be frail. The eFI includes 36 deficits, including comorbidities, symptoms, activity/mobility restrictions, social vulnerability, and care requirements. The IMH&W study team approached GP practices from Nottinghamshire, Derbyshire, Lincolnshire, and Leicestershire through the Clinical Research Network (East Midlands). There were 108 GP practices that invited patients to participate, with a baseline questionnaire, a cover letter from their GP, alongside a consent form, participant information sheet (PIS) and pre-paid return envelope.

The Pain Centre also promoted studies through social media and its website, resulting in public enquiries to join research projects. In most cases, these individuals were eligible for enrolment in IMH&W. The recruitment routes are shown in Table 2-1.

Table 2-1 IMH&W Recruitment routes

Recruitment Source	Number invited	Number enrolled
GP database	34,058	6,217
Community clinics (primary care clinics)	1,414	119
King's Mill (secondary care clinic)	591	187
Previous studies	4,339	810
Posters		48
Others (including social media, Age UK, telephone queries.)		160
Total	40,402	7,541

Number invited = those who were sent a PIS/Consent form; Number enrolled = those who provided research data at the time of or after consent
Source: This data were provided by the IMH&W Team in November 2020.

2.1.1.1 IMH&W participant inclusion and exclusion criteria

The inclusion and exclusion criteria for the IMH&W cohort were as follows (Millar et al., 2020):

Inclusion criteria:

- age ≥18 years
- ability to provide informed consent.
- having or being at risk of developing frailty, MSK pain or disability.

Exclusion criteria

- those unable to understand written English.
- those with major non-MSK conditions which were likely to prevent follow-up and inclusion in nested studies, for example, receiving dialysis and/or home oxygen, diagnosis of terminal cancer, unstable angina, severe heart failure, serious mental illness, and dementia end-of-life care pathway.

2.1.2 Variables

In this thesis, the focus is on the relationship between frailty and pain. Age, sex, and BMI were considered as potential covariates that could affect this relationship. These variables are explained in detail below. Frailty was

considered the primary outcome variable, with pain as the predictor, with the covariates age, sex, and BMI class. Sometimes, the research used pain as the outcome variable and frailty as the predictor, and the covariates remained: age, sex, and BMI class. However, depending on the specific aims of each study, other predictors were also explored.

2.1.2.1 Classification of frailty in IMH&W

2.1.2.1.1 FRAIL

The data presented in this study pertain to the primary outcome measure of frailty as determined by FRAIL (Morley et al., 2012), which employs five self-report items:

Fatigue, defined as feeling tired all or most of the time in the last four weeks = 1, utilising a 5-point Likert scale.

Resistance, defined as the ability to climb up ten steps without aids or assistance, was scored as 0: no or 1: yes.

Ambulation, defined as whether the participant has difficulty walking several hundred yards without aids or assistance, scored as 0: no or 1: yes.

Illness counts were determined based on self-report using a checklist of diagnoses with the question, 'has a doctor told you that you have any of these conditions or problems': angina, arthritis, asthma, cancer (not minor skin), chronic lung disease, congestive heart failure, diabetes, heart attack, hypertension, kidney disease, and stroke.

Loss of weight at baseline was calculated in response to two questions first, [weight 1-year ago]: 'one year ago how much did you weigh without shoes but with your clothes on?' and second [current weight] 'how much do you weigh with your clothes on but without shoes?' Percentage weight change was calculated as [(weight 1-year ago – current weight)/ weight 1-year ago] x 100. Scored <5% = 0, ≥5% in a year =1.

At follow-up, Loss of weight was calculated using the 'current weight' reported at baseline as the 'weight 1-year ago'.

The FRAIL criteria item scores were totalled (0-5) and classified into three ordinal categories based on these values: robust (0), prefrail (1-2) or frail (3-5). The current study combined robust and prefrail groups to give a non-frail category. The two-class model has been examined in other studies (Gardiner et al., 2015, Ge et al., 2019). The latter compared the cut-offs with Frailty Index using receiver operating characteristic (ROC) curves analysis.

2.1.2.1.2 Frail in Non-Disabled Questionnaire (FiND)

The IMH&W included a secondary frailty classification; the Frail in Non-Disabled Questionnaire (FiND) Questionnaire was designed to screen people who were frail in the absence of mobility disability (Cesari et al., 2014). This was used as a secondary outcome measure of frailty. FiND is a self-report questionnaire with five components described in the second column of Table 2-2. FiND uses measures similar to FRAIL (third column) and asks about the level of physical activity. Physical activity was defined as either regular (at least 2-4 hours per week) or none/sedentary. The FiND Questionnaire was not replicated verbatim; a modified FiND score was created as some FiND components were similar to those used for FRAIL items. However, the wording used in the IMH&W questions was as described for FRAIL when the two questions were similar. The exceptions were component C, which was calculated in accordance with FiND, and component E, which was included in its entirety in the IMH&W questionnaire.

FiND components A and B used FRAIL resistance and ambulation items; however, the scoring could be viewed differently as FRAIL scores for 'any' difficulty whilst FiND scores for 'a lot or unable.' Component D was substituted with FRAIL fatigue; although these questions may have overlapping concepts, they were not the same. Therefore, only two of the five components were identical to the FiND methodology. The classification was described as modified FiND (mFiND). FiND classifies any participant scoring 1 in either Item A or B as disabled. The remainder were then categorised, with anyone scoring 1 in Items C, D or E classified as frail. Participants whose score equals 0 in all items were classified as robust.

Table 2-2 indicates the wording used in FiND and FRAIL and the question as it appeared in IMH&W. FiND classifies participants as disabled, robust, or frail.

Table 2-2 Comparison of original FiND components with FRAIL items and IMH&W questions with scoring.

FiND component	FiND component	FRAIL item	IMH&W question
A	Resistance is defined as difficulty climbing a flight of stairs (a lot or unable = 1, some or none = 0).	**R**esistance: By yourself and not using aids, do you have any difficulty walking up 10 steps without resting? Yes = 1 No = 0	Resistance: By yourself and not using aids, do you have any difficulty walking up 10 steps without resting? Yes = 1 No = 0
B	Ambulation is defined as having difficulty walking 400 meters (a lot or unable = 1, some or none = 0)	**A**mbulation: By yourself and not using aids, do you have any difficulty walking several hundred yards? Yes = 1 No = 0	By yourself and not using aids, do you have any difficulty walking several hundred yards? Yes = 1 No = 0
C	Weight loss defined as involuntary weight loss >4.5 kg (yes = 1)	**L**oss of Weight ≥5% = 1 Calculated using (weight 1 year ago – weight at baseline)/ weight 1 year ago) x100	It is calculated using weight 1 year ago and weight at baseline.
D	Fatigue is defined as how often in the previous week participants felt everything was an effort or they could not get going (often or almost always, >3 a week = 1)	**F**atigue: How much of the time during the past 4 weeks did you feel tired? All of the time =1 Most of the time =1 Some of the time =0 A little of the time =0 None of the time =0	How much of the time during the past 4 weeks did you feel tired? All of the time =1 Most of the time =1 Some of the time =0 A little of the time =0 None of the time =0
E	Physical activity level is defined as regular, 2-4 hours per week = 0, and none or sedentary = 1.	Not included in FRAIL	Which is your level of physical activity? Regular activity at least 2-4 hours per week = 0; None or mainly sedentary = 1
	Not included in FiND.	Illnesses: ≥5/11 specified illnesses	A checklist of 11 conditions was reproduced.

2.1.2.2 Measures of pain in IMH&W

IMH&W used two different pain measures. The majority of chapters use NRS pain as the primary pain measure.

2.1.2.2.1 Numerical rating scale chronic joint pain intensity

Joint pain intensity was measured using a numerical rating scale (NRS). The NRS pain baseline was scored using the 11-point segmented visual analogue scale (McCaffery and Pasero, 1999); participants were asked :
"Over the past 4 weeks, how intense was your average pain or the average aching feeling in your most bothersome joint, where 0 is 'no pain', and 10 is 'pain as bad as it could be'?" (Millar et al., 2020)

NRS pain has been used extensively and is reliable for use with chronic pain and in older populations. (British Pain Society, 2019, Hawker et al., 2011,

Rodriguez, 2001). Clinical trials have previously indicated that a change in NRS pain of 2 points or 30% has clinical importance (Farrar et al., 2001).

2.1.2.2.2 McGill Pain Rating Index

The NRS pain measure described above is employed as a joint-specific measure. In contrast, the Pain Rating Index (PRI) from the McGill Pain Questionnaire (MPQ) is more representative of the subjective generalised pain experience (Melzack, 1975, Melzack and Torgerson, 1971). This multi-dimensional pain instrument comprises 78 pain descriptors in 20 sets of words, which categorise pain into a common intensity dimension; a higher score indicates more intense pain (Melzack, 1975). The descriptor rank value was based on the word position within each set. The Pain Rating Index equals the sum of the descriptor rank values, ranging from 1-78. Only one word may be ticked per set; if no words were selected, a zero score was allocated. Although a score of 0 is normally considered valid, it was unclear in the IMH&W survey whether the participant intended to make no response or had omitted the question, so total equalling zero values were treated as missing. The word lists are shown in Figure 2-2 Section C.

The descriptor words are divided into four subs-classes:

- sensory (sets 1-10 score range 0-42).
- affective (sets 11-15 score range 0-14).
- evaluative (set 16 score range 0-5).
- miscellaneous (sets 17-20 score range 0-17).

The Number of Words Chosen (NWC) is counted; this ranges from 0 to 20 and represents the number of sets selected. NWC has been shown to be a valid alternative to PRI (Melzack, 1975). The MPQ has been used extensively in the research of acute and chronic pain due to its high reliability and validity. A meta-analysis concluded that normative scores PRI across painful conditions range from 24 to 50% of the maximum scores (Wilkie et al., 1990).

Melzack and colleagues demonstrated that different pain conditions are represented with different words or descriptors, represented by four-sub

classes. Additionally, Wilkie and colleagues proposed in a meta-analysis of PRI that identifying words which were chosen by >20% of participants typified pain in that condition. PRI is thought to vary between pain conditions (Katz, 2011), and the scale can be used for both chronic and acute pain conditions. MPQ's psychometric properties have been assessed in different patient groups, for example, arthritis (Burckhardt, 1984). They found that sensory words, including 'aching,' were the most used sensory descriptors.

Advantages and Disadvantages of using the MPQ

The MPQ pain variable is used for acute and chronic pain. The 20-word lists are time-consuming to complete compared to the NRS (Hawker et al., 2011, Wilkie et al., 1990). Some lists can be omitted, which makes it difficult to know if this was intentional or accidental. The word lists are of differing lengths, so each subscale of MPQ seems likely to have different measurement properties; for example, word list 1 contains six words, and word list 2 contains two words. This is further extended to the four dimensions, as sensory has 10-word lists, affective has 5-word lists, evaluative has just one list, and miscellaneous has 4-word lists. Three of the domains appear to have closely grouped words. However, the miscellaneous includes a wide range of descriptors (for example, piercing, numb, cool, and nagging) which cover disparate pain qualities. Each subscale of MPQ seems likely to have different measurement properties/metrics. The groupings may be shaped by the beliefs and biases of MPQ's creators and could have influenced the scale.

The MPQ is usually accompanied by a present pain index similar to the NRS pain. However, this index was not included in this case, as it may include acute pain. The MPQ has been criticised as lacking specificity in evaluating the symptoms of neuropathic pain (Bouhassira et al., 2004).

A newer short-form of the MPQ seeks to incorporate present pain intensity alongside 15 pain descriptors (11 sensory and 4 affective) (Melzack, 1987, Katz, 2011). The short form has been used to evaluate responsiveness to treatment (Hawker et al., 2011, Lovejoy et al., 2012). This may have overcome some limitations of the long form, but the descriptors are still unevenly

grouped. The PRI is viewed as a measure of pain intensity. However, a scale of 0 to 78 is difficult to interpret intuitively.

2.1.3 Central Aspects of Pain in the Knee (CAP-Knee)

Pain hypersensitivity may be a response to high-intensity or prolonged exposure to pain and/or multi-site pain. Persistent nociceptive input drives central neural changes within the spinal cord and brain, subsequently amplifying the pain experience (Arendt-Nielsen et al., 2010). Simultaneously, the inhibitory system, which dampens pain sensation, also becomes dysfunctional, and there is a decrease in the inhibition (Arendt-Nielsen et al., 2010). The overall result is that a person with a dysfunctional pain system experiences a higher sensitivity to painful stimuli. While acute pain helps us identify and avoid potential harm and limits the use of an injured limb during healing, chronic pain may be viewed as maladaptive (Walters, 2019).

Central aspects of pain have been associated with fatigue (Lazaridou et al., 2018, Fawole et al., 2021), sleep disturbance (Campbell et al., 2015, Song et al., 2022), anxiety (López-Ruiz et al., 2019, Shigetoh et al., 2019) depression (Shigetoh et al., 2019), cognitive impairment (Rodríguez-Andreu et al., 2009), catastrophising (Shigetoh et al., 2019, Meints et al., 2019, Campbell et al., 2015), neuropathic-like pain (Hochman et al., 2011, Hochman et al., 2013, Moss et al., 2018, Blikman et al., 2018), and widespread pain distribution (Latremoliere and Woolf, 2009). These eight characteristics have been incorporated into the Central Aspects of Pain in Knee (CAP-knee) questionnaire (Akin-Akinyosoye et al., 2021, Akin-Akinyosoye et al., 2020). The CAP scores have been shown to have a shared factor referred to as CAP factor (CAPf); previously, this was referred to as the Central Mechanism Trait (CMT) (Akin-Akinyosoye et al., 2020). CAPf has a stronger association Pain Pressure Threshold (PPT) (which is believed to be an index of central pain hypersensitivity) than any of the individual characteristics. Thus, it is suggestive that a high CAP score may be indicative of a dysfunctional pain system. The eight items have overlapping characteristics affecting pain, mood, and cognition (Akin-Akinyosoye et al., 2021, Akin-Akinyosoye et al.,

2018b). High CAPf is associated with worse knee pain and predicts worse outcomes (Akin-Akinyosoye et al., 2020).

The CAP-knee questionnaire is shown in Figure 2-1 ,alongside the scoring. The first seven questions are based on a 4-point Likert scale. They address a single item each: neuropathic-like pain, fatigue, cognitive impairment, catastrophising, anxiety, sleep disturbance, and depression. Finally, pain distribution is mapped using a manikin in which participants shade any area in which they have experienced pain in the last 4 weeks.

Following Rasch analysis, the scoring was adjusted (Akin-Akinyosoye et al., 2020), with two categories condensed, and both scored as 2. The CAP-Knee items (questions 1-6) were scored as never = 0, sometimes =1, and always or often =2. The depression item (question 7) was reverse coded, and the categories were annotated as follows: never or sometimes =2, often =1 and always = 0. The manikin is scored 2 if the shaded area is both (i) any knee region and (ii) any other site below the waist. Score = 0 if shaded areas on the manikin do not include both (i) any knee region and (ii) any other site below the waist. Please note this is the original scoring scheme; following Rasch analysis, a revised scoring method was adopted.

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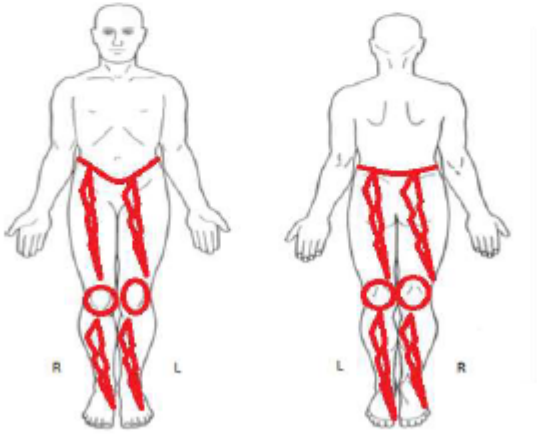
CAP-Knee (Central Aspects of Pain in the Knee) Scale – Scoring sheet

Name: _____ Date: _____

Please select the response that best describes how you have felt over the PAST *WEEK*. Please tick one box only per statement and try not to leave any statements blank.

	Never	Sometimes	Often	Always
1. Cold or heat touching my knee was painful	☐ 0	☐ 1	☐ 2	☐ 3
2. I generally felt tired	☐ 0	☐ 1	☐ 2	☐ 3
3. Knee pain stopped me concentrating on what I was doing	☐ 0	☐ 1	☐ 2	☐ 3
4. I kept thinking about how much my knee hurts	☐ 0	☐ 1	☐ 2	☐ 3
5. In general, I got sudden feelings of panic	☐ 0	☐ 1	☐ 2	☐ 3
6. Knee pain affected my sleep	☐ 0	☐ 1	☐ 2	☐ 3
7. I generally still enjoyed the things I used to enjoy	☐ 3	☐ 2	☐ 1	☐ 0

8. This final question is about pain you may have had in any part of your body. Please shade in the diagram below, to indicate where you have suffered any pain for most days in the last ***4 WEEKS***. By pain we also mean aching and/or discomfort. Please do not include pain due to feverish illness such as flu.



- Score of '3' if shaded areas on manikin includes both (i) any knee region, and (ii) any other another site below waist.
- Score of '0' if shaded areas on manikin does not include both (i) any knee region, and (ii) any other another site below waist.

Person ID: ☐☐☐

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Figure 2-1 CAP-knee scoring sheet

2.1.4 Covariables

The covariables of age, sex and BMI were selected *a priori* due to previously observed association with frailty and pain, as described in Chapter 1.

In all multivariable analyses, age (years), sex (male/female), and body mass index class (BMI) (underweight/normal/pre-obese/obese) were taken into consideration.

Age (years), sex (male/female), weight (kg), and height (m) were obtained from self-report questionnaires, from which BMI (kg/m2) was calculated. The categorisation criteria are described in Section 2.2.5.

Age was treated as categorical because although frailty is regarded as age-associated, the age of 80 years is frequently suggested as a threshold for higher rates of frailty (O'Caoimh et al., 2018). Rather than simply having a binary of under or over 80 years, I subdivided the <80 into decades and merged the over 80's.

I calculated BMI (kg/m2) using weight (kg) and height (m) obtained from self-report data. I treated BMI as a categorical variable because both underweight and obese might be associated with frailty and may exclude a simple linear association between frailty and BMI. The BMI was classified using the World Health Organisation (World Health Organization, 2021) categories: underweight <18.5; normal weight 18.5-24.9; pre-obesity 25.0-29.9; and obese. The sub-categories of obese were collapsed into a single 'obese' category of BMI>30 for clarity.

2.1.5 Data Sources and management

Data were from the IMH&W study questionnaire; this thesis uses data from baseline and 1-year follow-up. At the time of screening in February 2020, there were 7,074 participants who had completed baseline IMH&W questionnaires. The inclusion criteria for my study were as follows:

- completion of the five questions required for the FRAIL questionnaire. Specifically, Section A: questions 5 & 6, 9, Section D: questions 2, 3 & 5. The questionnaire is shown in Figure 2-2.
- All data were entered, cleaned, and signed off as valid by the IMH&W study team.
- aged ≥60 years.

The IMH&W included adults of all ages. However, frailty is often linked to old age, and previous studies have used different age thresholds. The FRAIL assessment tool is validated for individuals aged >40 years (Ravindrarajah et al., 2013). For my study, I decided to include data for participants 60 years and older because frailty is defined as age-related. Although people under this age may have frailty, I could not be certain that they did not have an underlying condition with similar functional impairments. This uncertainty may also exist for some participants aged ≥60, but this was less likely.

2.1.6 IMH&W questionnaire patient-reported outcome measures.

The IMH&W questionnaire includes multiple patient-reported outcome measures (PROMs). The IMH&W questionnaire has four sections; the entire questionnaire is shown in Figures 2-2 to 2-7.

Section A - demographic information including age, sex, ethnicity, height, weight currently and one year ago, smoking status, and alcohol consumption. Checklist selection of 18 medical conditions (11 from FRAIL (Morley et al., 2012), and a free-text box to capture additional medical conditions. Additionally, a free-text box to list medications, both prescription and over the counter.

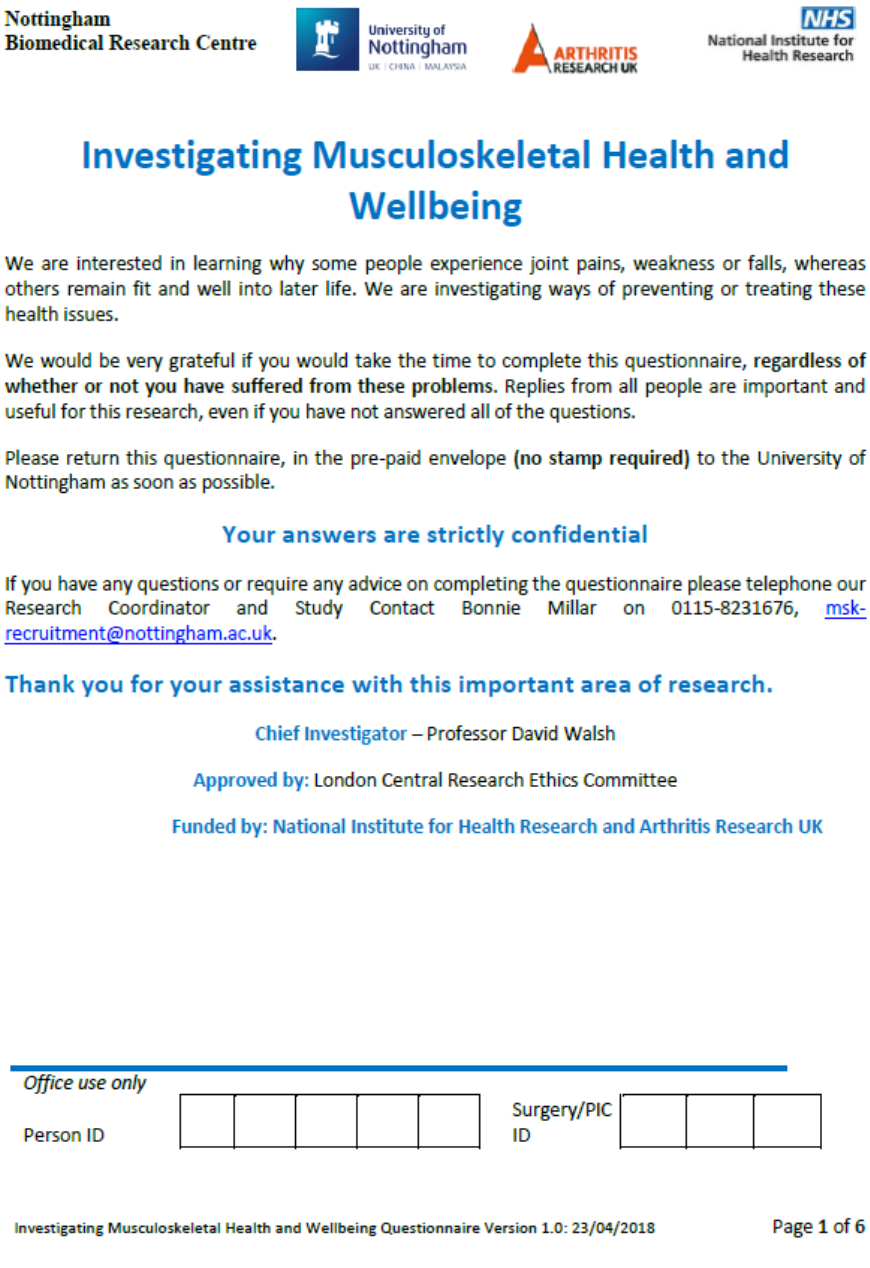
Section B –includes the CAP-Knee Questionnaire (Akin-Akinyosoye et al., 2021). This is described in Section 2.1.3.

Section C –pain questions: the presence of joint pain over the last 4 weeks; checklists selecting the most bothersome joint, 11-point Numeric Pain Rating Scale (NRS) average joint pain over 4 weeks (Ferreira-Valente et al., 2011).

Whether the most bothersome joint was painful or aching for most days of the last 4 weeks. The McGill Pain Questionnaire (MPQ) (Melzack, 1975, Melzack and Torgerson, 1971).

Section D –activities and general health: the amount of regular physical activity (at least 2-4 hours per week) or none/ mainly sedentary from the FiND questionnaire (Cesari et al., 2014). FRAIL Fatigue, Ambulation and Resistance items (Morley et al., 2012).

In summary, the IMH&W baseline questionnaire collected participant data on demographics, medical conditions, medications, Central Aspects of Pain in the Knee questionnaire (Akin-Akinyosoye et al., 2021). Information on joint aches and pains, and information on activities and general health, and the FRAIL questionnaire items (Morley et al., 2012).



Nottingham Biomedical Research Centre

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ARTHRITIS RESEARCH UK

NHS National Institute for Health Research

Investigating Musculoskeletal Health and Wellbeing

We are interested in learning why some people experience joint pains, weakness or falls, whereas others remain fit and well into later life. We are investigating ways of preventing or treating these health issues.

We would be very grateful if you would take the time to complete this questionnaire, **regardless of whether or not you have suffered from these problems**. Replies from all people are important and useful for this research, even if you have not answered all of the questions.

Please return this questionnaire, in the pre-paid envelope **(no stamp required)** to the University of Nottingham as soon as possible.

Your answers are strictly confidential

If you have any questions or require any advice on completing the questionnaire please telephone our Research Coordinator and Study Contact Bonnie Millar on 0115-8231676, msk-recruitment@nottingham.ac.uk.

Thank you for your assistance with this important area of research.

Chief Investigator – Professor David Walsh

Approved by: London Central Research Ethics Committee

Funded by: National Institute for Health Research and Arthritis Research UK

Office use only

Person ID | | | | | |

Surgery/PIC ID | | | |

Investigating Musculoskeletal Health and Wellbeing Questionnaire Version 1.0: 23/04/2018

Page 1 of 6

Figure 2-2 IMH&W Baseline Questionnaire page 1/6.

Section A: Information about you and your treatments

A1 What is your **date of birth**?

☐☐ Day ☐☐ Month ☐☐☐☐ Year

A2 What is your **sex**?

☐ Male ☐ Female ☐ Prefer not to say

A3 Choose one option that best describes your **ethnic group** or **background?**

☐ White ☐ Asian ☐ Black

Any other ethnic group (please describe)

A4 What is your **height**?

☐ Feet ☐☐ inches **OR** ☐☐☐ centimetres

A5 How much do you **weigh** with your clothes on but without shoes?

☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

A6 **One year ago** how much did you **weigh** without shoes but with your clothes on?

☐☐ stones ☐☐ pounds **OR** ☐☐☐ kilograms

A7 What is your **smoking** status?

☐ Smoker ☐ Ex-smoker **OR** ☐ Never smoked

A8 Do you drink usually 3 units or more of **alcohol** per day?
3 units might, for example, be 2 pints of lager, 2 glasses of wine or 3 single shots of spirit.

☐ Yes ☐ No

Figure 2-3 IMH&W Baseline Questionnaire page 2/6.

A9 **Has a doctor told you that you have any of these medical conditions or problems? If yes, please place a tick in the boxes provided.**

☐	Angina	☐	Heart attack
☐	Arthritis	☐	Heart failure
☐	Asthma	☐	Hypertension
☐	Back or spine problems	☐	Kidney disease
☐	Cancer (not minor skin cancers)	☐	Lung disease
☐	Dementia	☐	Osteoarthritis
☐	Diabetes mellitus	☐	Osteoporosis
☐	Fibromyalgia	☐	Rheumatoid arthritis
☐	Gout	☐	Stroke

Others (please specify any conditions not listed above)

A10 **Medicines including pain killers**
Please write down the names of any medications, including any pain killers, that you use. They can be prescriptions or bought over the counter.

Names of medications

Figure 2-4 IMH&W Baseline Questionnaire page 3/6.

Section B: CAP-Knee (Central Aspects of Pain in Knee) Scale

Please select the response that best describes how you have felt over the PAST *WEEK*. Please tick one box only per statement and try not to leave any statements blank.

	Never	Sometimes	Often	Always
1. Cold or heat (e.g. bath water) on my knee was painful	☐	☐	☐	☐
2. I generally felt tired	☐	☐	☐	☐
3. Knee pain stopped me concentrating on what I was doing	☐	☐	☐	☐
4. I kept thinking about how much my knee hurts	☐	☐	☐	☐
5. In general, I got sudden feelings of panic	☐	☐	☐	☐
6. Knee pain affected my sleep	☐	☐	☐	☐
7. I generally still enjoyed the things I used to enjoy	☐	☐	☐	☐

8. This final question is about pain you may have had in any part of your body. Please shade in the diagram below, to indicate where you have suffered any pain for most days in the last ***4 WEEKS***. By pain we also mean aching and/or discomfort. Please do not include pain due to feverish illness such as flu.

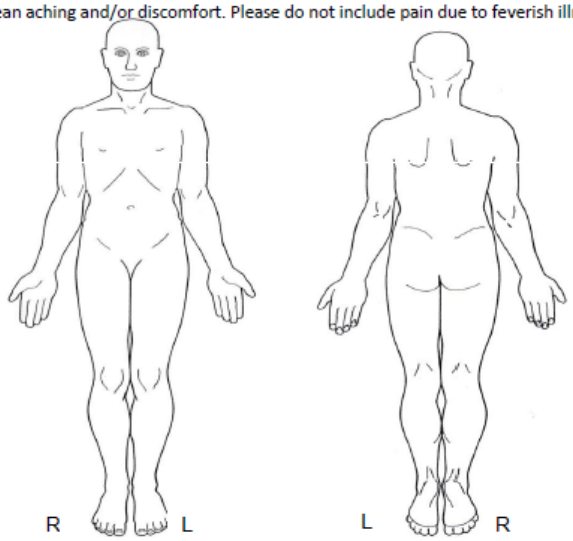


Figure 2-5 IMH&W Baseline Questionnaire page 4/6.

Section C: Joint Aches and Pains

C1. Over the **past 4 weeks**, have you had **pain** or **aching** in **any of your joints**?

☐ Yes ☐ No If you answer 'No', please move to section D.

Most bothersome joint

C 2. Over the **past 4 weeks**, where was your most bothersome joint pain or aching feeling? (Pick **one**)

☐ Jaw	☐ Wrist	☐ Neck
☐ Back or spine	☐ Knee	☐ Ankle
☐ Shoulder	☐ Hand or finger	☐ Foot or toe
☐ Elbow	☐ Hip	

C 3. Over the **past 4 weeks**, how intense was your **average pain** or the **average aching feeling in your most bothersome joint**, where 0 is 'no pain' and 10 is 'pain as bad as could be'?

No pain — Pain as bad as could be

0	1	2	3	4	5	6	7	8	9	10

C 4. Was your **most bothersome joint** painful for **most days** of the last **4 weeks**?

☐ Yes ☐ No

C 5. What does your pain **feel** like? Tick those words that best describe it. Leave out any category that is not suitable. Use only **one** word in each category.

1	2	3	4	5	6	7
☐ Flickering	☐ Jumping	☐ Pricking	☐ Sharp	☐ Pinching	☐ Tugging	☐ Hot
☐ Quivering	☐ Flashing	☐ Boring	☐ Cutting	☐ Pressing	☐ Pulling	☐ Burning
☐ Pulsing	☐ Shooting	☐ Drilling	☐ Lacerating	☐ Gnawing	☐ Wrenching	☐ Scalding
☐ Throbbing		☐ Stabbing		☐ Cramping		☐ Searing
☐ Beating		☐ Lancinating		☐ Crushing		
☐ Pounding						

8	9	10	11	12	13	14
☐ Tingling	☐ Dull	☐ Tender	☐ Tiring	☐ Sickening	☐ Fearful	☐ Punishing
☐ Itchy	☐ Sore	☐ Taut	☐ Exhausting	☐ Suffocating	☐ Frightful	☐ Grueling
☐ Smarting	☐ Hurting	☐ Rasping			☐ Terrifying	☐ Cruel
☐ Stinging	☐ Aching	☐ Splitting				☐ Vicious
	☐ Heavy					☐ Killing

Figure 2-6 IMH&W Baseline Questionnaire page 5/6.

15	16	17	18	19	20
☐ Wretched	☐ Annoying	☐ Spreading	☐ Tight	☐ Cool	☐ Nagging
☐ Blinding	☐ Troublesome	☐ Radiating	☐ Numb	☐ Cold	☐ Nauseating
	☐ Miserable	☐ Penetrating	☐ Drawing	☐ Freezing	☐ Agonizing
	☐ Intense	☐ Piercing	☐ Squeezing		☐ Dreadful
	☐ Unbearable		☐ Tearing		☐ Torturing

C 6. Any other comments?

Section D: Your activities and general health

D 1. Which is your level of physical activity?

☐ Regular physical activity (at least 2-4 hours per week) ☐ None or mainly sedentary

D 2. By yourself and not using aids, do you have any difficulty walking several hundred yards?

☐ Yes ☐ No

D 3. By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?

☐ Yes ☐ No

D 4. Do you have any difficulty gripping with your hands (e.g. opening a jam jar)?

☐ Yes ☐ No ☐ Some

D 5. How much of the time during the past 4 weeks did you feel tired?

☐ All of the time ☐ Most of the time ☐ Some of the time ☐ A little of the time ☐ None of the time

Thank you very much for taking the time to complete this questionnaire.

Figure 2-7 IMH&W Baseline Questionnaire page 6/6.

2.1.7 Data management

I reviewed and familiarised myself with the data and checked for discrepancies by applying data range criteria (Table 2-3 to 2-5). This helped me verify the data's accuracy and identify any errors. Any data that fell outside the specified range were considered to be missing data. I maintained a STATA 'do' file to record all the steps involved in data management and manipulation. Additionally, I retained intact all original variables to enable tracking of the origins of any variable or datum.

2.1.7.1 Missing Data

Missing data refers to any information that was supposed to be collected but was not. This may occur if a participant omits questions in a survey or does not respond in a follow-up study. In longitudinal studies, missing data can be described in terms of pattern, whereby participants fail to submit a question (item missingness), an entire survey or follow-up and return at a later timepoint (intermittent missingness) or never return to a study (dropout). Item missingness, intermittent missingness and dropouts can all occur simultaneously (Twisk and de Vente, 2002)

Understanding why data is missing is important, as it can affect the study's results. Missing data is common in research and can reduce the study's power and lead to biased results (Pigott, 2001, Kang, 2013, Rubin, 1976).

Most statistical methods need complete data, and many software programs exclude participants with missing data, which can cause bias. Bias occurs when non-responders differ from responders. Missing data can impact the accuracy of study results, so it's important to consider why data is missing to ensure accurate conclusions. (Kang, 2013, Altman and Bland, 2007).

The exact reason for item missingness data is often unknown. While patterns can be identified, the missingness mechanism can't be definitively determined. When dealing with missing data, it's important to be clear about assumptions and check their impact on the results. Missing data mechanisms

are described in statistical literature according to assumptions governing the mechanisms of missing data (Rubin, 1976).

2.1.7.1.1 Types of missing data

Missing Completely at Random (MCAR): This occurs when the probability of missing data is unrelated to any observed or unobserved measurements, for example, a dropped laboratory sample. Analyses based on available cases should lead to valid inferences under MCAR. However, confirming if data is truly MCAR is challenging, as additional information might suggest otherwise (Pigott, 2001, Bennett, 2001). For example, if a person fails to complete the survey because of their chronic pain, they also fail to enter a pain severity score. The missing value is directly related to the value of that variable (Pigott, 2001). If the data collection were being conducted at a clinical visit, it would be possible to understand why the data was missing and to mitigate the loss. In this case, the researcher could write for the participant. However, this is not possible in a postal survey (such as IMH&W). In the case of missing data in a survey, it is impossible to obtain direct empirical data about the response mechanism (Pigott, 2001).

Missing at Random (MAR): This happens when the missingness depends on other measured variables but not the unobserved data. For instance, missing IQ scores related to children's age. Likelihood-based methods are valid under MAR, but non-likelihood methods may be biased (Schafer and Graham, 2002). Cross-lagged path analysis is considered a likelihood-based method.

Missing Not At Random (MNAR): This type occurs when the missingness depends on the unobserved data. Statistical inference is generally invalid under MNAR due to the difficulty in knowing the missingness mechanism. Sensitivity analyses are necessary to explore inferences under MAR and MNAR assumptions (Pigott, 2001).

Researchers can use hypothesis tests to determine if the data is MCAR or MAR. For example, recoding the variable with missing data and performing chi-squared or t-tests to check for associations with other variables (Little,

1988). Additionally, surveys often use non-response weightings to ensure representative results, achieved by building regression models to predict non-response and using the inverse of predicted probabilities as survey weights.

2.1.7.1.2 Strategies for dealing with missing data.

There are various methods to handle missing data in statistical analysis. Below are some common approaches to create a complete dataset, which is then analysed as if it were the original dataset. The choice of method depends on the type of missing data (e.g., categorical or continuous) and the research question. (Pigott, 2001).

Available or complete case analysis: This method only analyses participants with complete data. It is not problematic when there is minimal missing data (Altman and Bland, 2007). This is unbiased if the data is MCAR. If there is a high proportion of complete cases, with only a few observations missing, 'little harm will be done' (Altman and Bland, 2007). The amount of missing data permitted varies. A missingness rate of <5% is regarded as inconsequential (Schafer, 1999). However, it is suggested that 10% is acceptable if the data is MAR (Bennett, 2001). Otherwise, it might be inefficient and may lead to biased estimates by underestimating the variability of the data (Schafer and Graham, 2002, Altman and Bland, 2007, Bennett, 2001). In logistic regression, listwise deletion gives valid inferences under broader conditions than linear regression when combined with a continuous independent variable (Allison, 2001).

Last Observation Carried Forward (LOCF): This method replaces missing observations with the last recorded value in longitudinal studies. For example, if blood pressure is recorded at each GP visit, if one item is missing, then using the LOCF makes sense. However, LOCF can distort estimates by underestimating the variance, but less so than mean imputation and lead to invalid statistical inferences, even if the data is MCAR (Altman and Bland, 2007, Schafer and Graham, 2002).

Simple Imputation of the Mean: This method substitutes missing data with the mean of recorded values from other participants. It only applies to continuous variables and can dilute associations between variables, leading to biased estimates and underestimated variances and confidence intervals (Altman and Bland, 2007, Schafer and Graham, 2002). The only advantage is that this method keeps the overall mean the same, but at the cost of underestimating variance (Little, 1988). This is considered unbiased if the data is MCAR (Schafer and Graham, 2002).

Imputation of the Regression Mean: This approach uses a regression model to predict and replace missing data. It provides unbiased estimates of means and regression coefficients. Still, it can result in variances and confidence intervals that are too small, because the imputed data are modelled on the best fit of available data. The model can be extended to include multiple variables without missing data (Altman and Bland, 2007). This method is considered unbiased for data that is MCAR or MAR (Schafer and Graham, 2002).

Worst outcome scenario: This method substitutes missing data with a single value based on the least desirable outcome, typically used for categorical variables. It introduces bias into coefficient estimates but can be useful in specific contexts, such as assuming participants with missing follow-up data in smoking cessation studies have returned to smoking (Altman and Bland, 2007).

Stochastic imputation: This method uses available data to generate information about the distribution of each missing value. There are multiple methods of stochastic imputation to try to calculate values for the missing data.

Simple Stochastic Imputation: This replaces each missing value with a randomly drawn value from a suitable distribution. The donors (participants with complete data) must be similar to those with missing data. Large sample sizes are typically needed. This method can yield valid coefficient estimates if the distribution is chosen appropriately, but variance estimators must

account for the source of information. 'Hot-deck' imputation is a simple stochastic imputation, where a participant with missing data is matched to a similar participant with complete data. This method is considered unbiased for MCAR and MAR, but it can cause underestimation of the variance, less than mean imputation, LOCF or using regression means (Schafer and Graham, 2002).

Multiple Stochastic Imputation (MI): This method repeats the imputation process several times (typically 3 to 5 times) to allow for random error. The number of imputations depends on the amount of missing data. For example, with 50% missing data, 5 imputations result in a standard deviation only 5% wider than using an infinite number of imputations (Pigott, 2001). More imputations are needed if there are multiple explanatory variables with missing data. The distributions of the imputations should be checked for similarity to each other and the original data. MI assumes data are MAR, though some statistical software may not require this assumption. The imputation model must match the analysis model, including interaction terms and the dependent variable. Limitations include that analysis takes extra time, hard drive space, and computer memory to run the models, and the non-uniqueness of coefficient estimates and standard errors due to the random process (Pigott, 2001).

Including variables with missing data as explanatory variables in the models enhances the credibility of the assumption that the data are MAR, reducing bias in the estimates and improving coefficient estimates.

2.1.7.2 Missing data in the IMH&W

The main outcome variable in this thesis is frailty. The inclusion criteria for these studies required that each participant could be classified according to the FRAIL scale. This will ensure there will be no missing data for this classification. I do not believe I could confidently calculate FRAIL by imputing missing data. All other data will be assessed for the percentage of missing data in the dependent variables pain, age, sex and BMI. If there is a low percentage of missing data, then complete case analysis will be conducted.

The planned analysis is logistic regression, which is robust to complete case analysis when used with missingness in a continuous independent variable.

Table 2-3 IMH&W data and data range criteria part 1

Variable	IMH&W Ref. 1	Variable Type 2	Data range criteria	Data Labels	Notes
Demographic characteristics of the study population					
Age	A1	Con	18-120 years		If blank, change to missing data.
Sex	A2	Cat	All	Male = 1 Female = 2 Prefer not to say = 3	If blank, change to prefer not to say
Ethnicity	A3	Cat	All	White = 1 Asian = 2 Black = 3 Other = 4	Free-text box = Other Labels 4-9 and free text were transformed to others. Later, this was transformed to white and non-white due to small numbers.
Baseline Weight	A5	Con	30-200 Kg		Entered as imperial or metric
Weight 1 year ago	A6	Con	30-200 Kg		Entered as imperial or metric
Weight change		Con	>20%		Calculated (A5-A6)
Height	A4	Con	0.9-2.5 metres		They were entered as imperial or metric.
BMI		Con	15-45		Calculated using height and baseline weight A4. (Weight in Kg / Height 2)
Smoking status	A7	Cat	All	Never Smoked = 0 Current Smoker = 1 Ex-smoker <12 months = 2 Ex-smoker >12 months = 3 Ex-smoker = 4 No Response = 5	There was no request for how long they have stopped, but some have written it on the form. This was later revised to Never smoked, current smoker or ex-smoker as the ex-smoker categories were inconsistent.
Alcohol status	A8	Cat	All	Yes = 1 No = 0 No Response = 2	≥3 units per day
Frailty Measures					
FRAIL Scale		Cat	All	Robust = 0 Pre-frail = 1-2 Frail = >3	The sum of the following five items is categorised using the values on the left.
Fatigue	D5	Cat	All	All of the time = 1 Most of the time =1 Some of the time =0 A little of the time =0 None of the time =0	How much of the time during the past 4 weeks did you feel tired?
Resistance	D2	Cat	All	Yes = 1 No = 0	By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?
Ambulation	D3	Cat	All	Yes = 1 No = 0	By yourself and not using aids, do you have any difficulty walking several hundred yards?
Illnesses	A9	Cat	All	0-4 = 0 5-11 = 1	Did a doctor ever tell you that you have [illness] Total 11 illnesses in FRAIL (there were 18 on the IMH&W)
Loss of weight	A6-A5	Cat	0-50%	≥5% change = 1 <5% change = 0	((weight 1 year ago – weight at baseline)/ weight 1 year ago) x100

1.IMH&W Ref. is the survey section, followed by the question number.
2. Variable type is continuous (Con) or Categorical (Cat).

Table 2-4 IMH&W data and data range criteria part 2

Variable	IMH&W Ref.1	Variable Type. 2	Data range criteria	Data Labels	Notes
Physical activity	D1	Cat	All	Regular activity at least 2-4 hours per week = 0 None or mainly sedentary = 1	Which is your level of physical activity?
Gripping difficulty	D4	Cat	All	Yes = yes/no Some = yes/no No = yes/no	Do you have any difficulty gripping with your hands? Entered as three binary questions
Pain measures					
NRS 0-10 scale	C3	Con	All	0-10	Average pain in past 4 weeks 0 = no pain
Joint pain over 4 weeks	C1	Cat	All	Yes = 1 No = 0	
Was your most bothersome joint painful for most days in the last 4 weeks?	C4	Cat	All	Yes = 1 No = 0	
Most bothersome joint location	C2	Cat	All	Yes = 1 No = 0 No Response = 2	Jaw, wrist, neck, back/spine, knee, ankle, shoulder, hand/finger, foot/toe, elbow, hip
Pain Rating Index (PRI)	C5	Con	>1	1-78	Words in each set were ranked consecutively from 1; the highest score was recorded for each set. PRI was calculated = sum of the values of all sub-classes. Sets may be skipped.
Sensory	C5	Con	>1	Word sets 1-10	Total for sub-class
Affective	C5	Con	>1	Word sets 11-15	Total for sub-class
Evaluative	C5	Con	>1	Word set 16	Total for sub-class
Miscellaneous	C5	Con	>1	Word sets 17-20	Total for sub-class
Number of words chosen (NWC)	C5	Con	>1	1-20	Calculate the number of chosen words
CAP-Knee					
Central Pain Mechanisms	B1-7	Con	All	Never = 0 Sometimes = 1 Often = 2 Always = 3	For adjusted scores, 'Always' was labelled 3; in CAP-Knee, it was condensed with 'Often' scoring 2. NB B7 was reverse-scored and condensed as above.
Manikin CAP-Knee Score	B8	Cat	All	Knee region 5,6,26,27 Below waist Sectors 1-8 and 22-31	Score = 2 if the shaded area on the manikin includes both (i) any knee region, and (ii) any other site below the waist. Score = 0 if shaded areas on the manikin do not include both (i) any knee region and (ii) any other site below the waist.
CAP-Knee score	B1-8	Cat	All	0-24 unadjusted or 0-16 adjusted	Calculate using B1-B8
Manikin Sector Count	B8	Con	All	Sector 1-46	Number of sectors shaded

1.IMH&W Ref. is the survey section, followed by the question number.
2. Variable type is continuous (Con) or Categorical (Cat).

Table 2-5 IMH&W data and data range criteria part 3

Variable	IMH&W Ref. 1	Variable Type. 2	Data range criteria	Data Labels	Notes
Bothersome weight-bearing joints	C2	Cat	Back / spine, knee, hip, ankle, foot/toe,		Calculate if the most bothersome joint is a weight-bearing joint. Also, checking the manikin scores
Clinical Variables					
Morbidity Count	A9	Con	All	Yes = 1 for each condition No = 0 for each condition	18 conditions. Plus, free text There were 11 conditions included as part of the FRAIL Scale
Medication	A10	Cat	All	Yes = 1 No = 0	Is the medication on the WHO analgesic scale?
Analgesic medication	A10	Cat	All	Paracetamol = 1, Ibuprofen = 2, Naproxen = 3, Codeine = 4, Dihydrocodeine = 5, Co-codamol = 6, Tramadol = 7, Morphine =8, Diamorphine =9, Pethidine =10, Fentanyl =11, Buprenorphine =12, Oxycodone =13, Gabapentin =14, Pregabalin =15, Amitriptyline = 16, Medications Not Provided =17	If the medication was on the WHO analgesic scale Multiple labels were possible
Non-analgesic medication	A10	FT	All	Free text	If the medication was not on the WHO analgesic scale
Medication Count		Con	All		Calculate the number of medication labels.

1.IMH&W Ref. is the survey section, followed by the question number.

2. Variable type is continuous (Con) or Categorical (Cat) or Free-text (FT).

2.1.8 IMH&W data at 1-year follow-up extraction

Follow-up (1-year) data were provided in July 2020, and the questionnaire was similar to the baseline. The questions were unchanged for this thesis. The data management procedures for cleaning and processing the data developed for the baseline data were applied to the follow-up data.

2.1.8.1 Augmentation of FRAIL

After the initial analysis of the baseline IMH&W data, it became clear that the five items of FRAIL were unequally reported. Fatigue, resistance, and ambulation met the FRAIL criteria more often than illness or loss of weight items. I felt the weight item might be poorly reported due to recall bias, but this could not be improved without collecting clinical data. The IMH&W was designed as a self-report questionnaire and was not designed to collect clinical data.

However, it was possible to augment the 'illness-item' using data from the IMH&W survey. I ascertained these illness-items from:

1. **FRAIL checklist** - Illness is defined within FRAIL as ≥5/11 specified illnesses or morbidities. The IMH&W included a checklist of conditions, prefaced with the question, 'has a doctor told you that you have any of these conditions or problems.' This list included the 11 FRAIL illnesses (and 7 other conditions were listed, but only those listed in FRAIL were employed) (Figure 2-2).

Some checklist boxes could create overlap; for example, arthritis, osteoarthritis, and rheumatoid arthritis were included. Care was taken to count a tick in any of these as one for FRAIL classification (arthritis) rather than three.

2. **Free-text** - In the IMH&W study, there was a free-text box labelled "other conditions," which was used by 1,393 participants. Some participants duplicated the information in the checklists, while others provided information that could have been ticked but was not. The IMH&W study team attempted to type the information exactly as it

was written on the paper questionnaire. While checklist data can be easily processed using statistical software, the free-text medical data requires further processing. I extracted and classified these data using criteria developed by consensus between myself, DAW, and JRFG (Table 2-9). To ensure accuracy, two reviewers (myself and Dr Shahtaheri) independently checked a sample of 100 participants and confirmed its reliability [ICC = 0.94, (95%CI 0.91 to 0.96), $p < 0.001$].

3. **Medications** – In the IMH&W study, participants self-reported medications by free text and/or prescriptions. I, DAW and JRFG reviewed and edited the list of participant medications to include only those medications specifically used for conditions included in the FRAIL-illness item based on information in the British National Formulary (Table 2.6). Illnesses were coded by algorithm, as above, according to each participant's self-reported use of these specific medications. For example, if a participant reported insulin, I inferred they had diabetes mellitus even if they had not listed it in the checklist or free text. Two reviewers (myself and Dr Shahtaheri) independently checked a sample of 100 participants and confirmed its reliability [ICC= 0.98, (95%CI 0.97 to 0.99), $p<0.001$].

The majority of the analysis described in the following chapters uses the information supplied via the morbidity checklists described in the original FRAIL, as this has been validated by others (Morley et al., 2012, Susanto et al., 2018).

The results of the augmentation are shown in Chapter 3.

Chapter 5 used augmented FRAIL data, encompassing the additional morbidity classifications from the free-text or medication data alongside other comorbidity indices.

Table 2-6 Illness-specific medications part 1

Diabetes	**Lung disease**	**Angina**
Alogliptin	drugs in the class mucolytics	Glyceryl trinitrate:
Basaglar insulin	Carbocisteine	1-glyceryl nasal spray
Bolamyn SR	1-Mucodyne Capsules	2-gtn spray (mouth spray)
Dapagliflozin	2-Carbocisteine capsules	3-gtn tablets
Dulaglutide		4-nitromin spray
Empagliflozin	**Asthma**	5-nitrolingual pump spray
Forxiga	Drugs in the class selective beta2-agonists (short-acting)	Ranolazine
Gliclazide	Salbutamol:	Nicorandil
Glimepiride	Salamol easi-breathe cfc-free inhaler	Isorbide mononitrate
Glucophage	Ventolin 100micrograms/dose evohaler	Isorbide dinitrate
Humulin	Drugs in the class inhaled corticosteroids:	Tardisc xl
Insulin	1-beclometasone dipropionate	Monomil xl
Januvia	Qvar easi-breathe inhaler	Isotard x
Jardiance	Clenil modulite inhaler	
Glimepiride	2-budesonide with formoterol	
Glucophage	Symbicort 100/6 turbohaler	
Humulin	3-beclometason with formoterol	**Osteoarthritis, gout**
Insulin	Fostair nexthaler® 200/6	Colchicine
Januvia	4-fluticasone with salmeterol	Alluprinol
Jardiance	1-airflusal	Febuxostat
Levemir insulin	2-seretide evohaler	
Levo linagliptin	5-beclomethasone dipropionate	**Osteoporosis**
Linagliptin	Becotide 50 inhaler	put in a conditional argument if Zoledronic acid, Alendronic acid or Ibandronic acid then osteoporosis.
Liraglutide	8-budesonide	
Metabet	Pulmicort turbohaler	If prednisolone and Raloxifene hydrochloride, Denosumab: 1-Denosumab 60/lml 2-Denosumab (Prolia) Do not code as osteoporosis
Metformin	9-fluticasone with salmeterol	
Novomix	1- seretide evohaler	Zoledronic acid1-Alendronic acid
Pioglitazone	2-seretide 250 accuhaler	2-Ibandronic acid
Sitagliptin	3-sirdupla inhaler	Raloxifene hydrochloride
Sukkarto	Others:	Denosumab:
Synjardy	Uniphyllin continus	1-Denosumab 60/lml
Toujeo		2-Denosumab (Prolia)
Trajenta		
Victoza		
Vipidia		
Zicron		

Table 2-7 Illness-specific medications part 2

Renal disease	RA + connective tissue disease	Hypertension
Lanthanum	Put in a conditional argument (rutuximab if not lymphoma), Sulfasalazine & infliximab if not ulcerative colitis/ Crohn's	Calcium-channel blockers:
Fosrenal	Drugs in the class tumour necrosis factor alpha (tnf-a) inhibitors:	Amlodipine
	Etanercept	Diltiazem hydrochloride
Cancer	Benepalil solution for injection pre-filled syringes	Angitil SR 90 capsules
Anastrozole	Enbrel solution for injection pre-filled myclic pens	Slozemcapsules
Tamoxifen	Erelzsolution for injection pre-filled syringes	Zemtard capsules
Bicalutamide	Drugs in the class of disease-modifying anti-rheumatic:	Nifedipine
Oxaliplatin	Leflunomide tablets	Adalat tablets
Imatinib	Drugs in the class t-cell activation inhibitors:	Felodipine
Hydroxycarbamide	Abatacept	Folpik XL tablets
	Orencia solution for injection pre-filled syringes	Parmid XL tablets
AIDS	Drugs in the class interleukin inhibitors:	Felodipine tablets
Efavirenz	Tocilizumab	Vascalpha modified-release tablets
Atripla	Adalimumab	Coracten XL capsules
	Benepali	Lacidipine
Dementia	Betamethasonevalerat	Lercanidipine hydrochloride
Donepezil	Hycophenalate	Securon SR tablets
Memantine	Hydroxychloroquine	Drugs in the class non-diuretic thiazide:
	Levo humira	Indapamide
	Metoject	Drugs in the class anti hypertensives, centrally acting:
	Nivestim	Moxonidine
	Methrotexate	Drugs in the class vasodilator antihypertensives:
	Sulphasalazine	Riociguat
	Leflunominde	
	All anti-tnfs (unless psoriasis or inflammatory bowel disease, rituximab, tocilizumab)	**AT1 inhibitors: -**
	Infliximab	Candesartan
	Cyclophosphamide	Eprosartan
	All anti-tnfs (unless psoriasis or inflammatory bowel disease, rituximab, tocilizumab)	Irbesartan
		Losartan
		Olmesartan
		Olmesartan Medoxomil
		Telmisartan
		Valsartan

Table 2-8 Illness-specific medications part 3

Depression	Neurological	Ulcer disease
Depefex XL capsules	Dopamine precursor drugs:	Put in a conditional argument, include *azole or rantidine if not taking NSAIDS or concomitant steroid
Citalopram tablets	Co-careldopa	Drugs in the class proton pump inhibitors:
Cipramil	1- Co-careldopa tablets	Lansoprazole
Imipramine	2- Sinemet tablets	Omeprazole
Lofepramine	Co-beneldopa (ingredients: levodopa and benserazide):	Pantoprazole
Mirtazapine	1-Co-beneldopa capsules	Rabeprazole sodium
Lithium	2-Madopar tablets	Pariet gastro-resistant tablets
Phenelzine	Dopamine receptor agonists:	Rabeprazole gastro-resistant tablets
Reboxetine	Acute drug-induced dystonic reactions	Drugs in the class include antacids, alginate
	3- Repinex XL tablets	Gaviscon
Anxiety & Panic Disorders	4- Pramipexole modified-release tablets	Drugs in the class calcium:
Diazepam	5- rotigotine patches	Calcium carbonate
Nitrazepam tablets	Antimuscarinic drugs:	Rennie chewable tablets
Lorazepam	Trihexyphenidyl hydrochloride	Cortiment®
	1-Trihexyphenidyl 2mg tablets	Drugs in the class h2-receptor antagonists:
Visual impairment	2-Procyclidine 5mg tablets	Ranitidine
(Includes glaucoma irrespective of visual impairment)	drugs in the class monoamine-oxidase b inhibitors	Ranitidine tablets
Drugs in the class antimuscarinics:	Rasagiline	Drugs in the class
Cyclopentolate hydrochloride	1-Rasagiline tablets	Sodium bicarbonate
Minims cyclopentolate hydrochloride eye drops	2-Azilect tablets	Sodium bicarbonate tablets
Drugs in the class prostamides:	Catechol-o-methyltransferase inhibitors are a class of drugs	Peptac Peppermint Flavour Antacid
Bimatoprost with timolol	Entacapone tablets	
Bimatoprost eye drops	Other:	**No specific drug for the condition**
Drugs in the class prostaglandins and analogues:	1-Ongentys hard capsules	Congestive heart failure
Latanoprost	2-stanek tablets (levodopa with carbidopa and entacapone)	Degenerative disc disease
Travoprost	2-amantadine hydrochloride tablets	myocardial infarction
Timolol 5mg/ml eye drops		cerebrovascular disease
Drugs in the class beta blocking agents, non-selective:		peripheral vascular disease
Timolol maleate		connective tissue disease
		Liver disease
		Hearing impairment
		Hemiplegia
		Comorbidity information required
		diabetes end with end organ damage of retinopathy, neuropathy, or nephropathy

Table 2-9 Illness criteria for the classification of free text

Illness condition	Illness inclusion criteria
Diabetes	Include type 1 or 2 diabetes on medication; exclude if pre-diabetic or controlled by diet alone.
Cerebrovascular disease	Include stroke or TIA; cavernous angiomas, multiple brain, brain aneurysm, and brain haemorrhage.
Hypertension	Hypertension or high blood pressure
Angina	Angina also includes those who had coronary artery bypass grafts and those initially admitted with unstable angina. Include those who report the insertion of stents and any heart bypass.
Congestive heart failure	Include heart failure and exertional or paroxysmal nocturnal dyspnoea.
Myocardial infarction	Include if any heart attack old or new, include cardiac arrest.
Osteoarthritis, gout	Osteoarthritis, gout, and arthritis
Rheumatoid arthritis + connective tissue disease	Include all inflammatory arthritis, including ankylosing spondylitis, psoriatic arthritis, RA, and inflammatory systemic conditions such as polymyalgia rheumatica, systemic lupus erythematosus, lupus, polymyositis, seronegative arthritis.
Asthma	Include any form of possible reversible airway obstruction, whether or not there is additional fixed obstruction or other lung pulmonary deficits. This means that a patient reporting to have only COPD who is prescribed one of these will also be classified as having asthma.
Lung disease	Include any non-reversible-airway limitation. Chronic obstructive pulmonary disease (COPD), acquired respiratory distress syndrome (ARDS), emphysema, pulmonary embolism, and thromboembolic pulmonary hypertension or permanent lung impairment such as resection.
Renal disease	Include patients on dialysis, those who had a transplant, and those with uraemia.
Cancer	Include all cancers, tumours or mention of chemotherapy/ radiotherapy or other cancer treatment regardless of when it occurred. Exclude minor skin cancer.

2.1.8.1.1 Classification of Morbidity

The study aims to examine factors which might explain the relationship between pain and frailty. Therefore, it is important to distinguish between morbidity and frailty and ensure they do not share definitions. The FRAIL illness item is scored as present when there are ≥5/11 illnesses. This appeared to be a high threshold; many people had three or four morbidities; I wanted to explore whether the type of morbidity affected the threshold.

Separating frailty from morbidities and disability is difficult, as they have overlapping concepts. Frailty is associated also with multi-morbidity (two or more long-term health conditions (Barnett et al., 2012). In fact, multi-morbidity is an integral part of frailty identification tools based on the cumulative deficit model (Rockwood and Mitnitski, 2007, Wade et al., 2017, Rodríguez-Sánchez et al., 2019, Shega et al., 2012, Chen et al., 2019, Chaplin et al., 2023) and FRAIL (Morley et al., 2012). Accumulated deficits, including those from morbidities, represent multi-organ decline and contribute to frailty classification (Rockwood and Mitnitski, 2007, Clegg et al., 2016).

The accumulated deficit models count comorbidities as deficits. However, it is important to try to account for which morbidities may affect whether a person is regarded as frail. This can help identify those who are at risk of becoming frail.

There were two stages to this study, firstly, to examine whether analysis of free text and medications could augment the FRAIL illness item. Secondly, to confirm that the FRAIL illness items adequately measure the comorbidity burden.

Several comorbidity indices have been conceived, which have differing priorities. I reviewed the existing literature on comorbidity indices; it was evident that some indices were unsuitable for use with the IMH&W data, which relies on self-reported information. Several comorbidity indices were designed for use within hospitals, where detailed records, including test results and specific diagnoses, are available. For example, the IMH&W

checkbox for cancer cannot provide information on whether it has metastasised or is a solid tumour or even when the cancer occurred. These are the kinds of questions used in the morbidity indices, particularly those utilising weighting. Weighting involves scoring morbidities based on their impact on the individual. This study was designed post-hoc; therefore, I could not influence which data were collected. Therefore, it was necessary to use indices that could be employed with the available data. Also, participants supplied additional information, such as the dates of diagnosis, although this information was not requested. This was a useful addition as it permitted allowed the classification of cancer (within 5 years).

2.1.8.1.1.1 Comorbidity Indices

The comorbidities and the weighted score are shown in Table 2-10.

The Elixhauser Comorbidity Indices were developed for use with large hospital administration data. This led to the Elixhauser Total Score (ETS) and Elixhauser (EPS); the latter is the weighted version (Elixhauser et al., 1998). These indices predicted mortality and morbidity comparably (England et al., 2015). However, they require a large amount of data that were not available without access to patient medical records.

The Rheumatic Disease Comorbidity Index (RDCI) was designed to be used with rheumatic disease and has been shown to be effective for use with self-report data, and is able to predict mortality (England et al., 2015). This index has been used with rheumatoid arthritis, osteoarthritis (OA), systemic lupus erythematosus, or fibromyalgia (Michaud and Wolfe, 2007). This is a short index with only 9 items, so any missing or amended item will have a greater impact on the score.

The Charlson Comorbidity Index (CCI) is widely used to predict mortality (Charlson et al., 1987). The CCI has several modified versions; one commonly adopted is the Charlson-Deyo (CDI), which condenses the cancer categories from four to two. It has been validated and performs comparably with the CCI

(Deyo et al., 1992); the weighting values remain the same. The CDI has published guidelines on how to classify comorbidities.

The Functional Comorbidity Index (FCI) focuses on function (Groll, 2004). In a comparison of different indices, the FCI was found to be a poor predictor of mortality (England et al., 2015). However, it is frequently used in rehabilitation settings where its ability to predict functionality is particularly valued. Groll and colleagues list the guidelines on the FCI comorbidities included.

There is overlap between these comorbidity indices and the illnesses included in FRAIL, as displayed in Table 2-9. I decided to include two indices the FCI and CDI which have differing but complementary focuses. By comparing information using these and FRAIL, I aimed to gain an overall indication of the burden of morbidity in this population.

Table 2-10 Comparison of comorbidity indices.

Index	Range	Weighted	Formula
RCDI	0 to 9	Yes	2 x lung disease + [2 x (heart attack, **other CV**, OR stroke) OR + x hypertension] + **fracture** + depression + diabetes + cancer + (**ulcer or stomach problem**)
ETS	0 to 30	No	**metastatic cancer** + **liver disease** + **lymphoma** + (CHF + **paralysis**) + (weight loss + **other neurological disorder**) + (**cardiac arrhythmias** + **renal failure + fluid or electrolyte disorder**) + (**pulmonary circulation disorder** + **solid tumour without metastasis**) + (**chronic pulmonary disease** + **coagulopathy**) + **PVD** + (AIDS + alcohol abuse + diabetes, **complicated + diabetes, uncomplicated** + hypertension + **hypothyroidism** + peptic ulcer disease + **psychose**s + RA/**collagen vascular disease**) + valvular disease + (**blood loss anaemia + deficiency anaemia)** + depression x obesity + **drug abuse**
EPS	-19 to 89	Yes	12 x **metastatic cancer** + 11 x **liver disease** + 9 x **lymphoma** + 7 x (CHF + **paralysis**) + 6 x (weight loss + **other neurological disorders**) + 5 x (**cardiac arrhythmias** + **renal failure** + **fluid or electrolyte disorder**) + 4 x (**pulmonary circulation disorder** + **solid tumour without metastasis**) + 3 x (**chronic pulmonary disease** + **coagulopathy**) + 2 x **PVD** + 0 x (**AIDS** + **alcohol abuse** + diabetes, **complicated + diabetes, uncomplicated** + hypertension + **hypothyroidism** + **peptic ulcer disease** + **psychose**s + RA/**collagen vascular disease**) -1 + x **valvular disease** -2 x (**blood loss anaemia** + **deficiency anaemia**)-3 x depression - 4 x obesity -7 x **drug abuse**
CDI	0 to x6	Yes	6 x (**metastatic solid tumour + AIDS**) + 3 x (**severe or moderate liver disease**) + 2 x (**hemiplegia** + renal disease + diabetes **with end-organ damage** + **tumour without metastasis + lymphoma** + **leukaemia**) + MI + CHF + **PVD** + stroke + dementia + COPD + connective tissue disease + ulcer + **mild liver disease**
FCI	0 to 18	No	Arthritis + osteoporosis + asthma + COPD + angina + CHF + MI + **neurologic disease** + stroke + **PVD** + diabetes + **upper GI disease** + depression + anxiety + **visual impairment** + **hearing impairment** + degenerative disc disease + obesity

Abbreviations: RDCI -Rheumatic Disease Comorbidity Index; CV -cardiovascular; CDI -Charlson-Deyo Index; AIDS -acquired immunodeficiency syndrome.
MI -myocardial infarction; CHF -congestive heart failure; PVD -peripheral vascular disease; COPD -chronic obstructive pulmonary disease.
FCI -Functional Comorbidity Index; GI -gastrointestinal; ETS -Elixhauser Total Score; EPS -Elixhauser Point System; RA -rheumatoid arthritis.
Source: adapted from (England et al., 2015)

The items in **bold** were not available via the IMH&W checklist; some could be extracted from free text.

2.1.8.1.1.2 The Charlson Comorbidity Index and Functional Comorbidity Index

The FCI lists 18 conditions, and the FRAIL scale 11 conditions, both are unweighted. The original CCI lists 19 conditions; scores range from 0-37 due to weighting. The shortened 17-item CDI was utilised (Deyo et al., 1992). CDI had a category named 'rheumatologic diseases.' In categorising the IMH&W data, this category was defined as rheumatoid arthritis and connective tissue disease.

Table 2-11, indicates the morbidities included for each index and the weighting given for CDI. The morbidity results are shown in Table 2-11. The data generated in this section are reported in Chapter 3 and Chapter 5.

2.1.8.1.1.2.1 Free text of morbidity conditions

The free-text information varied in quality; participants included lots of information, although it was not directly requested. For example, many included the cancer treatment dates; this is required for the CDI index, which counts any cancer in the last 5 years. The CDI was developed primarily for hospital records, which may affect its accuracy. The FCI was developed for self-reporting; its illness definitions were more straightforward to interpret, with less medicalised language. FRAIL does not include illness definitions, so previous studies may have used different interpretations. Finally, CDI uses medical records which include the severity or recency of symptoms; however, FRAIL cannot accommodate these factors and may suffer recall bias (Spencer et al., 2002, Althubaiti, 2016). Some conditions may be reported that were no longer current, for example, angina, may be reported, despite the individual having received a bypass graft and no longer experiencing angina.

Table 2-11 Comparison of FRAIL with 2 comorbidity indices: morbidities and weighting.

Morbidity	Charlson-Deyo Comorbidity Index (weighting)	Functional Comorbidity Index	FRAIL Scale
AIDS	6		
Angina		1	1
Anxiety or panic disorders		1	
Any cancer	2		1
Asthma		1	1
Cerebrovascular disease	1	1	1
Congestive heart failure	1	1	1
Degenerative disc disease		1	
Dementia	1		
Depression		1	
Diabetes with end organ damage	2	1	
Diabetes without end-organ damage	1		1
Hearing impairment		1	
Hemiplegia	2		
Hypertension			1
Lung diseases	1	1	1
Metastatic solid tumour	6		
Mild liver disease	1		
Moderate or severe liver disease	3		
Moderate or severe renal disease	2		1
Myocardial infarction	1	1	1
Neurological		1	
Osteoarthritis & gout		1	1
Osteoporosis		1	
Peripheral vascular disease	1	1	
RA & connective tissue disease	1		
Ulcer disease	1	1	
Visual impairment		1	
Body Mass Index >30		1	
Maximum score	33	18	11

Abbreviation: RA – Rheumatoid arthritis,
Sources: Charlson et al., (1987); Morley et al., (2012) and Groll, (2004)

2.1.8.1.2 Classification of medications

Free text was also supplied in the medications box [A10] of the IMH&W questionnaire booklet in response to the question, 'Please write down the names of any medications, including any pain killers, that you use. They can be prescriptions or bought over the counter.' Some participants attached their repeat prescription lists.

To categorise medications, similar procedures were adopted to those previously described for morbidities. This included two steps: firstly, to classify analgesia, and secondly, to classify medication that inferred a specific morbidity. For example, insulin is only used to treat diabetes.

2.1.8.1.2.1 Analgesia

Dr Shahtaheri and I made a comprehensive list of all analgesics and classified them, as shown in Table 2-9. The full details of the individual analgesics in each category are available in Appendix A. The list was compiled with reference to the British National Formulary (Joint Formulary Committee, 2020), and the product list for painful conditions (PNC166) was produced by The Clinical Practice Research Datalink (Datalink, 2018). The list was reviewed and agreed upon by clinicians DAW and JRFG.

Table 2-12 Analgesic classification classes

Analgesic Class
Paracetamol
Neuropathic or central
Strong opioids
Weak opioids
Systemic NSAIDS
Cream NSAIDS
Capsaicin Cream
Analgesic Other
Non-MSK anti-neuropathic

I coded the analgesia lists using an algorithm that I wrote. Some medications, such as co-codamol, contain paracetamol and codeine and are classified as both paracetamol and weak opioids. There were many spelling variations and brand names. My computer algorithm results were compared with those of

Dr Shahtaheri (SS) who used manual spreadsheet and classified each morbidity based on the criteria, to ensure reliability. The algorithm coded 3209 specific medications and SS coded 3179, a difference of 30. Discrepancies were, in the first instance, mainly due to duplication because 25 times a medication name had been typed twice during the input. The manual system eliminated duplicates, whereas the computer algorithm did not. The duplicated data were removed from the field. The remaining discrepancy rate was below 5%, so it was agreed that the discrepancy rate was acceptable.

At this point, descriptives were produced, and I broke down the data further. This permitted a count of opioids reported and whether a Gabapentinoid or Tricyclic was reported for central/neuropathic analgesia. I recoded these into sub-classes and individual medications.

2.1.9 Self-report assessment

Large quantitative surveys often employ self-report methodology. The main advantage is this efficiently acquires large amounts of data in a relatively inexpensive manner. The IMH&W is composed of several validated questionnaires, such as FRAIL (Morley et al., 2012), the Central Aspects of Pain in Knee (CAP-Knee) (Akin-Akinyosoye et al., 2021), and the McGill Pain Questionnaire (Melzack, 1975). The disadvantage of questionnaires is the lack of objectivity compared to other methods, such as imaging and QST, but these techniques are costly and time-consuming. Also, they limit who can take part as a clinical visit is required. They also do not measure the same thing, for example, pain is a subjective experience. Therefore, a questionnaire is a good way to investigate pain.

The Self-report for IMH&W used paper format in the first two waves and allowed participants to return their completed questionnaires via post. Participants completed the forms at home in their own time. This meant participants who might find attending a clinical assessment difficult due to their health or caring responsibilities could be included.

Using self-report is regarded as an indirect measure; there is likely to be some inaccuracy in some items, as discussed in the biases Section2.2.4.This may have introduced some classification errors.

2.2 Risk of Bias and the IMH&W Questionnaire

Survey research can be influenced by various types of research bias, which can affect the accuracy and validity of the findings and subsequent interpretation (Althubaiti, 2016). Bias can arise at various stages of the research process, including study design, data collection, analysis, and interpretation. Understanding and mitigating bias is essential to ensure the reliability, validity, and generalizability of research findings. This type of measurement error may be systematic and constant or variable. The following describes common types of bias in survey data and how they relate to the data collected in the IMH&W survey.

2.2.1 Non-response bias

In order for surveys to yield accurate and meaningful results, it is crucial to achieve a high response rate. The percentage of non-respondents and the extent to which their characteristics differ from the study population can significantly impact the accuracy of the results. This is known as non-response bias, and reducing it is vital to ensure the reliability of the findings (Barclay, 2002).

There are various reasons why certain groups, such as males, ethnic minorities, and those from disadvantaged backgrounds, may not respond to surveys. This type of bias can make the results less applicable to the general population and reduce their accuracy (Bowling and Ebrahim, 2005). For instance, 98% of the respondents to the IMH&W questionnaire were ethnically white, which introduces bias as the results may only reflect the experiences of white individuals. This imbalance is a common issue in surveys conducted in the UK. Often, research exhibits gender imbalance; whilst there was a slightly higher proportion (55%) of females who completed IMH&W in a large database, this is less problematic than surveys which are single-sex or

very unbalanced. Previous frailty research has often focused on single-sex cohorts (Megale et al., 2018, Morley et al., 2012, Susanto et al., 2018), which limits their generalisability.

2.2.2 High attrition

High attrition occurs through natural loss (i.e., death), geographic relocation or refusal over time. Unfortunately, people with frailty have a higher mortality risk, thus increasing attrition due to being frail and/or other morbidities, which are more prevalent in older people (Ravindrarajah et al., 2013). It may be those with the most severe frailty die at an earlier age than those who are less frail. Many factors, including lifestyle, genetics, and employment history, may influence the degree of frailty and rapidity of development.

2.2.3 Recall bias.

Recall bias occurs when survey respondents inaccurately remember or report past events or experiences (Spencer et al., 2002, Althubaiti, 2016). Various factors, such as time, forgetfulness, emotions, and personal biases or guessing, can influence people's memories. This bias can lead to inaccuracies in responses, particularly when asking about distant or complex events. Survey datum relies heavily on recalling events. The IMH&W participants were asked to recall their health data, such as health conditions, and this may be challenging as no date restrictions were included. In the classification of frailty, my methods used data which may be subject to recall bias. For example, asking someone to recall their weight one year ago is likely to be difficult, either because participants do not know or may not have weighed themselves for some time. Many participants were older people and may experience difficulties in monitoring their own weight due to accessibility issues. In other studies, for example, the Australian Longitudinal Study on Women's Health (Susanto et al., 2018). The participant weights, which also used FRAIL, were clinically recorded. This may result in this measure being understated, and this potentially could result in misclassification in FRAIL.

2.2.4 Self-report bias

This is the difference between a true value and a self-reported value. This may be conscious or unconscious on the part of the participant. Response bias refers to the tendency of survey respondents to answer questions inaccurately or in a way that they believe is socially desirable rather than providing their true opinions or behaviours. This bias can arise due to social desirability bias (respondents providing answers they perceive as more socially acceptable) or acquiescence bias (tendency to agree with statements regardless of content). Participants may give socially desirable answers; for example, people may prefer to say they are non-smokers because smoking is viewed negatively. This may also be true of weight; people may feel embarrassed if they know they weigh more than what is considered healthy.

2.2.5 Question Wording Bias

To minimise bias, the IMH&W and ACHING used validated measures and, where possible, used UK English versions. The phrasing of survey questions can introduce bias if they are misleading, ambiguous, or confusing. Biased wording can influence respondents' understanding of the question or lead them to answer in a particular way. Careful attention should be given to question formulation to minimise this bias. Using items or questionnaires with established reliability and validity reduces bias, which was the case with the IMH&W questionnaire. Additionally, measures must be validated in different countries, cultures, or languages. This includes different versions of English, such as the USA and the UK. For example, the original Pittsburgh Sleep Questionnaire uses the American phrase ‘what time have you gotten up’ (Buysse et al., 1991). The UK version selected for the ACHING study (Chapter 7) used the Pittsburgh Sleep Questionnaire-UK version [PSQI_AU1.2_eng-GB.pdf]. This changed the phrase to ‘what time have you usually got up in the morning’.

The validated measure for the research population being tested should be applied where possible. In the IMH&W, the McGill Pain Questionnaire used American word descriptors of pain. These words may be unfamiliar to UK participants, for example, 'lancinating.' Additionally, there are words which may be problematic for those with a low reading ability or vocabulary (Main, 2016). In the UK, the guidance for government websites and information sheets is that written materials should be aimed at a reading age of 9 years (Government Digital Service, 2023). While every effort was made to discuss the layout and employ lay language in consultation with Patient Participation Involvement groups, measures validated elsewhere may not be optimal.

2.2.6 Sampling or selection bias

This occurs when the sample used in the survey does not accurately represent the target population. It can happen if certain groups are underrepresented or excluded from the sample, leading to non-generalizable results, and it occurs whenever non-random samples are assembled. For example, if a survey is conducted only among people who report pain, it may not be representative of the broader population. I acknowledge that recruiting people with or at risk of pain or frailty would influence results. However, my research questions sought to explore the relationship between pain and frailty, and this may mean that my results might not be generalisable to people at low risk of pain and frailty.

2.2.7 Order Bias

The order in which questions are presented can impact responses (Bowling and Ebrahim, 2005). The primacy effect occurs when earlier questions have a stronger influence, while the recency effect refers to the influence of later questions. Respondents may also develop a pattern of response based on the initial questions, affecting their subsequent answers. Reversing the order of responses is sometimes used to disrupt this pattern. There is one item for depression, which is reverse-coded in CAP-knee.

2.2.8 Bias summary

Researchers must be aware of biases and employ appropriate strategies to minimise their impact on survey results. This may involve many factors, including but not limited to careful sample selection, clear and unbiased question design, and the use of standardised, validated, and reliable measurement tools. The use of effective survey administration techniques, such as ensuring clear instructions are provided and using data analysis methods that take account of potential biases.

2.2.9 Data selection criteria employed in this thesis.

Other studies have selected different age cut-offs, and FRAIL has been validated for use with people aged 40 years and older (Ravindrarajah et al., 2013). Countries and regions across the world vary widely in their life expectancy and healthy life expectancy. This may result in frailty being observed at a younger age in a region where life expectancy is low and vice versa.

A cut-off of 60 was selected, based on definitions of frailty as being age-related and following precedent from previous research which enables comparability. Whilst those below 60 years may meet many of the criteria that are indicative of frailty, it is not possible to know without clinical observations whether these participants are frail or have morbidities that share aspects with frailty. Whilst this is true for those aged over 60 there is more likelihood that they could be frail rather than those who are younger.

2.3 Statistical analyses

The type of analysis depends on the research question and the type of data. Several principles guided the analysis, which apply to the following chapters.

2.3.1 Descriptive analysis

Initial analysis was run to provide descriptive statistics, summarise the percentage of categorical data, and evaluate normality and frequency distributions in the continuous data. This includes the calculation of standard

deviation and range where appropriate and, if data does not have a normal distribution, using the median and interquartile range. The assumption of normality was assessed statistically for continuous variables using the Shapiro-Wilk test and visually using histograms (Kirkwood and Sterne, 2010).

The type of variable used determines the type of statistical test employed.

Categorical data which have a perceived order, for example, frailty, has three categories: robust, pre-frail and frail, and the order of data is referred to as ordinal. Ordinal outcome variables can be used with ordinal logistic regression. However, binary, or dichotomous data (frail / non-frail) permits the use of logistic regression analysis.

Continuous variables, if normally distributed, can be used in linear regression, for example, NRS pain. However, this is not an absolute and raises a question of whether normality is sufficient to invalidate linear regression.

2.3.1.1 Ordinal data

Ordinal responses to questions such as 'I generally felt tired' with a choice between four Likert response categories: Never, Sometimes, Often or Always. This allows the individual to express their level of agreement with the statement. In questionnaires, it is common to have some items that are reverse-coded; this is the case with B7 on the CAP-knee questionnaire, using the same categories as above, but the boxes are scored in reverse order. Reverse coding aims to reduce response bias by altering the wording so that they are opposite or negative to the other questions.

There is controversy about whether ordinal data, such as Likert responses, can be treated as interval data and subject to parametric analysis (Carifio and Perla, 2008) (depending upon normal distribution). However, it has been demonstrated that parametric tests can be used with Likert scales as the tests are robust even if normal distribution is violated to a small extent (Norman, 2010). However, this relies on having a minimum sample of between 5 to 10 observations per group.

2.3.2 Association testing

For normally distributed data, I used parametric analyses of association (Pearson correlation and Linear regression models). For non-parametric data, I used Spearman's rank correlation coefficient or logistic regression models) Correlations were assessed using Spearman rho and bootstrapped to derive confidence intervals.

Data that do not follow a normal distribution can be skewed either positively (longer tail on the right) or negatively (longer tail to the left). Sometimes, skewed data can be corrected using various methods, such as log transformation. In the case of IMH&W, however, it was not possible to correct any data. Kurtosis is the measure of whether the distribution curve is flattened relative to a normal distribution; there is no method to correct kurtosis (Kirkwood and Sterne, 2010).

2.3.2.1 Correlations

I used the non-parametric Spearman's rank correlation coefficient to test the strength of association between two variables; it assumes the variables are independent and have an order or rank. The resultant Spearman's rho (rs) is between -1 and +1, depending on whether there is a negative or positive relationship between the two variables. A value of 0 means there was no association. This test does not produce confidence intervals but does provide a p-value; a strong correlation may not be statistically significant in a small sample and vice versa in a large sample.

Confidence intervals for Spearman's rho were calculated using bootstrapping, which is a resampling method. A 95% confidence interval is the range within which your estimate will fall 95% of the time (if you keep repeating the experiment). Bootstrapping resamples the data to give the range of values that are included in 95% of the repeats. In this thesis, Resampling was carried out 10,000 times for each time that bootstrapping was used.

2.3.2.2 Categorical associations

For categorical variables, if both the outcome and explanatory variables were multi-category (≥2), then I performed a Chi-squared test (X^2). For example, to assess the association of frailty and BMI class. The Chi-squared test determines if there is a significant difference between two proportions. The analysis produced X^2 and p values. If there were <5 values in a cell of the contingency table, then I utilised Fisher's exact test, which uses an exact test, whereas chi-squared relies on approximation.

2.3.2.3 Linear regression models

If the outcome variable is continuous, for example, NRS Pain, then a linear regression model may be employed. Linear regression models make four assumptions:

- There is a linear relationship between the outcome and the explanatory variable (checked using a scatterplot).
- The outcome variable is normally distributed for each value of the explanatory data, known as homoscedasticity (checked by testing whether the distribution of residuals is normally distributed).
- The standard deviation of the outcome value is the same for each value of the explanatory variable.
- Each observation is independent (i.e., one per participant).
- Parametric tests are very robust, and if they can be used, they should be (Fagerland, 2012).

In the studies that follow, in which NRS pain was the outcome. The data were treated as a continuous variable with a normal distribution.

2.3.2.4 Ordinal logistic regression models

Ordinal response regression models, or proportional odds models, describe the relationship between an ordered categorical response (outcome) variable and one or more explanatory (independent) variables. FRAIL is the outcome for most of the following chapters. In the initial work, I employed ordinal logistic regression to account for the three categories incorporated: robust,

pre-frail, and frail. When carrying out logistic regression, there are five assumptions and post-hoc checks (Stoltzfus, 2011).

- The dependent variable is measured at an ordinal level.
- One or more independent variables are continuous, categorical, or ordinal.
- Absence of multi-collinearity (when two or more independent variables are highly correlated).
- There should be an adequate number of events for each independent variable (estimated at 10-20 events for each covariable).
- Proportional odds - each independent variable has an identical effect at each cumulative split of the ordinal dependent variable.

When ordinal logistic regression was required, I employed the 'gologit2' package developed for use in STATA (Williams, 2016). This ran the model and calculated the odds ratio at each level of both the outcome and explanatory variables. If the assumption of parallel lines was met, the model was condensed into one odds ratio.

The results following this method were interpreted as indicating that the frailty level has a different magnitude of association with the explanatory variable and/or covariables. For example, the odds ratio of an increased risk of subsequent frailty in a robust individual differs from that of someone who is prefrail.

2.3.2.5 Logistic regression models

FRAIL was described in terms of a binary classification of frail/non-frail. This analysis was used in all the papers and most abstracts relating to this thesis.

Logistic model assumptions include:

- The outcome is binary.
- Absence or low multicollinearity.
- Each observation is independent.
- Linearity of the explanatory variables and log odds.

- A large sample size, at least 10 cases per variable in the model.

An advantage of logistic regression is that it does not require a linear relationship between the outcome and explanatory variables, nor that residuals are normally distributed or homoscedastic.

The odds ratio is reported as the increased odds per unit. For example, if the adjusted odds ratio (aOR) for being frail is 1.68 (95%CI 1.57 to 1.79) per unit increase of NRS pain. This means that for each unit of NRS pain, there is an increased likelihood of frail classification. So, for someone with an NRS = 4, that would be the equivalent of a four-fold increase in the likelihood of being classified as frail.

2.3.3 Other statistical tests and methods

Most of the following chapters used the methods above and the data. However, two other methods were also used.

2.3.3.1 Standardised regression coefficients

Standardised coefficients, also known as beta coefficients or standardised regression coefficients, are used in statistical analysis to compare the relative importance and impact of different variables in a regression model. They are useful when the variables in the model have different units of measurement or scales (Schielzeth, 2010, Tranmer and Elliot, 2008). For example, in IMH&W, two measures of pain were used: a numerical rating scale (0-10) and McGill Pain Rating Index (0-78). It is not easy to compare these measures because the scales are so different.

Method: standardised coefficients are calculated by generating z scores ((value-mean)/ standard deviation) by standardising each variable to have a mean of zero and a standard deviation of one. This standardisation allows for a direct comparison of the magnitude and impact of different variables on the dependent variable (Tranmer and Elliot, 2008).

Interpretation: Standardised coefficients represent the change in the outcome variable, measured as multiples of its standard deviation. This

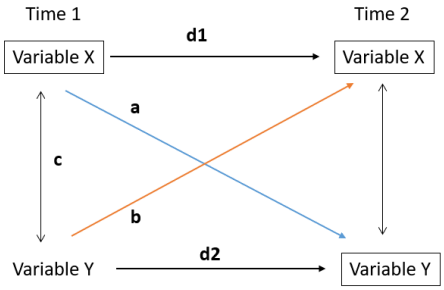
standardised metric makes it easier to compare the relative impact of different predictors. It allows researchers to assess the importance of variables based on the strength of their associations (Tranmer and Elliot, 2008).

Generalizability: Standardised coefficients are not affected by changes in the scale or units of measurement of the variables. This makes them more generalisable and allows researchers to compare results across different studies or populations (Paternoster et al., 1998).

It is important to understand that while standardised coefficients provide valuable information, they do not convey the practical significance or real-world meaning of the effects. Interpreting the standardised coefficients should be done in conjunction with the context of the study and the variables involved.

2.3.3.2 Cross-lagged path analysis (CLPA)

This type of path analysis was used in Chapter 4. Two-wave cross-lagged path modelling permitted simultaneous exploration of plausible causal pathways in non-experimental data; simultaneous associations between pain and frailty, alongside frailty and pain, were modelled, trying to remove the possible reciprocal influences that might confound separate analyses. Adjustments were also made for sex, age, and BMI at both baseline and 1-year. Each arrow represents the pathway and is interpreted in the same manner as a regression coefficient. Figure 2-1 provides an example alongside the interpretation.



'a' and 'b' : cross-lagged correlations
'c': synchronous correlations indicated by a two-headed arrow.
'd1' and 'd2' autocorrelations
If 'a' is substantially different from zero, we can conclude that X causes Y.
If 'b' is substantially different from zero, we can conclude that Y causes X.
If 'a' and 'b' are both substantially different from zero, we can conclude bi-directionality.

Figure 2-8 Example of cross-lagged path analysis.
Source: adapted from (Anderson and Kida, 1982)

The use of standardised regression coefficients permitted comparisons of the strengths of the paths. Maximum likelihood estimation methods were used to deal with binary outcome, which did not produce root mean square error of approximation (RMSEA) values (Allison et al., 2017). The effect size for cross-lagged path modelling, using standardised regression coefficients, was interpreted as follows: 0.03 indicated a small effect, 0.07 a moderate effect and 0.12 a strong effect (Orth, 2022). Orth reports there are several reasons that the CLPA interpretation differs from the usual regressions; the associations are estimated over a period of time, so there is assumption that longitudinal associations are smaller than concurrent associations. Also, the CLPA automatically adjusts for the baseline variable, which accounts for a large amount of any regression; in this instance, we measure the change. Furthermore, the CLPA takes account of the concurrent correlation between the variables at baseline, so again, it restricts the amount of change that can be measured. When conducted simultaneously, these factors result in smaller coefficients, so the interpretation of the effect is correspondingly affected. The software used to perform CLPA was Mplus 8.5 (Muthén, 1998-2017).

2.3.3.3 Cronbach's alpha

The Cronbach's alpha was calculated to measure the reliability of a construct that was summed from several individual items. It measures internal

consistency, which is the extent to which the items measure the same construct, for example, frailty (Tavakol and Dennick, 2011). If there is an extremely high value, it may suggest that the measure is unidimensional, whereas a lower score indicates a more multi-dimensional construct or heterogeneous items.

The following were proposed as guidelines for interpreting the Cronbach alpha: unacceptable <0.5; poor 0.6 to ≥0.5; 0.7 to >0.6 questionable; 0.8 to ≥7 acceptable; 0.9 to ≥0.8 good; and ≥ 0.9 excellent (Tavakol and Dennick, 2011).

2.3.3.4 Inter-rater reliability testing

There are two reasons to check reliability: firstly, that the rater has achieved sufficient skill to record the measurement accurately, and secondly, that the equipment and/or method being used provides repeatable measures.

The intraclass correlation coefficient (ICC) was used to assess the reliability between raters. ICC depends on the assumptions of an ANOVA model (below). ICC is biased if these assumptions are not met. A second agreement index is the concordance correlation coefficient (CCC), which does not rely on ANOVA assumptions and is, therefore, non-parametric (Chen and Barnhart, 2008).

ANOVA assumptions for ICCs:

1. The responses for each factor level have a normal population distribution.
2. These distributions have the same variance (homogeneity of variance).
3. The data are independent.

These assumptions were checked using histograms or the Shapiro-Wilk statistical test.

There are different ways of calculating ICC; I chose to use the mixed-effects model; in this instance, the two raters are regarded as a fixed effect. This is for a model in which the raters are of interest. The results should not be generalised to other raters. There are two forms of calculation: one produces

asymptotic confidence intervals, and the other produces z-transformed confidence intervals.

For the interpretation of ICC and CCC results, the following criteria were used: <0.5 = poor, 0.5–0.74 = moderate, 0.75–0.9 = Good and >0.91 = Excellent (Middlebrook et al., 2020).

The Bland-Altman method was used to assess agreement between two continuous measures by calculating the mean difference and constructing limits of agreement (Bland and Altman, 1986)The Bland-Altman method explores the differences between two measures, using means and standard deviations of the differences to form a scatter plot graph. The difference between two paired measurements is plotted against the mean of the two measurements, providing a visual representation of this distribution of the measures.

The Bland-Altman method can also rate how two frailty tools agree or disagree in their frailty classification. For IMH&W, this involved comparing FRAIL and FiND classifications.

2.3.3.5 Z tests

Z-tests were used to compare the strengths of regression coefficients or the changes between coefficients in separate models (Clogg et al., 1995), where values ≥±2 were interpreted as significantly different coefficients.

$$Z=b1-b2(\sqrt{SEb1^2+SEb2^2})$$

B = beta coefficient, 1 or 2 = model number, SE = standard error.

2.3.4 Validation of electronic versus paper IMH&W reliability

I checked the reliability of FRAIL classification in IMH&W wave 3, comparing the reliability of self-reported data for participants who reported using different reporting media, namely electronic and paper.

Participants (n=168) completed an IMH&W questionnaire and repeated this measure using the electronic format within 3 weeks. I calculated the FRAIL

items and the classification to explore the consistency between versions, and I additionally compared medications and morbidities reported.

Reliability and agreement were compared using ICC and kappa statistics. Continuous variables (were compared using ICC. Kappa statistics for Likert scales and >2 responses were calculated using weighted methodology (squared penalties).

2.4 Summary of methods

In this chapter, I have described the methods that were used to prepare and analyse the IMH&W data. If deviations or adaptations were made, they will be detailed in the specific chapter.

CHAPTER 3 CROSS-SECTIONAL ASSOCIATION OF JOINT PAIN WITH FRAILTY.

3.1 Introduction

In Chapter 1, I described the association between frailty and chronic pain in cohort studies (Veronese et al., 2017b, Bindawas et al., 2018, Misra et al., 2015, Wade et al., 2016, Rodríguez-Sánchez et al., 2019). A systematic review of prospective longitudinal studies showed that people with chronic pain were twice as likely to become frail during the following year compared to people without pain, suggesting that chronic pain may play a causal role in the development of frailty. However, the relationship between chronic pain and frailty is complex. Chronic pain might make the transitions from non-frail to frail states more likely or make the transitions from frail to non-frail states less likely. Pain has been described as a marker of vulnerability and proposed as an additional criterion in frailty phenotyping (Lohman et al., 2017). Confirming the association within the IMH&W cohort will help determine if my study supports the findings of other cohort studies and the extent of the association with demographic factors. This will also permit me to situate the cohort by comparing the IMH&W with other UK cohorts.

This study aims to examine the cross-sectional association of chronic pain with frailty in the Investigating Health Musculoskeletal and Wellbeing cohort.

This study has several objectives:

- to examine the contribution of the items to the classification and the internal consistency of FRAIL.
- to compare two phenotyping tools, FRAIL and FiND, to explore whether FiND can be used to support the findings of FRAIL.
- to examine the pain measures used in IMH&W and test their validity.
- to examine the association of FRAIL and demographic variables of age, sex and BMI class.
- between joint pain with the demographic variables of age, sex, and BMI class.

- to assess the cross-sectional association between joint pain and frailty in the IMH&W cohort.

3.2 Methods

Design: Cross-sectional analysis of cohort data at baseline. The general methods are in Chapter 2.

3.2.1 Participants

Eligible participants were aged ≥60 years and who completed the IMH&W baseline survey, including all items of the FRAIL scale.

3.2.2 Variables

3.2.2.1 FRAIL classification

Described in Section 2.1.2.1.1 2.2. and included the augmented version of FRAIL described in 2.1.8.1. This chapter initially explores frailty using FRAIL, which has three classifications: robust, pre-frail, and frail. Later, FRAIL was dichotomised to ensure that clinical frailty was present rather than mobility-related issues, which may be found in a pre-frail group.

3.2.2.2 FiND frailty classification.

This was used as a secondary outcome measure of frailty. FiND is a self-report questionnaire with five components. I employed a modified version described as modified FiND (mFiND) in Section 2.1.2.2. Individuals were classified using mFiND as disabled, robust, or frail.

3.2.2.3 NRS joint pain and other covariables

NRS joint pain is described in 2.1.2.2.1, and the co-variables of age, sex and BMI are described in 2.1.4.

3.2.2.4 Most bothersome joint

IMH&W used tick boxes for participants to indicate their most bothersome joint: jaw, back or spine, shoulder, elbow, wrist, knee, hand or finger, hip, neck, ankle, and foot or toe. Participants were encouraged to ‘Pick one,’ but many indicated more than one box; if this was the case, each joint ticked was recorded.

3.2.3 Data analysis

Initial analysis was run to provide descriptive statistics, summarising the percentage of categorical data, and evaluating normality and frequency distributions in the continuous data. This included calculation of standard deviation and range where appropriate, and if data does not have a normal distribution, tested using the Shapiro-Wilk test, using the median and interquartile range.

Internal consistency for items was calculated using Spearman's rank correlation coefficient, calculating all possible internal components. Cronbach's alpha was calculated for the five FRAIL items to assess construct reliability.

Correlation coefficients were interpreted as follows: 0.1 = weak or small, 0.30 as moderate and ≥0.50 as strong or large (Kirkwood and Sterne, 2010).

Cohen's kappa coefficients were calculated to determine the agreement between the FiND questionnaire and the reference instrument of FRAIL. Kappa was calculated using R and the 'vcd' package.

Cohen's kappa statistics were interpreted as follows: 0-0.20 = indicated no agreement, 0.21-0.39 as minimal, 0.40-0.59 as weak, 0.60-0.79 as moderate, 0.80-0.90 as strong and >0.90 as almost perfect (McHugh, 2012).

Z-tests were used to compare the strengths of regression coefficients or the changes between coefficients in separate models (Clogg et al., 1995). Z values ≥±2 were interpreted as indicating significant differences.

Multivariable ordinal logistic regression was used for analysis with frailty as the dependent variable, as described in Chapter 2; this meant there were different odds ratios for the different levels of FRAIL.

3.3 Results

Data from 2,185 participants were analysed (Figure 3-1). The median age was 74 (range 60-96) years, and 1,202 (55%) were female. At baseline, 438 (20%) were classified as frail, 1,971 (90%) reported joint pain NRS≥1, and the mean (SD) NRS at baseline was 5.5 (2.5). IMH&W descriptives are shown in Table 3-2 & Table 3-3.

3.3.1 The IMH&W cohort

The IMH&W database was searched for data matching the eligibility criteria previously described in February 2020. The IMH&W included adults aged ≥18 years. The inclusion criteria for this study were age ≥60 years and all FRAIL criteria to be completed. There were 3,716 (53%) participants with at least one FRAIL criterion missing.

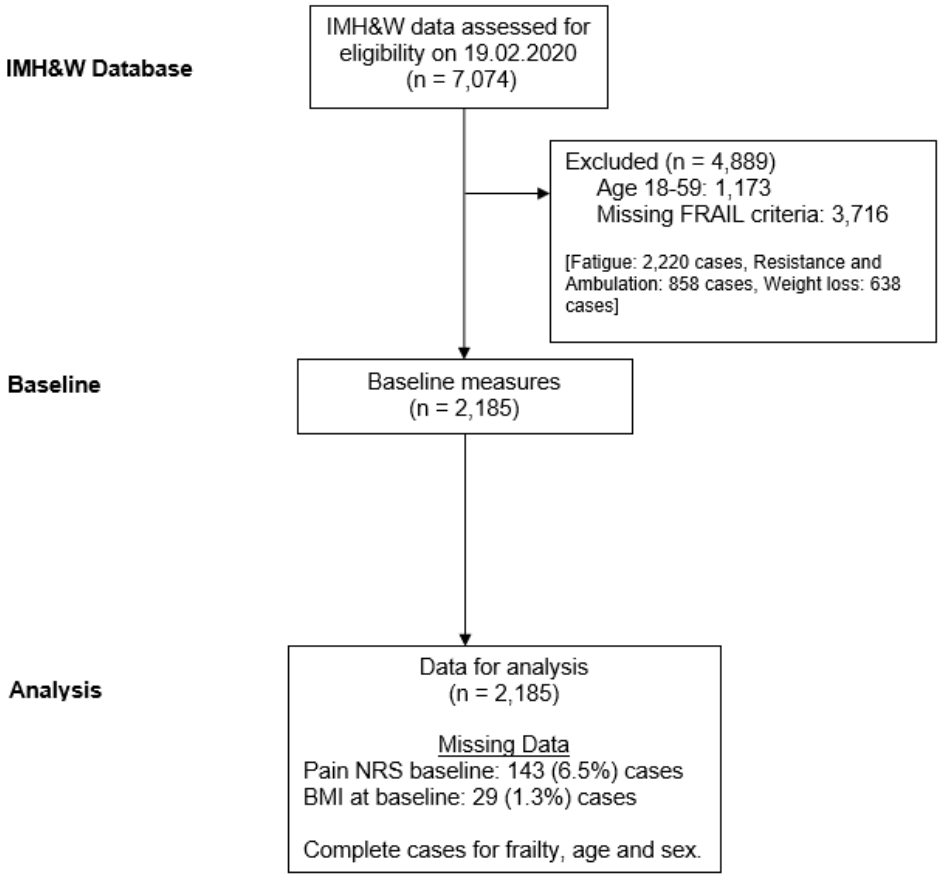


Figure 3-1 IMH&W Consort flow diagram for cross-sectional study.

The selected participants who matched the criteria for this study were compared with the IMH&W cohort in the same age range (≥60 years) (Table 3-1). The study group had a similar median age and proportion of females, but a higher proportion of white ethnicity than the IMH&W cohort. However, both groups had a very high proportion of white individuals. The study group had a higher mean pain than the IMH&W cohort. The IMH&W group had a higher proportion of individuals who recorded zero pain, 341 (10%), compared to 72 (4%) in the study group.

Table 3-1 IMH&W cohort and Frailty study subgroup in individuals aged ≥60 years.

	IMH&W (n=3,729)	Frailty study group (n=2,185)	P-value
Age, median	72.9	73.2	0.0102
Age range (years)	60-103	60-96	
Gender: female n (%)	2, 052 (55)	1,202 (55)	NS
Ethnicity: white n (%)	3,467 (93)	2,152 (99)	<0.001
Joint Pain (NRS), mean (SD)	5.1 (2.7)	5.5 (2.5)	<0.001

3.3.1.1 Indices of multiple deprivation (IMD) decile

The indices of multiple deprivation (IMD) measure deprivation from postcode areas. IMDs combine information from seven domain indices: income; employment; crime; health and disability; education, skills and training; barriers to housing and services; and living environment. These are calculated and ranked using deciles to group geographic areas within England into ten equal groups, representing a range of deprivation. In this scale, the most deprived areas are decile 1 and the least deprived areas are decile 10 (GOV.UK, 2019). The IMH&W has representation from 1 to 10. This data was collected by using the postcode that the participant provided. The IMD is therefore based on the area where participants live and is not provided directly by individual participants. The Indices of Deprivation assess the relative deprivation levels across 32,844 small areas or neighbourhoods in England, known as Lower Super Output Areas. Each area receives a score and rank in seven different domains of deprivation, which are then combined to form the overall Index of Multiple Deprivation. Nottingham was ranked 11/317 most deprived district in England in 2019 (GOV.UK, 2019). Whilst Nottinghamshire is ranked 9/26 of the most deprived shire Counties in England.

Table 3-2 IMH&W Characteristics at baseline with FRAIL classification, n =2185

Variable	Total	Frail (438)	Non-frail (1,747)
Sex			
Female, n (%)	1,202 (55)	290 (24)	912 (76)
Male, n (%)	982 (45)	148 (15)	834 (85)
Prefer not to say, n (%)	1 (0.05)		1
Age (years), mean (SD)	73.9 (7.1)	74.5 (7.7)	73.7 (7.0)
Median (IQR)	73 (69-79)	74 (69-80)	
Age group			
60-69 years, n (%)	635 (29)	129 (20)	506 (80)
70-79 years, n (%)	1,072 (49)	180 (17)	892 (83)
>80 years, n (%)	478 (22)	129 (27)	349 (73)
Body Mass Index (kg/m^2),			
Mean (SD)	27.8 (5)	29.6 (5.7)	27.3 (4.6)
Median (IQR)	27.3 (24-31)	29.1 (26-33)	26.8 (24-30)
BMI Classes#			
Underweight, n (%)	30 (1)	9 (30)	21 (70)
Normal, n (%)	653 (30)	82 (13)	571 (87)
Pre-obese, n (%)	831 (39)	141 (17)	690 (83)
Obese, n (%)	642 (30)	194 (30)	448 (70)
Ethnicity			
White, n (%)	2152 (99)	428 (20)	1724 (80)
Smoking Status			
Never smoked, n (%)	1,001 (46)	178 (18)	823 (82)
Ex-smoker, n (%)	1,083 (50)	229 (21)	854 (79)
Current Smoker, n (%)	99 (5)	31 (31)	68 (69)
Alcohol Status			
≥3 units daily, n (%)	269 (12)	42 (16)	227 (84)
Physical Activity (weekly)			
Regular (2-4 hours), n (%)	1,562 (73)	201 (13)	1,361 (87)
None or Sedentary, n (%)	576 (27)	221 (38)	355 (62)
Indices of Multiple Deprivation decile, median (IQR) (1-10 most deprived to least deprived)	8 (5-9)	8 (5-9)	8 (5-9)
Recruitment route			
GP Surgery	1,972 (90)	383 (19)	1,589 (81)
Previous studies	191 (9)	45 (24)	146 (76)
Other	22 (1)	8 (36)	14 (64)
FRAIL classification			
Robust	934 (43)		1,747 (100) *
Prefrail	813 (37)		
Frail	438 (20)	438 (100)	

Abbreviations: SD – standard deviation; IQR – interquartile range; NRS – numerical rating scale 0-10; BMI – body mass index; Number of observations for each variable varies; 2185 relates to complete FRAIL and age data. Non-frail is robust and prefrail combined.
#WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese
Percentage = column-wise for the Total column, row-wise for the frail and non-frail classifications.

Table 3-3 IMH&W Baseline pain characteristics (n=2185)

Variable	Total	Frail (438)	Non-frail* (1,747)
Joint Pain (NRS)			
Mean (SD)	5.5 (2.5)	7.36 (1.8)	4.9 (2.4)
Median (IQR)	6 (4-7)	8 (6-9)	5 (3-7)
Morbidity, n (%)			
Angina	228 (10)	78 (34)	150 (66
Arthritis	1,477 (68)	374 (25)	1,103 (75)
Asthma	413 (19)	121 (29)	292 (71)
Cancer	237 (11)	52 (22)	185 (78)
Diabetes	386 (18)	114 (30)	272 (70)
Heart Attack	150 (7)	51 (34)	99 (66)
Heart Failure	63 (3)	27 (43)	36 (57)
Hypertension	856 (39)	185 (22)	671 (78)
Kidney Disease	124 (6)	43 (35)	81 (65)
Lung Disease	185 (8)	71 (38)	114 (62)
Stroke	145 (7)	43 (30)	102 (70)
Most bothersome joint¥, n (%)			
Jaw	16 (1)	4 (1)	12 (1)
Neck	349 (18)	94 (22)	255 (17)
Shoulder	477 (24)	138 (32)	339 (22)
Elbow	113 (6)	44 (10)	69 (4)
Wrist	227 (11)	65 (15)	162 (10)
Hand or Finger	463 (23)	109 (25)	354 (23)
Back or spine	739 (37)	212 (49)	527 (34)
Hip	446 (23)	129 (30)	317 (21)
Knee	730 (37	195 (45)	535 (35)
Ankle	236 (12)	73 (17)	163 (11)
Foot or toe	315 (16)	93 (22)	222 (14)
McGill Pain Questionnaire, median (IQR)			
Sensory	9 (5-14)	13 (8-19)	8 (4-13)
Affective	0 (0-2)	2 (1-5)	0 (0-1)
Evaluative	2 (0-3)	3 (1-4)	1 (0-2)
Miscellaneous	1 (0-4)	4 (1-6)	1 (0-3)
Pain Rating Index (PRI)	13 (7-22)	22 (13-32)	11 (6-19)
Number of words chosen (NWC)	5 (3-9)	9 (5-12)	5 (3-8)

Abbreviations: IQR – interquartile range; Number of observations for each variable vary; 2185 relates to complete FRAIL and age data. *Robust and prefrail combined

¥The question asked for the most bothersome joint (ONE); however, many participants filled out multiple boxes, and these were all recorded.

The morbidity totals include data collected from tick boxes, medications, and free text.

Percentage = column-wise for the Total column, row-wise for the frail and non-frail classifications.

3.3.2 The contribution of the items to the classification of FRAIL

In this study of 2,185 IMH&W participants, 934 (43%) were classified using FRAIL as robust, 813 (37%) as prefrail and 438 (20%) as frail. Table 3-4 shows the frequency of frailty items reported.

Table 3-4 Frequency of the FRAIL items in IMH&W cohort (n=2185)

Number of positive FRAIL items	N (%)	Classified
0	934 (43)	Robust
1	463 (21)	Prefrail
2	350 (16)	Prefrail
3	328 (15)	Frail
4	102 (5)	Frail
5	8 (0.4)	Frail

The items had heterogeneous contributions to FRAIL classification. The total column in Table 3-5, indicated that ambulation was the most frequently reported criteria in this cohort, followed by resistance and fatigue, and that loss of weight and illnesses were the least reported criteria.

Table 3-5 Frequency of FRAIL items in IMH&W cohort at baseline (n=2185)

FRAIL Items	Total, n (%)	Prefrail, n (%) *	Frail, n (%) #
Fatigue	623 (29)	239 (29)	384 (88)
Resistance	679 (31)	271 (33)	408 (93)
Ambulation	838 (38)	408 (50)	430 (98)
Illnesses	85 (4)	24 (3)	61 (14)
Loss of weight	370 (17)	221 (27)	149 (34)

* Prefrail included 1-2 items for each participant. # Frail included 3–5 items for each participant. No items were reported by participants classified as robust. Prefrail and Frail % were calculated as the number of reports/number of participants in the FRAIL category.

3.3.3 Internal Consistency of FRAIL

Each item was correlated with the total FRAIL score with the item removed (4 items). The strongest correlations were for the resistance and ambulation items (each r_s= 0.59, p<0.001), and the weakest correlation was observed for the loss of weight item (r_s= 0.08, p<0.001) (Table 3-6). The Cronbach's alpha of the FRAIL items of 0.61 was interpreted as 'questionable' 0.7 to ≥0.6 (Tavakol and Dennick, 2011).

Table 3-6 The internal consistency of FRAIL (N=2,185)

FRAIL Item	Cronbach's alpha if the item is removed
Fatigue	0.52
Resistance	0.42
Ambulation	0.41
Illnesses	0.63
Loss of weight	0.68
Overall Cronbach's alpha	0.61

Table 3-7 illustrates two findings. Firstly, each FRAIL item was correlated with NRS pain; the strongest correlation was between ambulation and NRS pain (r_s= 0.47, p<0.001), and the weakest correlation was between loss of weight and NRS pain (r_s= 0.09, p<0.001). Secondly, the odds ratio of having a deficit in an item increased per unit of NRS pain. For example, the likelihood of having a resistance deficit increased by an odds ratio of 1.62, (95%CI 1.54 to 1.71), p<0.001 per unit of NRS pain. Mean (SD) NRS pain was 5.4 (2.5), thus resulting in a five-fold increase in the odds of having a resistance deficit.

Table 3-7 The association between FRAIL items and NRS pain (n=2042)

FRAIL Item	Spearman's rho	OR (95%CI)	P value
Fatigue	0.38	1.49 (1.42,1.57)	<0.001
Resistance	0.44	1.62 (1.54, 1.71)	<0.001
Ambulation	0.47	1.62 (1.54, 1.70)	<0.001
Illnesses	0.10	1.27 (1.15, 1.41)	<0.001
Loss of weight	0.09	1.32 (1.23, 1.41)	<0.001

Abbreviations: CI – confidence interval; OR – odds ratio.

3.3.4 Augmentation of FRAIL

Table 3-7 indicates how many extra morbidities were identified using the augmentation procedures described in Chapter 2.

Table 3-8 The number of additional morbidities indicated by free text extraction.

Morbidity	Medications indicate morbidity	Morbidity ticked	Morbidity not ticked, but in medication.
Diabetes*	349	439	41
Asthma*	349	438	98
Lung disease*	24	162	10
Hypertension*	422	890	138
Angina*	106	220	20
Gout	93	205	9
Rheumatoid Arthritis	98	226	31
Osteoporosis	87	251	31
Dementia	2	12	1
Cancer*	19	225	7
	2553	3351	386

* Included in FRAIL; the others were in IMH&W checklists
Note: This is only for the medication which indicated additional morbidity

Table 3-9 Morbidity count by checklist and augmentation (n=6,342)

Morbidity	Check-list [1]	Free text [2]	Medications [3]	Total
	n	n	n	n, (%)
Arthritis	1447	21	9	1477 (68)
Hypertension	779	42	35	856 (39)
Degenerative disc disease	767	24	0	791 (36)
Upper gastro-intestinal	0	26	658	684 (31)
Asthma	325	7	81	413 (19)
Diabetes without complications	349	12	25	386 (18)
Osteoporosis	218	4	29	247 (11)
Cancer	201	30	6	237 (11)
Angina	197	14	17	228 (10)
Lung disease	139	38	8	185 (8)
Myocardial Infarction	150	0	0	150 (7)
Stroke	126	19	0	145 (7)
Kidney disease	116	10	0	124 (6)
Depression	0	23	81	104 (5)
Visual impairment	0	34	57	91 (4)
Chronic Heart Failure	60	2	1	63 (3)
Neurological	0	35	21	56 (3)
Anxiety	0	18	22	40 (2)
Lower Gastro-intestinal	0	29	0	29 (1)
Hearing impairment	0	12	0	12 (0.5)
Diabetes with complications	0	12	0	12 (0.5)
Dementia	9	0	0	9 (0.4)
Liver disease	0	7	0	7 (0.3)
Peripheral vascular disease	0	6	0	6 (0.3)
Hemiplegia	0	1	0	1 (<0.1)
AIDS	0	1	0	1 (<0.1)
Subtotal illnesses in FRAIL (11)	3,889	196	182	4,264
Subtotal illnesses not in FRAIL (15)	994	220	868	2,078
Total morbidities identified	4,883	413	1,050	6,342

Abbreviations: AIDS – Acquired immune deficiency syndrome. Items in bold are included in FRAIL; non-frail illnesses are extra morbidities from the Charlson and Functional Comorbidity Indices.
Diabetes is classified as painful if the participant reports complications such as neuropathy (Charcot foot) and retinopathy.
1 - morbidity appeared in the checklist. This included all FRAIL illnesses plus degenerative disc disease, osteoporosis, and dementia. 2 - morbidity appeared in free text only. 3 - morbidity is inferred from medication only.

Note: there is an order of precedence to columns; the morbidity is counted as present in the following order: 1) checklist, 2) free text, 3) medication, and counted once even though it may be originally reported in all three ways.
1159 (53%) of participants reported free text morbidities, and 2088 (96%) reported medications

Table 3-9 indicates the number of participants classified using the original FRAIL and the augmented version. The original frail used only tick boxes. Eight further participants were classified as frail using the augmented frail, in which free text morbidities and medications were used to detect the illness-items. The same proportion of participants was found in each class.

Table 3-10 Comparison of FRAIL original compared to augmented.

FRAIL classification	Original n (%)	Augmented n (%)
Robust	939 (43)	934 (43)
Prefrail	816 (37)	813 (37)
Frail	430 (20)	438 (20)
Total	2185	2185

3.3.4.1 Medications

There were 128 participants (67 females,52%) who did not report taking any medication. The remaining 2,522 reported at least one medication. The maximum number of reported medications for one person was 25. There were 2,430 participants with medication data in this field.

3.3.4.1.1 Analgesia

Descriptives were produced, and to complete a more accurate report, I broke down the data further. Identifying which opioids were reported, whether a Gabapentinoid or Tricyclic was being reported for central/neuropathic analgesia. So, I recoded these into sub-classes and individual medications. The descriptive tables of analgesia count and frequency by sex and age group are shown in Appendix A2 Tables 1 and 2.

3.3.4.1.1.1 Evaluation of analgesia free-text data extraction

The extraction permits an in-depth analysis of the number of analgesic classes that participants reported. Unfortunately, the data regarding dose was not available, and this is a limitation. This goes further than previous studies, analysing all the reported analgesia and classifying them by individual medications and analgesic classes. The KPIC investigation has similar amounts of opioids and NSAIDs reported (Sarmanova et al., 2018), which is consistent with the current cohort. Whereas the UK Biobank reports far lower usage of

opioids (Macfarlane et al., 2020), this was expected, as they report their participants are likely to be healthy individuals. In comparison, IMH&W recruited people with or at risk of MSK disease.

3.3.4.2 Summary of augmentation of FRAIL

- Ultimately, augmenting FRAIL to include more 'illnesses-item' information did not alter the FRAIL classification greatly. The same proportion of individuals were observed in each classification (Table 3-10), so the augmented FRAIL data was not included in the papers arising from this thesis.

3.3.5 The comparison between two frailty classification tools.

In the study of 2185 participants using mFiND, 839 (38%) participants were classified as robust, 419 (19%) as frail, and 927 (42%) as disabled (Figure 3-2). Using FRAIL, 934 (43%) of participants were classified as robust, 813 (37%) as prefrail, and 438 (20%) as frail (Figure 3-3). Table 3-11 shows the discordance between mFiND and FRAIL classifications.

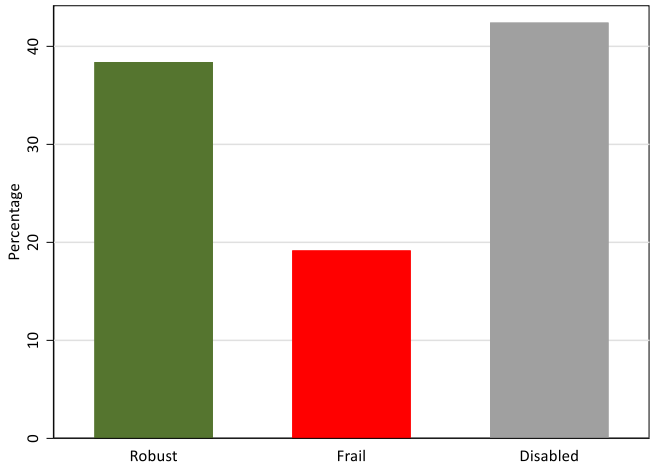


Figure 3-2 Classification of IMH&W participants using mFiND.

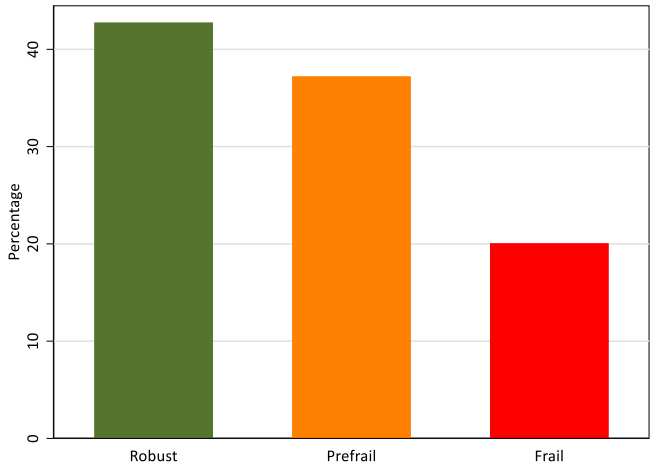


Figure 3-3 Classification of IMH&W participants using and FRAIL.

In the robust category, 817 (37%) of participants who were classified as robust by FRAIL were classified as robust in mFiND, as shown in Table 3-11. However, only one person (<0.01%) was classed as frail by both tools.

Table 3-11 Cross tabulation of FRAIL and FiND categories.

		mFiND category			
		Robust, n (%)	Frail, n (%)	Disabled, n (%)	Total
FRAIL	Robust	817 (37)	117 (5)	0 (0)	934 (43)
Category	Prefrail	22 (1)	301 (14)	490 (22)	813 (37)
	Frail	0 (0)	1 (0)	437 (20)	438(20)
Total		839 (38)	419 (19)	927 (42)	2185

The robust and frail categories were examined for agreement, omitting the disability category from mFiND and the prefrail from FRAIL, as indicated in Table 3-12. The Kappa calculation for the Robust and Frail categories of FRAIL and mFiND resulted in a Kappa score of 0.012, which was not significant (p=0.31) and is interpreted as “no agreement” (McHugh, 2012).

Table 3-12 Kappa table for Robust and Frail categories in FRAIL and FiND

		FiND		
		Robust	Frail	Total
FRAIL	Robust	817	117	934
	Frail	0	1	1
Total		817	118	935

3.3.6 Association of covariables with FRAIL classification

The associations of covariables with the ordinal FRAIL classification are shown in Appendix B1. The following shows the association with the binary frailty classification of frail/ non-frail.

3.3.6.1 Frailty classification by sex

There was significant heterogeneity of FRAIL between sexes X^2 =27.67, p<0.001 (Figure 3-4). In the IMH&W, 290 (24%) of females were classed as frail compared to 148 (15%) of males.

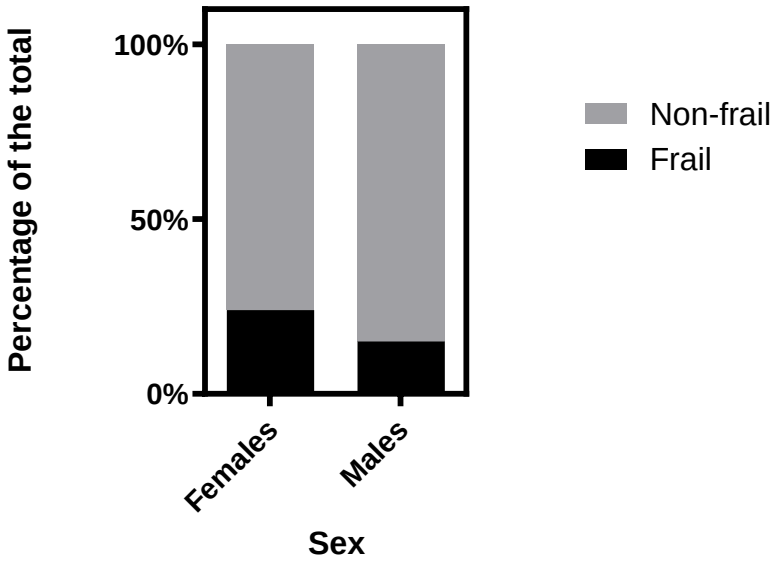


Figure 3-4 IMH&W FRAIL classification by sex (n=2184)

3.3.6.2 Frailty classification by age group

In the IMH&W cohort, participant ages ranged from 60 to 96 years; the median was 74, and IQR=69-79. When age was categorised, the relationship between age and frailty appeared to have significant heterogeneity (X^2 =21.49, p<0.001). There was a higher proportion of people aged ≥ 80 years who were classified frail (n=129, 27%) compared to those who were <80 years (n=309, 18%). *Figure 3-5*((When age was treated as a continuous variable, the correlation between age and FRAIL was r_s= 0.09, p<0.001 (Figure 3-5).

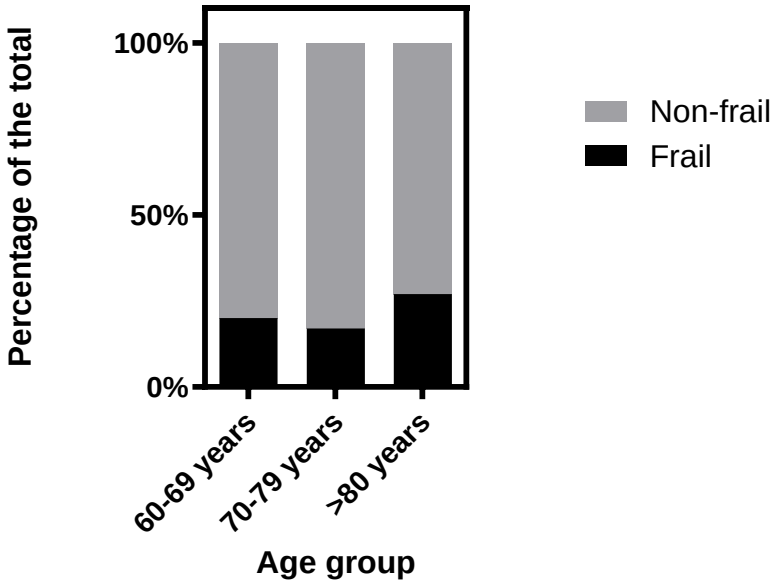


Figure 3-5 IMH&W FRAIL classification by age group (n=2185)

3.3.6.3 Frailty classification by Body Mass Index class.

In the IMH&W cohort, the median BMI was 27.3, IQR=24-31. There was significant heterogeneity of frailty between BMI classes (X^2 =72.40 p<0.001). There was a greater proportion of participants who were frail and were classified as underweight, pre-obese, and obese, compared to those with a normal BMI (Figure 3-6). However, it should be noted that only 30 participants were recorded as underweight. There appeared to be a U-shaped distribution; this was important for future analysis as it indicated that BMI should be categorised for future analyses rather than treated as ordinal or linear.

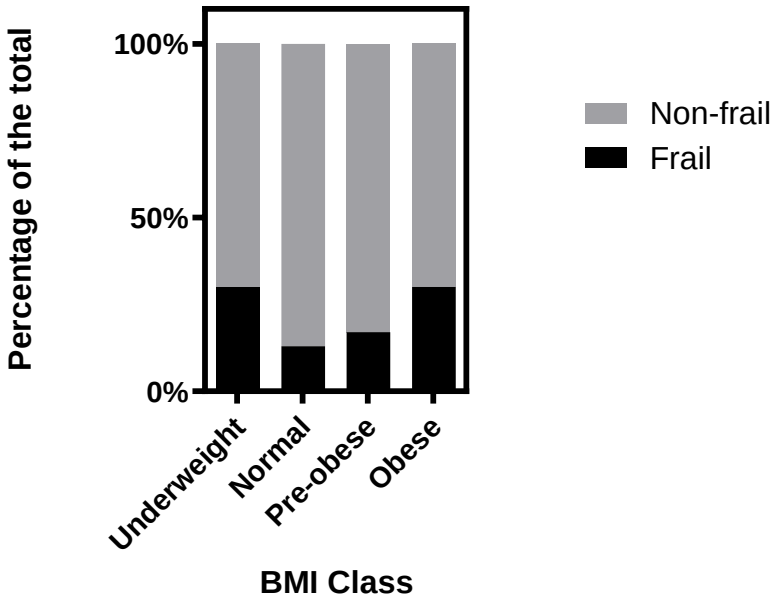


Figure 3-6 IMH&W FRAIL classification by Body Mass Index class (n=2156)

WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

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3.3.7 Examination of the pain measures used in IMH&W.

3.3.7.1 Pain Numerical Rating Score

Of the 2,185 IMH&W participants, 2,042 (93%) completed the NRS pain question reporting a mean (SD) NRS pain of 5.5 (2.5).

The Shapiro-Wilk test was significant ($p<0.001$), indicating the NRS pain scores had a significantly different distribution from normal (skewness=-0.27, and kurtosis=2.41) (Figure 3-7).

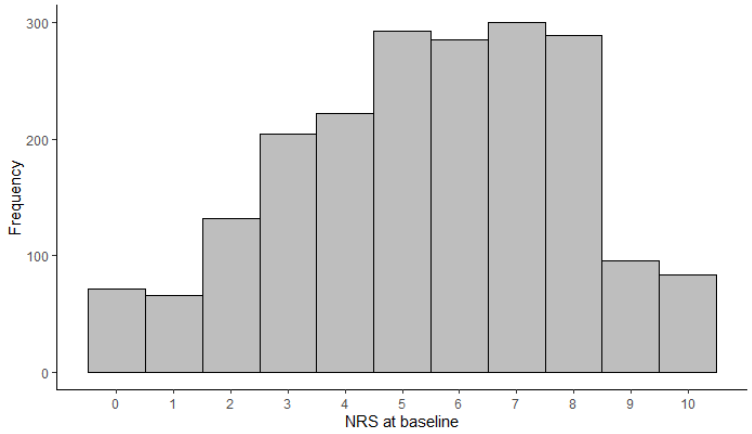

Figure 3-7 NRS pain histogram (range 0-10)

3.3.7.2 Missing data

There was no missing data for the frailty classification, age, and sex. There were 29 participants (1.3%) who did not provide height or weight data within the criteria described in Table 2-3, preventing the calculation and classification of BMI. There were 143 (6.5%) participants who did not respond to the NRS joint pain question. Table 3-13 illustrates that there were some heterogeneities in baseline characteristics between those who completed the NRS pain question and those who did not report joint pain. Non-responders to the NRS question were more likely to be male, non-obese, non-frail, and aged 70-79.

Table 3-13 Characteristics of participants with missing NRS pain data at baseline compared with those who reported NRS pain.

Variable	Baseline NRS 0-10 N=2042	NRS missing. N = 143	Chi-square value	P value
Age group, n (%)			10.06	0.007
60-69 years	609 (30)	26 (18)		
70-79 years	986 (48)	86 (60)		
≥80 years)	447 (22)	31 (22)		
Sex, n (%)			12.36	<0.001
Female	1144 (56)	58 (41)		
Male	898 (44)	84 (59)		
BMI class, n (%)			9.74*	0.019
Underweight	28 (1)	2 (1)		
Normal)	595 (30)	58 (41)		
Pre-obese	780 (39)	51 (36)		
Obese	612 (30)	30 (21)		
FRAIL classification, n (%)			56.43	<0.001
Robust	831 (41)	103 (72)		
Prefrail	780 (38)	33 (23)		
Frail	431 (98)	7 (2)		

*Fishers exact

Abbreviations: BMI – body mass index

#WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

3.3.7.3 McGill pain questionnaire

A total of 1,952 (89%) of IMH&W participants responded to MPQ wordlists, and 1,942 (89%) responded to both NRS pain and MPQ. The median (IQR) PRI was 13 (7-22) (Figure 3-8). The median (IQR) NWC was 5 (3-9) (Figure 3-9). The scores for the sub-classes of MPQ are shown in Table 3-3.

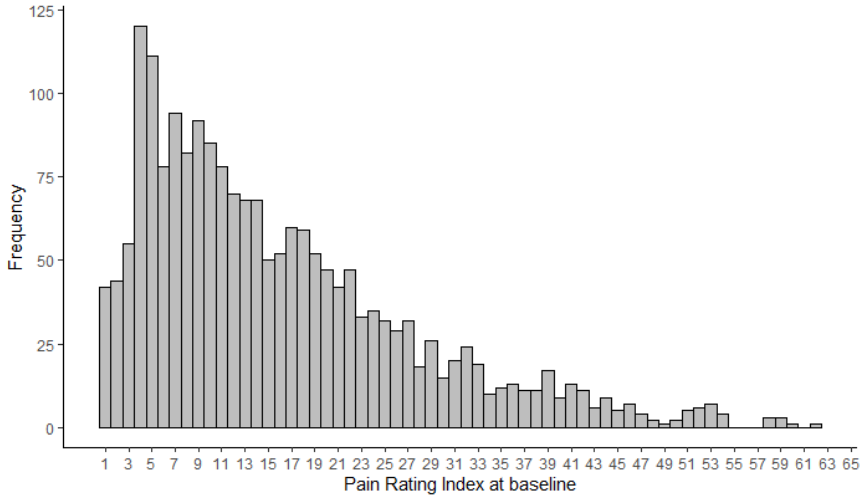

Figure 3-8 Pain Rating Index Histogram (range 1-78)

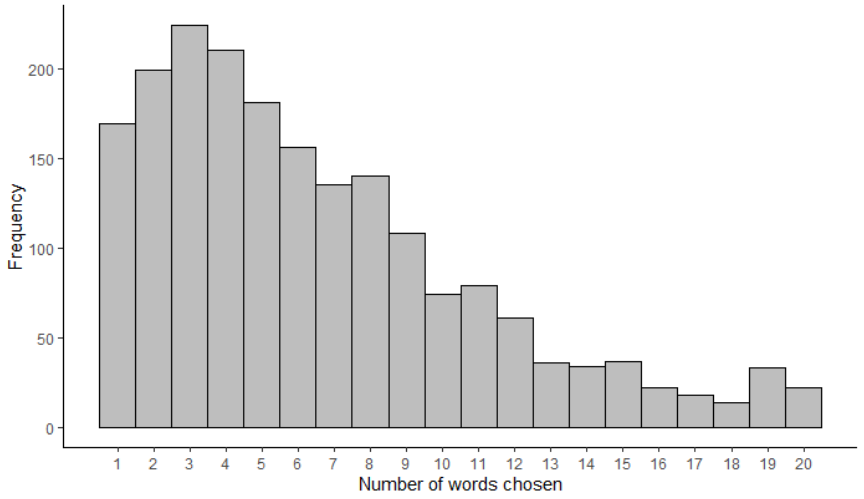

Figure 3-9 Number of Words counted histogram (range 1-20)

MPQ Missing data.

There were 233 (11%) participants who did not respond to any word list in the MPQ. There were some heterogeneities in baseline characteristics between those who completed some MPQ word lists and those who did not respond between sexes (X^2=10.93); age group (X^2=16.06); BMI class (X^2=21.48); and FRAIL category (X^2=109.45), all p<0.001. There was a higher proportion of non-responders who were male, aged 70-79 years, of normal weight, and robust than responders.

Commonly chosen words.

In IMH&W, 11 words were selected by >20% of participants Table 3-14.

Table 3-14 McGill Pain Questionnaire commonly chosen words.

Pain aspect	Frequency, n (%)
Sensory:	
Aching	954 (49)
Sharp	587 (33)
Tender	540 (30)
Stabbing	508 (28)
Throbbing	493 (29)
Shooting	473 (27)
Gnawing	442 (24)
Affective	
Tiring	539 (30)
Evaluative*	
Annoying	420 (22)
Troublesome	405 (22)
Miscellaneous	
Nagging	653 (36)

These are words chosen by >20% of participants.
*The two evaluative words appeared in the same word list.

3.3.7.4 Correlation between pain measures

NRS pain had a moderate positive correlation with PRI, which was of similar strength to the correlation with NWC (Table 3-14). The two McGill values were highly correlated with each other.

Table 3-15 Correlation between the NRS pain and McGill pain measures

	Spearman's rho	95% CI	P-value
NRS and PRI	0.54	0.51, 0.57	<0.001
NRS and NWC	0.50	0.47, 0.53	<0.001
PRI and NWC	0.96	0.95, 0.96	<0.001

3.3.8 Association of covariables with pain.

3.3.8.1 The association of NRS pain with sex classification

Mean (SD) NRS pain scores varied by sex; females reported a mean of 5.79 (2.55), and males reported a mean of 5.01 (2.41). A student *t*-test indicated females had a significantly higher mean NRS pain level when compared to males by 0.77, (95%CI 0.56 to 0.99), p<0.001. (Figure 3-9).

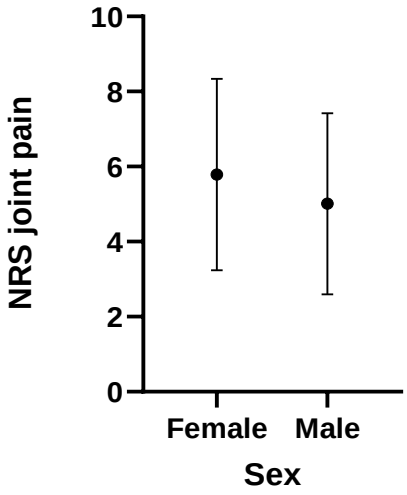

Figure 3-10 Mean NRS joint pain by sex classification.

3.3.8.2 The association of NRS pain with age group classification.

The same age groups as used with FRAIL classification were employed. The mean NRS pain with 95% CI is shown in Figure 3-11. A chi-squared test indicated significant homogeneity between age group and NRS pain, F (2,2039) =5.46, p=0.004, the lowest NRS pain was reported by people 70-79 years.

When age was used as a continuous variable, there was a negative association between greater age and lower NRS pain. However, this was not statistically significant using Spearman's rank correlation coefficient (rs=-0.03, p=0.1234).

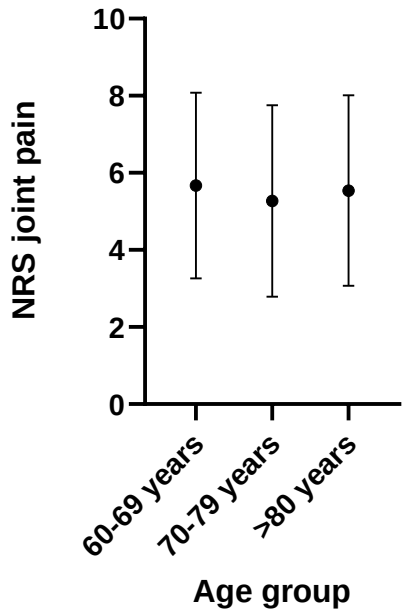

Figure 3-11 Mean NRS joint pain by age group classification.

3.3.8.3 The association of NRS pain with Body Mass Index class

Higher mean NRS pain intensity was associated with increased BMI as shown in Figure 3-12. There was a significant heterogeneity between NRS pain and BMI class, $F(3,2011) = 28.99$, $p<0.001$. There were only 30 participants classed as underweight.

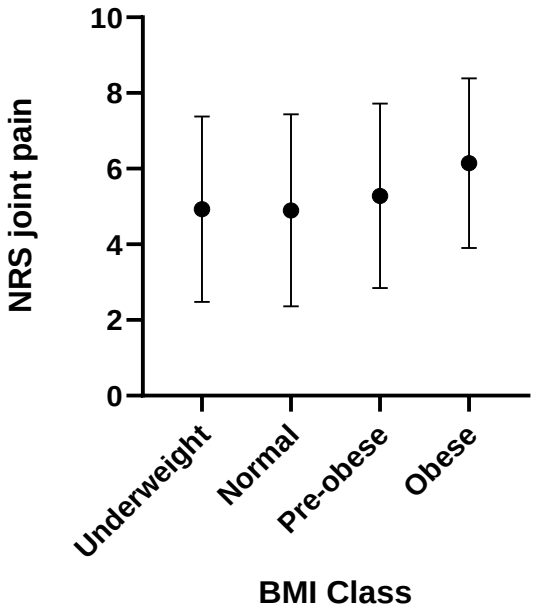

Figure 3-12 Mean NRS pain by Body Mass Index class.

WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

3.3.8.4 The cross-sectional association of pain with frailty

There is a significant strong positive correlation between NRS pain and frailty (r_s= 0.41, (95%CI 0.38 to 0.44), p<0.001).

Figure 3-13 indicates how the proportion of frailty changes between levels of pain. People who were non-frail had a lower range of NRS scores, whilst those who were frail had pain in the higher NRS range.

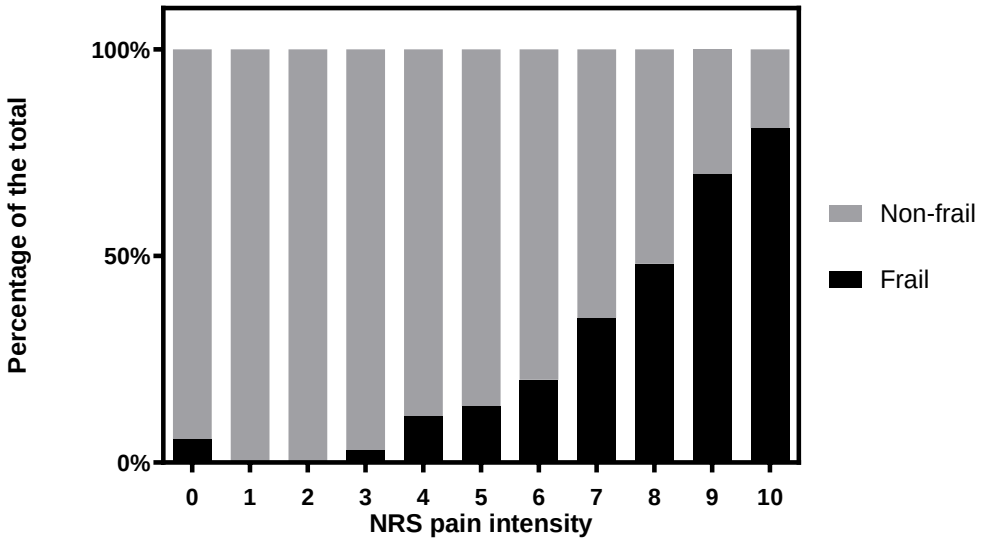

Figure 3-13 Percentage of FRAIL classification by NRS pain scores.

An ordinal logistic regression of FRAIL and NRS pain indicated the unadjusted odds ratio for a higher FRAIL category was 1.72, (95%CI 1.61 to 1.84) per unit increase in NRS pain (p<0.001).

3.3.9 Bivariate association of frailty and pain with the co-variables.

There was a bivariate association between frailty and pain β=0.54 (0.48, 0.61), p<0.001. The following are the bivariate associations of FRAIL and NRS pain with other co-variables (Table 3-16).

Table 3-16 Bivariate associations of FRAIL classification and pain with the co-variables.

Variable	**FRAIL** **β Coef. (95%CI)**	**NRS Pain (0-10)** **β Coef. (95%CI)**
NRS Pain (0-10)	0.54 (0.48, 0.61), p<0.001	Not included.
Sex:		
Male,	Ref	Ref
Female	0.61 (0.39, 0.83), p<0.001	0.77 (0.56, 0.99), p<0.001
Age		
60-69 years	Ref	Ref
70-79 years	-0.22 (-0.48, 0.29), p=0.082	-0.40 (-0.65, -0.15), p=0.002
≥80 years	0.38 (0.10, 0.66), p=0.008	-0.12 (-0.42, 0.18), p=0.421
BMI Classes[#]		
Underweight	1.15 (0.33, 1.97), p=0.006	0.03 (-0.89, 0.94), p=0.95
Normal	Ref	Ref
Pre-obese	0.41 (0.11, 0.71), p=0.007	0.38 (0.13, 0.64), p=0.004
Obese	1.14 (0.85, 1.43), p<0.001	1.25 (0.98, 1.52), p<0.001

Data are from n=2,185 participants.
Abbreviations: BMI – Body Mass Index; β Coef – beta coefficient; CI – 95% confidence intervals; Ref - reference group. #WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

Regression models

The ordinal models are shown in Appendix B2.

3.3.9.1 Logistic model – binary frailty

As discussed in Chapter 2, a binary classification of FRAIL using frail/ non-frail was used in which robust and prefrail were collapsed into one category. This aimed to ensure that frailty was present rather than just mobility-related issues, which may be found in a prefrail group.

Table 3-17. indicates the adjusted odds ratio (aOR) for being frail is 1.68, (95%CI 1.57 to 1.79) per unit increase of NRS pain. Additionally, being aged ≥80 years and being underweight or obese showed a significant association with frailty.

Table 3-17 FRAIL (binary) with pain and baseline characteristics.

Variable	aOR (95%CI)	P-value
NRS pain (0-10)	1.68 (1.57, 1.79)	<0.001
Sex		
Female	1.22 (0.95, 1.58)	0.112
Age group		
60-69 years	Ref	
70-79 years	0.97 (0.72, 1.29)	0.816
≥80 years	1.95 (1.40, 2.71)	<0.001
BMI class[#]		
Underweight	2.85 (1.11, 7.33)	0.029
Normal	Ref	
Pre-obese	1.33 (0.95, 1.84)	0.092
Obese	2.29 (1.65, 3.17)	<0.001

Abbreviations: aOR adjusted odds ratio; 95%CI – 95% Confidence Intervals; BMI – body mass index
[#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese

The missing data for NRS pain were imputed using two simple methods. If the regression analysis above was recalculated with those with missing pain data recorded as 0, then the aOR of being frail was 1.61 (95%CI 1.51 to 1.71) per unit increase in pain. If the mean NRS was used to replace missing data, the aOR of being frail was 1.70 (95%CI 1.59 to 1.82). This suggests that the missing data made little difference, as the aOR values would be included in the confidence intervals indicated. Following on from this, a complete case analysis was adopted for this thesis.

3.3.9.2 Pain regression models

A linear regression model indicated that the adjusted beta coefficient for the different frail levels, shown in Table 3-18. Also, it indicated that groups with older age were associated with lower pain. Female sex and obesity were associated with higher pain.

Table 3-18 Associations of frailty with NRS pain and other baseline characteristics

Variable	**β coef. (95%CI)**	**P-value**
FRAIL		
Robust	Ref	
Prefrail	1.53 (1.32, 1.74)	<0.001
Frail	3.00 (2.74, 3.26)	<0.001
Sex		
Female	0.45 (0.26, 0.64)	<0.001
Age group		
60-69 years	Ref	
70-79 years	-0.30 (-0.51, -0.08)	0.007
≥80 years	-0.32 (-0.59, -0.06)	<0.001
BMI class#		
Underweight	-0.38 (-1.18, 0.43)	0.358
Normal	Ref	
Pre-obese	0.30 (0.7, 0.52)	0.010
Obese	0.67 (0.43, 0.92)	<0.001

The outcome measure is NRS pain (continuous). The model is pain with frailty adjusted for age, sex, and BMI class. Abbreviations: β coef. – beta coefficient; 95%CI – 95% Confidence Intervals
#WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.
$R^{2=}$ 0.2683

3.3.9.3 Pain with frailty as a binary classification

A binary variable was used for frailty, shown in Table 3-19. This analysis also indicated that older age groups were associated with lower pain than the youngest age group. Female sex and obesity were associated with an increase in pain.

Table 3-19 Association of binary frailty with NRS pain and other baseline characteristics

Variable	β coef. (95%CI)	P-value
FRAIL	2.19 (1.94, 2.43)	<0.001
Sex		
Female	0.60 (0.41, 0.80)	<0.001
Age group		
60-69 years	Ref	
70-79 years	-0.30 (-0.51, -0.08)	0.007
≥80 years	-0.32 (-0.59, -0.06)	<0.001
BMI class[#]		
Underweight	-0.39 (-1.23, 0.45)	0.362
Normal	Ref	
Pre-obese	0.36 (0.12, 0.45)	0.003
Obese	0.89 (0.63, 1.15)	<0.001

The outcome measure is NRS pain (continuous). The model is pain with frailty adjusted for age, sex, and BMI class. Abbreviations: β coef. – beta coefficient; 95%CI – 95% Confidence Intervals; BMI – body mass index.
[#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.
$R^{2=}$ 0.1946

3.4 Discussion

Current joint pain severity was associated with frailty in the IMH&W cohort, even after adjusting for baseline age, sex, and BMI class. Additionally, frailty was associated with pain. This could be indicative of a bidirectional association. This study established the associations between pain and frailty but also explored age and BMI variables; findings informed how variables would be treated in the chapters that follow.

The measures of fatigue, resistance and ambulation were reported more frequently than illness or loss of weight. When FRAIL was augmented to supplement the illness classification by extracting the free-text and medication data to indicate which FRAIL illnesses were present, this increased the number of morbidities identified. However, it resulted in only 8 extra participants being classified as frail. In the following chapters, the original checklist version will be employed.

Several studies demonstrate that a higher proportion of females are classified as frail (Zhang et al., 2018, He et al., 2019); this is also reflected in the IMH&W cohort. There was an association between FRAIL and BMI classes. This indicated that higher BMI is associated with increased levels of frailty; this supports evidence found in other studies (Hubbard et al., 2010). The IMH&W recruited more people who were frail and overweight; this may be important when I examine other variables, such as pain. Any mechanisms linking frailty with pain may be different in those who were overweight rather than those who were underweight. If participants were obese or pre-obese, they might be less likely to report an unexpected weight loss of 5%, either because it is not unexpected or because they have a higher starting weight. The FRAIL tool, like the Fried Phenotype, uses loss of weight as a criterion. However, in IMH&W, only 30 participants were underweight, and they were not all classified as frail. Therefore, it is not possible to draw any inferences about the underweight group. The small number of people who were underweight was surprising, as frailty is associated with loss of weight. This may be because the loss of weight criterion was underreported. It may also be that loss of

weight is more likely in those with severe frailty, and those individuals may be less likely to respond to a questionnaire survey due to the effort required. The IMH&W questionnaire booklet could be completed over several sessions, but this might be challenging for those who were experiencing all five of the FRAIL criteria; 8 (0.4%) people met all 5 criteria, and 102 (5%) met 4 criteria.

Although FRAIL and FiND classified robust participants similarly, they differed in their classification of frailty. They were not interchangeable, and the FRAIL classification will be used in all future chapters. FiND originated as a screening tool to identify people who were frail, without a mobility impairment and were viewed as at risk of becoming disabled. Cesari et al. (2014) demonstrated that FiND is good at identifying people who were frail and who do not have a mobility impairment. However, people with severe frailty may also have a mobility impairment. FiND would classify people who were severely frail as disabled if they answered yes to the resistance or ambulation items (A and B). Therefore, using the FiND tool, the frail numbers were understated, and the disabled numbers were overstated. In the robust category, there is high agreement between tools; regarding the 934 people classed as robust in FRAIL, 87% would also be classified as robust in FiND. This indicated there is consistency between the way FRAIL and FiND categorise robust and non-robust people. However, they sub-classify non-robust people in different ways, as they have different priorities. The label of ‘frail’ in both FRAIL and FiND is not the same construct, even though they share the same name; this is because FiND frail includes only 3 items rather than the five items of FRAIL. These differences mean that FiND cannot be used in these studies to support the findings of FRAIL.

The two pain measures used in this study, NRS pain and PRI, were moderately associated; they do not attempt to measure an identical construct. PRI is viewed as a measure of generalised body pain, while NRS pain measures joint pain. The NRS pain values may vary depending on the lead question for the question used. However, it is possible to be confident that people in IMH&W cohort were reporting pain in a way that is consistent with the two scales that

measure pain. The single-response NRS pain question received more responses than the multi-response PRI items. The MPQ had word lists that could be omitted, making it difficult to differentiate between a zero and no pain response. The NRS pain was used in primary analysis as pain intensity (severity) is the main focus of this thesis. PRI was used for secondary analysis and to confirm findings as it measures pain qualities and may be representative of more generalised pain.

Greater joint pain severity was associated with female sex and obesity. Participants classified as frail reported greater levels of joint pain severity. NRS pain was associated with frailty in frailty regression models, and frailty was associated with NRS pain in pain regression models.

My findings confirmed the findings from other cohorts that chronic pain is associated with frailty (Bindawas et al., 2018, Veronese et al., 2017b, Megale et al., 2018, Blyth et al., 2008, Rodríguez-Sánchez et al., 2019, Sodhi et al., 2019, Wade et al., 2017, Shega et al., 2012, İlhan et al., 2019, Misra et al., 2015).

In agreement with other research, females in IMH&W cohort reported higher NRS pain than men (Parsons et al., 2007, Bartley and Fillingim, 2013). It may be that women respond differently to how they report pain or in how they experience pain. Psychosocial processes such as pain coping mechanisms and stereotypes may influence the pain intensity reported (Felpeto et al., 2019, Schwarz et al., 2019). However, in NRS pain between the sexes mean difference was 0.77, (95%CI 0.56 to 0.99), which is less than the clinically important difference of 2. (Farrar et al., 2001).

Data show there was heterogeneity between age groups, with the middle group reporting worst pain. This could be a result of the recruitment in which people with osteoarthritis and other rheumatic disorders were more likely to have been recruited to the cohort. Previous research has predominantly shown that increased age is associated with higher levels of chronic pain (Fayaz et al., 2016). However, Parsons and colleagues found that the

prevalence of chronic pain peaked in people aged 55-64 (50%), and after that, it appeared to decline (Parsons et al., 2007).

There was a correlation between NRS pain levels and BMI. As BMI increases, pain levels also increased; this is consistent with other research findings (Okifuji and Hare, 2015, Thomazeau et al., 2014). Higher pain levels may result in lower levels of physical activity, resulting in weight gain. BMI may also be affected by some medications, including analgesia (Thomazeau et al., 2014), and underlying health conditions such as depression (Stunkard et al., 2003).

A report of the prevalence of moderate and severe chronic pain in a European survey suggested two-thirds of respondents had moderate pain (NRS 5,6, or 7), and a third had severe pain (NRS 8, 9 and 10) (Breivik et al., 2006). In the IMH&W cohort, moderate pain was reported in 878 (40%) participants and severe pain in 469 (21%) participants.

This study had several strengths and some weaknesses. In the analysis, I included the co-variables as age, sex, and BMI previously linked to both pain and frailty, which could otherwise have introduced confounding. Previous research has frequently focused on single-sex cohorts, which limits generalisability (Megale et al., 2018; Susanto et al., 2018). Although FRAIL has been used worldwide, in the UK, it has been reported only for older British men (Papachristou et al., 2017). The IMH&W cohort was not an epidemiologically representative sample of the population, and the relatively high prevalence of pain and frailty in the sample reflects the recruitment processes. Whilst this means this study cannot derive the population prevalence of pain or frailty, sampling issues can affect the association between variables, for example, selecting a statistical collider, but were not thought to do in this study. There was a minor difference between using the original or augmented FRAIL. In the ascertainment of frailty, the methods used self-report data, which may be subject to recall bias (Spencer et al., 2002, Althubaiti, 2016). Whilst this may have introduced some classification errors, I believe such errors would reduce the precision of my results rather than introduce systematic bias. The methods for classifying frailty were

limited, as are all classifications of frailty, as there is currently no definitive measure of vulnerability to challenge. This study explored the relationship with the most common types of joint pain, and it may be that lower-limb pain has a stronger relationship with frailty than those previously tested due to its relationship with weight-bearing and mobility. Previous studies exploring the relationship between pain and frailty have been limited by using categorical indicators of pain (yes/no). In contrast, I used a validated 11-point ordinal measure, which has enough points to treat as continuous. This would enable an examination of a dose-response (e.g., greater pain, greater risk of frailty).

The IMH&W cohort has a large number of participants and a reasonable proportion of people with frailty. A cohort consisting of all frail or non-frail participants would not allow a comparison to be made between classes.
The current study is cross-sectional but will form part of a longitudinal study; having data at baseline in the mid-range (IQR=4-7) allows scores to increase or decrease.
The percentage of people classified as frail was higher than that expected in the general population. The overall prevalence of frailty in the IMH&W cohort was 20%. The European prevalence of physical frailty is estimated at 11% for community-dwelling adults aged 65 years (Santos-Eggimann et al., 2009). The ≥ 80 years category in the IMH&W cohort has a lower frailty prevalence of 29% than the European estimate of 50% (O'Caoimh et al., 2018). However, 90% of IMH&W participants were invited by their GP.

I obtained similar findings using two different pain measurement tools (Pain Rating Index and NRS). However, pain is a complex, multidimensional symptom, and other pain measurement tools could give different results.

In summary, a cross-sectional analysis has unveiled a correlation between chronic pain and frailty. Yet, as the association has merely been observed, it remains undetermined if pain causes frailty or vice versa. Additional research utilising follow-up data is required to ascertain the directionality of this association.

CHAPTER 4 LONGITUDINAL ASSOCIATION OF PAIN WITH FRAILTY.

4.1 Introduction

The previous chapter demonstrated that chronic pain was associated with frailty and that frailty was associated with pain. Such an association poses a question of a bidirectional relationship. This has significance as if each leads to the other, a vicious cycle (Skúladóttir et al., 2020) can result in each accelerating the development of the other. Interrupting this cycle with an intervention, such as improved pain management, may result in a decline in both pain and frailty.

I aimed to examine whether there is a unidirectional or bidirectional relationship between joint pain and frailty; using two-wave cross-lagged path modelling which permits simultaneous exploration of plausible causal pathways between pain intensity and frailty at baseline and 1-year.

Chronic pain might make the transitions from non-frail to frail states more likely or less likely. This chapter will explore whether there is a dose-response relationship between pain and frailty.

The study objectives were:

- to examine the directional association between pain NRS and frailty.
- assess whether there was a dose-response relationship between pain and frailty.

4.2 Methods

Chapter 2 describes the methods, and the following relates to any particular methods or adaptations for this study.

4.2.1 Participants and data sources

Participants were from the Investigating Musculoskeletal Health and Wellbeing (IMH&W) study.

The inclusion criteria for the current study required participants to be aged ≥60 years at baseline and have completed all items of the FRAIL questionnaire at both baseline and 1-year.

It was important for this study, in which the objective was to study transition, that I used data with two time points, so only data from people who had completed baseline and 1-year were included.

4.2.2 Variables

4.2.2.1 Frailty

The primary outcome variable used in this study was a binary frail/non-frail classification derived from FRAIL (Morley et al., 2012). Throughout this chapter, the illness counts were determined by the method using the original FRAIL; this is that checklists indicated which illnesses the participant had self-declared.

4.2.2.2 Joint pain

Joint pain intensity was measured using a numerical rating scale (NRS). Participants were asked: `over the past four weeks, how intense was your average pain or the average aching in your most bothersome joint,' where 0 is 'no pain', and 10 is 'pain as bad as could be'? In this chapter, any reference to pain NRS refers to joint pain NRS.

Additionally, pain NRS was categorised as either in the range 0 to 3, or ≥4, corresponding to acceptable or unacceptable pain, based on the Patient Acceptable Symptom State (PASS) threshold (Georgopoulos et al., 2021). PASS

represents the threshold of pain which a patient would accept for the remainder of their life.

4.2.2.3 Co-variables

The previous chapter identified the co-variables of age, sex and BMI class as having an association with pain and frailty, and these were included in this analysis. Data collection and statistical analyses were described in Section 2.1.4.

4.2.3 Statistical analysis

Data were summarised using means and standard deviation for normally distributed continuous variables, medians and IQR for non-normally distributed variables, and n (%) for dichotomous variables. Normality was assessed graphically using histograms and statistically using the Shapiro-Wilk test. Differences between groups were evaluated using Student *t*-tests or Mann-Whitney U tests for continuous variables, a Chi-squared test for categorical variables and Fisher's exact test when <5 in a category.

Multivariable cross-sectional analyses investigated associations between joint pain and frailty with the co-variables. Age, sex, and BMI class were selected *a priori*; other co-variables were included if $p<0.05$ in prior bivariate analysis. Categorical variables were classified as a binary outcome (absent/present) in all logistic regression models. Continuous variables were used in all linear regression models. All multivariable statistical models were adjusted for the same co-variables. Transitions in frailty were calculated by comparing baseline frailty classification with 1-year, and mean pain was calculated for those who did transition and compared with those who did not. Transitions between PASS pain were categorised (acceptable or unacceptable) at baseline, and 1-year were determined within frail and non-frail categories.

Two-wave cross-lagged path modelling permitted simultaneous exploration of plausible causal pathways in non-experimental data compared to an independent exploration of association; joint pain and frailty were adjusted for sex, age, and BMI class at both baseline and 1-year. The use of

standardised regression coefficients permitted comparisons of the strengths of the paths. As frailty was categorical, the model used maximum likelihood estimation, which did not produce root mean square error of approximation (RMSEA) values (Allison et al., 2017). The effect size for cross-lagged path modelling, using standardised regression coefficients, was interpreted as follows: 0.03 indicates a small effect, 0.07 a moderate effect and 0.12 a strong effect (Orth, 2022).

4.3 Results

Data from 1,179 participants who met eligibility criteria were examined (Figure 4-1). The median age was 73 (IQR 69 to 78) years, and 628 (53%) were female. At baseline, 176 (15%) were classified as frail, 1060 (90%) reported joint pain, and 816 (74%) reported joint pain NRS≥4 (Table 4-1). Mean (SD) NRS at baseline was 5.2 (2.5).

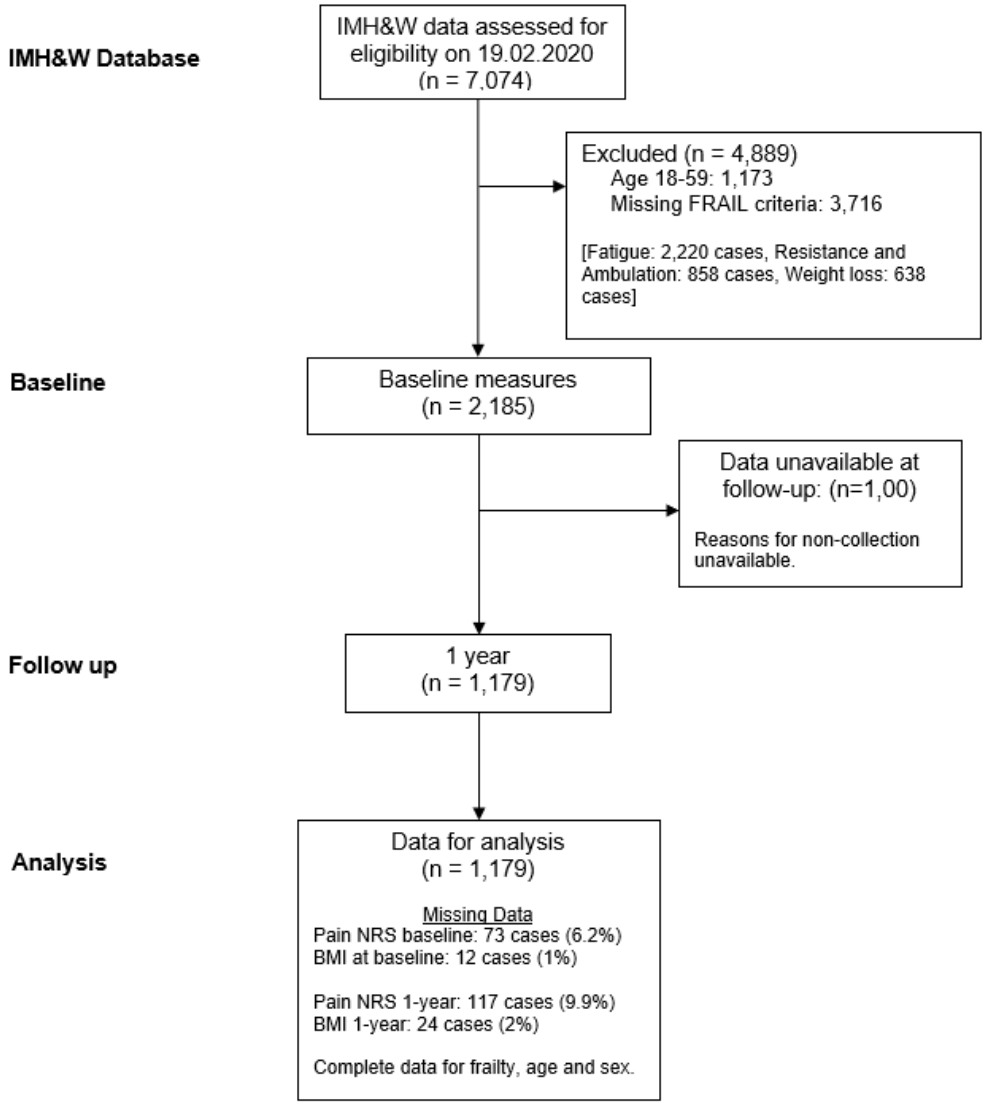

Figure 4-1 IMH&W Consort flow diagram for longitudinal study.

4.4 Cross-sectional associations at baseline

In bivariate analyses, higher NRS joint pain, female sex, and obesity were associated with frailty (Figure 4-2, Table 4-1). Female sex and obesity were associated with joint pain NRS (Table 4-1). Unacceptable pain was reported by 99% of participants classified as frail at baseline (Figure 4-2). Females reported more severe joint pain NRS (mean (SD) 5.59 (2.47) than did males 4.73 (2.37), ($p<0.001$), and obesity was associated with higher joint pain NRS compared to 'normal' BMI ($r_s=0.20$, $p<0.001$). There was an association between higher BMI class and frailty, with a higher proportion of frail participants who were obese 82 (48%) than in the lower BMI classes ($X^2 = 44.05$, $p<0.001$).

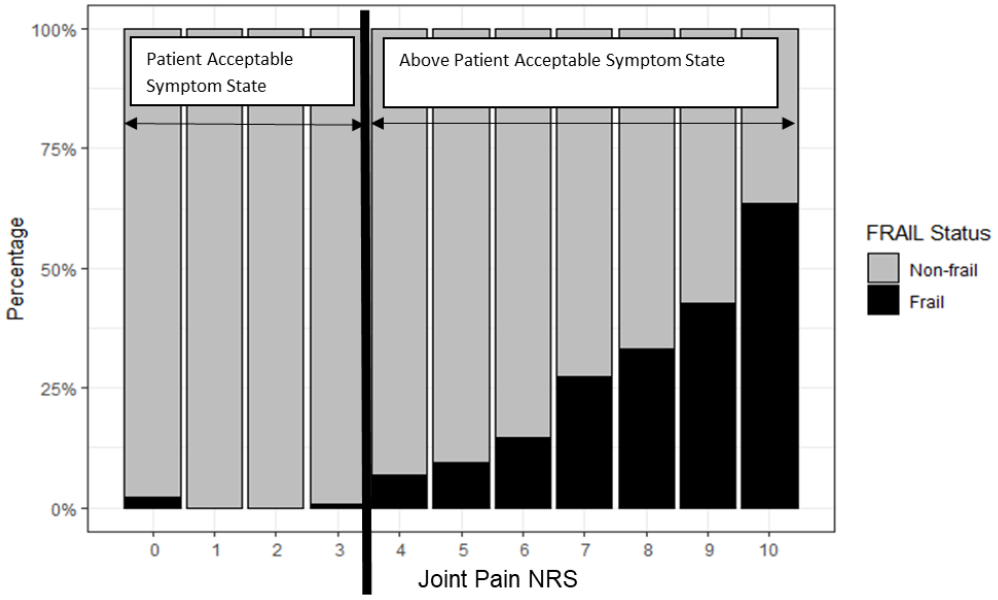

Figure 4-2 Distribution of baseline joint pain scores by FRAIL classification including Patient Acceptable Symptom State threshold (n=1106).

Table 4-1 Characteristics of IMH&W participants at baseline and their bivariate association with frailty classification and pain.

Variable	All participants N = 1,179	Non-frail N=1,003	Frail N=176	Bivariate association with frailty, OR (95%CI)	Bivariate association with joint pain NRS, β (95%CI)
Sex					
Female, n (%)	628 (53)	502 (80)	126 (20)	2.51 (1.77, 3.57), p<0.001	0.86 (0.57, 1.15), p<0.001
Male, n (%)	551 (47)	501 (91)	50 (9)	Ref	Ref
Age (years), median (IQR)	73 (69-78)	73 (69-78)	73 (69-79)	1.005 (0.98, 1.03), p=0.716	-0.02 (-.04, -0.002), p =0.034
Ethnicity					
White, n (%)	1,165 (99)	995 (85)	170 (15)	Ref	Ref
Non-white	13 (1)	8 (62)	5 (38)	3.65 (1.18, 11.31) p=0.024	1.24 (-.16, 2.64), p =0.083
BMI Class#, n (%)					
Underweight	17 (1)	13 (76)	4 (24)	3.25 (1.00, 10.58), p=0.049	-0.005 (-1.22, 1.21), p=0.994
Normal	371 (32)	339 (91)	32 (9)	Ref	Ref
Pre-obese	452 (39)	399 (88)	53 (12)	1.41 (0.89, 2.23), p=0.147	0.32 (-0.28, 0.66), p=0.071
Obese	327 (28)	244 (75)	83 (25)	3.60 (2.32, 5.59), p<0.001	1.29 (0.92, 1.66), p<0.001
Joint Pain (NRS)					
mean (SD)	5.2 (2.5)	4.8 (2.4)	7.4 (1.7)	1.79 (1.62, 1.98), p<0.001	NA
median (IQR)	5 (3-7)	5 (3-7)	8 (6-8)		
Pain category, n (%)					
Acceptable (NRS 0-3)	290 (26)	288 (99)	2 (1)	Ref	NA
Unacceptable (NRS≥4)	816 (74)	646 (79)	172 (21)	38.46 (9.48, 156.09), p<0.001	NA
Indices of multiple deprivation decile, median (IQR) (1-10) ¥	8 (5-9)	8 (5-9)	8 (5-9)	p=0.2392 at all levels	p=0.2114 at all levels
Route of recruitment, n (%)					
General Practitioner	1072 (91)	913 (85)	159 (15)	Ref	Ref
Previous studies	101 (8.5)	86 (85)	15 (15)	1.00, (0.56, 1.78), p<0.996	0.06 (-0.45, .58), p=0.805
Other	6 (0.5)	4 (67)	2 (33)	2.87 (0.52, 15.81), p=0.226	1.32 (-0.66, 3.30), p=0.191

Abbreviations: SD – standard deviation; IQR – interquartile range; NRS – numerical rating scale 0-10; BMI – body mass index; OR – odds ratio; CI – 95% confidence intervals; β – Beta coefficient; Ref – reference; NA – not applicable. Number of observations for each variable vary. Data were from n=1095 participants

#WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese. ¥ 1 most deprived to 10 least deprived.

Missing data at baseline by category: Frailty=0; Sex= 0 Age = 0; NRS = 75; BMI = 12; Ethnicity= 1

Distributions of individual FRAIL items and a summary of the reported criteria are given Table 4-2 and 4-3 respectively. The unadjusted association between each FRAIL item and pain NRS are shown in Table 4-4.

Table 4-2 Responses to items meeting FRAIL criteria (n=1,179).

FRAIL (Y/N)	Total, n (%)	Non-frail, n (%)	Frail, n (%)
Fatigue	287 (24)	130 (13)	157 (89)
Resistance	366 (31)	197 (20)136 (14)	163 (93)
Ambulation	299 (25)	137 (14)	171 (97)
Illness	29 (3)	7 (1)	22 (13)
Loss of weight	180 (15)	122 (12)	58 (33)

Total non-frail =1003, frail = 176

The percentage is the proportion of a group who reported meeting the FRAIL criterion. For example, 287 (24%) of participants reported feeling tired all or most of the time. Of the 1003 people classified as non-frail, 130 (13%) reported feeling tired all or most of the time, and of the 176 people classified as frail, 157 (89%) reported feeling tired all or most of the time. Participants are classified as frail if they meet ≥3 criteria.

Table 4-3 Summary of the number of FRAIL criteria reported (n=1,179).

FRAIL criteria	Baseline, n (%)	1-year, n (%)
0	579 (49)	592 (50)
1	258 (22)	238 (20)
2	166 (14)	184 (16)
3	135 (11)	139 (12)
4	39 (3)	22 (2)
5	2 (0.2)	4 (0.3)

Participants are classified as frail if they meet ≥3 criteria.

Table 4-4 The unadjusted association between FRAIL items and NRS pain (n=1106)

FRAIL Item	Spearman rho	OR (95%CI)	P value
Fatigue	0.38	1.51 (1.41, 1.62)	<0.001
Resistance	0.44	1.69 (1.56, 1.83)	<0.001
Ambulation	0.46	1.66 (1.54, 1.79)	<0.001
Illnesses	0.08	1.25 (1.06, 1.48)	0.008
Loss of weight	0.08	1.10 (1.03, 1.18)	0.005

Abbreviations: CI – confidence interval; OR – odds ratio.

In multivariable regression, higher joint pain NRS, female sex, BMI class and age were associated with frailty at baseline (Table 4-5).

Table 4-5 Associations of NRS pain and other characteristics at baseline with frailty at baseline and 1-year.

		Frailty	
		Baseline	1-year
Baseline Factor	Interval/category	aOR (95%CI)	aOR (95%CI)
Frailty	(non-frail, frail)	NA	13.24 (8.43, 20.80), p<0.001
Joint Pain	Pain (NRS 0-10)	1.72 (1.56, 1.92), p<0.001	1.28 (1.15, 1.43), p<0.001
Sex	Male	Ref	Ref
	Female	1.81 (1.22, 2.68), p=0.003	1.39 (0.89, 2.17), p=0.15
Age	Years	1.03 (1.00, 1.06), p=0.026	1.04 (1.01, 1.08), p=0.006
BMI Class[#]	Underweight	3.30 (0.83, 13.08), p=0.089	0.25 (0.02, 2.47), p=0.233
	Normal	Ref	Ref
	Pre-obese	1.48 (0.89, 2.46), p=0.129	1.41 (0.79, 2.47), p=0.251
	Obese	2.69 (1.63, 4.42), p<0.001	2.96 (1.66, 5.27), p<0.001
Pseudo r^2		0.2259	0.3409

The outcome measure is frailty (binary). The baseline model is frailty with pain adjusted for age, sex, and BMI class. The 1-year model is 1-year frailty adjusted for baseline factors of frailty, pain, age, sex, and BMI class. Data were from n=1095 participants.

Abbreviations: NRS – numerical rating scale (0-10); BMI – Body Mass Index; aOR –adjusted odds ratio**;** CI – 95% confidence intervals; Ref - reference group. NA - Not Applicable

[#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

4.4.1 Participants lost to study.

Chapter 3 described the baseline data from 2,185 participants. Of those, 1,179 participants completed the 1-year questionnaire. This effectively meant that 1,006 (46%) participants were lost to follow-up, although some did complete later waves of the IMH&W study. Those who completed baseline and 1-year questionnaires differed slightly from those who completed only one wave. In this study, they were more likely to report lower pain, be less frail, be slightly younger and less likely to be obese, as shown in Table 4-6. The data for the 'Baseline only' were shown in Chapter 3. Tables 2-2 and 2-3.

Table 4-6 Difference between the baseline and 1-year in IMH&W

Variable	Total	Baseline only N=2185	Baseline and 1-year N=1179	p-value*
NRS pain (0/10): mean (SD)	5.45 (2.5)	5.74 (2.4)	5.19 (2.4)	<0.001
Female, n (%)	1,202 (55.0)	574 (57.1)	628 (53.3)	0.072
Age (years): mean (SD)	73.9 (7.1)	74.56 (7.5)	73.28 (6.8)	<0.001
Age group, ≥80 proportion	478 (21.9)	259 (25.8)	219 (18.6)	<0.001
BMI class, obese proportion	642 (29.8)	315 (31.9)	327 (28.0)	0.033
Frail, n (%)	438 (20.0)	259 (25.8)	179 (15.2)	<0.001

*t-test or, Mann-Whitney or Chi-squared tests were performed depending on the data

4.5 Longitudinal associations of baseline variables with pain and frailty at 1-year.

At 1-year, 165 (14%) participants were classified as frail, and 1062 (90%) responded to the joint pain NRS question. Of whom 766 (72%) participants reported pain of NRS ≥4, mean (SD) pain NRS was 5.0 (2.5).

Unadjusted bivariate analysis showed that each unit of baseline pain was associated with an increased risk of 1-year frailty classification [OR 1.60, (95%CI 1.46 to 1.76), p<0.001]. In multivariable regression, baseline pain remained associated with 1-year frailty classification (aOR 1.28, (95%CI 1.14 to 1.43), p<0.001) adjusted for baseline frailty, sex, age, and BMI class (In multivariable regression, higher joint pain NRS, female sex, BMI class and age were associated with frailty at baseline (Table 4-5).

Table 4-5Unadjusted bivariate analysis showed frailty at baseline was associated with more severe pain at 1-year β =2.01, (95%CI 1.62 to 2.39), p<0.001. In multivariable regression, baseline frailty remained associated with 1-year pain severity β =0.56, (95%CI 0.50 to 0.61), p<0.001 adjusted for baseline pain, sex, age, and BMI class (Table 4-7).

Table 4-7 Associations of frailty at baseline and other characteristics with joint pain at baseline and 1-year.

		Pain	
		Baseline (n=1095)	1-year (n=1004)
Baseline Factor	Interval/category	β Coef (95%CI)	β Coef (95%CI)
Frailty	(non-frail, frail)	2.29 (1.91, 2.66), p<0.001	0.39 (0.04, 0.75), p=0.027
Joint pain	Pain (NRS) (0-10)	NA	0.56 (0.50, 0.61), p<0.001
Sex	Male	Ref	Ref
	Female	0.63 (0.36, 0.90), p<0.001	0.33 (0.09, 0.58), p=0.008
Age	Years	-0.01 (-0.03, 0.01), p=0.226	0.00 (-0.02, 0.02), p=0.783
BMI Class[#]	Underweight	-0.48 (-1.60, 0.65), p=0.408	-0.55 (-1.63, 0.52), p=0.312
	Normal	Ref	Ref
	Pre-obese	0.33 (0.00, 0.65), p=0.047	0.27 (-0.02, 0.56), p=0.069
	Obese	0.93 (0.58, 1.29), p<0.001	0.55 (0.23, 0.87), p=0.001
r^2		0.1829	0.3747

The outcome measure is pain (continuous variable). The baseline model is pain with frailty adjusted for age, sex, and BMI class. The 1-year model is 1-year pain with baseline frailty adjusted for baseline factors of pain, age, sex, and BMI class.

Abbreviations: NRS – numerical rating scale (0-10); BMI – Body Mass Index; β Coef - Beta coefficient; 95%CI – confidence intervals; NA – not applicable; Ref= reference group.
[#]WHO classification for BMI, underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

4.6 Bidirectional association of joint pain and frailty

To determine whether these findings in bivariate and multivariable models might indicate bidirectional relationships between pain and frailty, cross-lagged path modelling was utilised, including both pain and frailty both at baseline and 1-year, together with covariables of age, sex and BMI class (Figure 4-3)

Pain baseline at predicted higher 1-year pain [β 0.55, (95%CI 0.51 to 0.59), p<0.001], and frailty classification at baseline predicted 1-year frailty [β 0.40, (95%CI 0.34 to 0.47) p<0.001] (Figure 4-3). There was a strong effect of higher pain at baseline predicting 1-year frailty [β 0.25, (95%CI 0.14 to 0.36) p<0.001], and a small to moderate effect frailty at baseline predicting higher 1-year pain [β 0.06, (95%CI 0.003 to 0.11), p=0.040]. Standardised beta coefficients are shown in Table 4-8.

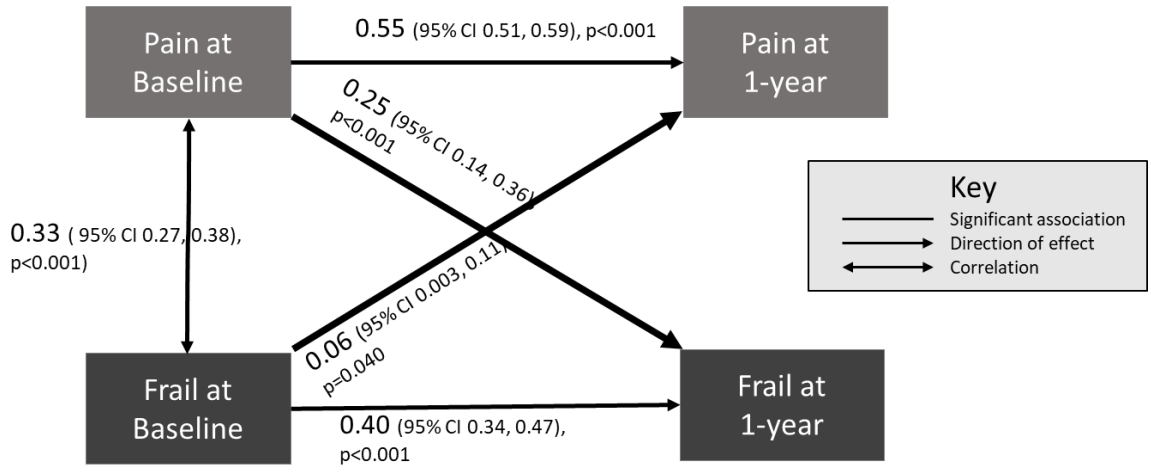

Figure 4-3 Cross-lagged path analysis model showing standardised regression coefficients of the relationship between joint pain and frailty at baseline and 1-year, adjusted for age, sex and BMI (n=995).
Abbreviation: CI – 95% confidence intervals.

Table 4-8 Standardised beta coefficients of pathway analysis.

To	From	Std β Coef	95% Confidence Intervals		p-value
NRS1	FRAIL0	0.06	0.01	0.10	0.040
NRS1	NRS0	0.55	0.51	0.59	<0.001
NRS1	SEX	0.07	0.03	0.11	0.009
NRS1	AGE	0.01	-0.03	0.05	0.069
NRS1	BMI1	0.09	0.05	0.14	<0.001
FRAIL1	FRAIL0	0.40	0.35	0.46	<0.001
FRAIL1	NRS0	0.25	0.16	0.34	<0.001
FRAIL1	SEX	0.06	-0.02	0.14	0.194
FRAIL1	AGE	0.12	0.05	0.20	0.008
FRAIL1	BMI1	0.15	0.07	0.22	0.001
BMI1	BMI0	0.93	0.92	0.94	<0.001
BMI1	SEX	-0.00	-0.02	0.02	0.871
BMI1	AGE	-0.04	-0.05	-0.02	0.002
BMI0	SEX	-0.04	-0.09	0.01	0.235
BMI0	AGE	-0.16	-0.21	-0.11	<0.001
SEX	AGE	-0.04	-0.09	0.01	0.225
NRS0	SEX	0.20	0.15	0.25	<0.001
NRS0	AGE	-0.03	-0.08	0.02	0.338
NRS0	BMI0	0.19	0.14	0.24	<0.001
FRAIL0	SEX	0.16	0.11	0.21	<0.001
FRAIL0	AGE	0.06	0.01	0.11	0.050
FRAIL0	BMI0	0.22	0.17	0.27	<0.001
NRS0*	FRAIL0*	0.33	0.28	0.37	<0.001

*Note: Pathways NRS0 and FRAIL0 are correlated and, therefore, bidirectional.
Abbreviations: NRS- numerical rating scale; BMI – body mass index; the suffix number refers to the timepoint 0 = baseline and 1= 1-year.

4.7 Joint pain and frailty changes and transitions between baseline and 1 year.

The number of participants who were classified as frail at 1-year was 165 (14%) compared with 176 (15%) at baseline. However, 127 (11%) participants had changed their frailty status between baseline and 1-year; 58 (5%) transitioned from non-frail to frail and 69 (6%) transitioned from frail to non-frail (Table 4-9).

Table 4-9. Longitudinal transitions of frailty status over one-year.

Frailty status transitions		Total	Mean NRS	p-value
Baseline	1-Year	n (%)	(95%CI)	
Non-frail	Frail	58 (5)	6.44 (5.8, 7.1)	<0.001
Non-frail	Non-frail	947 (80)	4.68 (4.5, 4.8)	
Frail	Non-frail	69 (6)	7.15 (6.8, 7.5)	0.1872
Frail	Frail	105 (9)	7.5 (7.1, 7.9)	

Abbreviations: Abbreviations: NRS – numerical rating scale (0-10);95%CI – confidence intervals.

The mean (SD) joint pain NRS was 5.0 (2.5) at 1-year compared to 5.2 (2.5) at baseline. A similar proportion of participants experienced 'unacceptable' pain 766 (72%) at 1-year and 816 (74%) at baseline.

People who transitioned from non-frail to frail classification reported more severe pain at baseline (NRS mean 6.4, (95%CI 5.8 to 7.1) than those who remained non-frail (NRS mean 4.7, (95%CI 4.5 to 4.8). Each unit increase in joint pain NRS at baseline was associated with a greater risk of becoming frail at 1-year [OR 1.42, (95%CI 1.25 to 1.63), p<0.001]. However, no significant difference in baseline pain severity was found between those who transitioned from frail to non-frail classification and those who remained frail (NRS mean 7.2, (95%CI 6.8 to 7.5) and 7.5, (95%CI 7.1 to 7.9), p=0.187) (Table 4-9). Pain was not significantly associated with becoming non-frail [OR 1.13, (95%CI 0.94, 1.35), p=0.188].

There were 215 (21%) participants who transitioned between pain acceptability categories. 93 (9%) people transitioned from acceptable pain at

baseline to unacceptable pain at 1-year, and 122 (12%) transitioned from unacceptable pain to acceptable pain. (Table 4-10).

Table 4-10 Transition of PASS scores by frailty status.

PASS pain state		**Baseline**		**1-Year**		
Baseline	**1-Year**	**Frail, n (%)**	**Non-Frail, n (%)**	**Frail, n (%)**	**Non-Frail, n (%)**	**Total, n (%)**
Acceptable	Unacceptable	1 (1)	92 (99)	5 (5)	88 (95)	93 (9)
Acceptable	Acceptable	1 (1)	144 (99)	5 (3)	140 (97)	145 (14)
Unacceptable	Acceptable	12 (10)	110 (90)	7 (6)	115 (94)	122 (12)
Unacceptable	Unacceptable	161 (25)	494 (75)	146 (22)	509 (78)	655 (65)

People who transitioned from unacceptable to acceptable pain were less likely to be frail at baseline (n=11, 9%) than were those who continued with unacceptable pain (n=157, 24%, X^2 = 13.57, p<0.001). Of the (n=92, 9%) people who transitioned from acceptable to unacceptable pain, one person was frail at baseline (Table 4-11). Due to low numbers, this was not analysed further. Logistic regression analysis found that unacceptable pain at 1-year was predicted by baseline unacceptable pain (aOR 6.54, (95%CI 4.67 to 9.15), p<0.001) and baseline frailty classification (aOR 2.76, (95%CI 1.46 to 5.21), p=0.002), each adjusted for age, sex, and BMI.

Table 4-11 Pain acceptability transitions

Baseline	1-year	Total, n (%)	Frail at baseline, n (%)	Non-frail at baseline, n (%)	Frail at 1-year, n (%)	Non-frail at 1-year, n (%)	p-value
Acceptable	Unacceptable	93 (39)	1 (1)	92 (99)	5 (5)	88 (95)	
Acceptable	Acceptable	145 (61)	1 (1)	144(99)	5 (3)	140 (97)	NA
Unacceptable	Acceptable	122 (16)	11 (9)	111 (91)	6 (5)	116 (95)	<0.001
Unacceptable	Unacceptable	655 (84)	157 (24)	498 (76)	143 (22)	512 (78)	

Abbreviations: NRS – numerical rating scale (0-10); CI – Confidence intervals.
Note there were two t-tests: firstly, for people non-frail at baseline who transitioned to frailty compared to those who remained non-frail, and secondly, for people frail at baseline who transitioned to non-frailty compared to those who remained frail.
There were too few people with NRS<4 and frail to examine a statistical association. People with NRS≥4 at baseline and frailty at baseline X^2= 13.57

4.8 Discussion

This study confirmed that joint pain was strongly associated with current frailty, and furthermore that joint pain was also associated with future frailty in the IMH&W cohort, even after adjusting for baseline age, sex, BMI class, and frailty status. Greater pain severity increased the risk of transitioning from a non-frail to a frail state over one year of follow-up but did not appear to be a significant barrier to the transition from a frail to a non-frail state over the same time. Additionally, I observed a small to moderate association between frailty classification and future joint pain, over one-year. These findings support the hypothesis that the relationship between joint pain and frailty is bidirectional.

My findings confirmed the directional pathway that baseline pain is predictive of future frailty (Megale et al., 2018, Veronese et al., 2017b, Shega et al., 2012, Wade et al., 2017), and people can transition between frailty and non-frail classifications (Romero-Ortuno et al., 2021). In contrast to previous studies (Megale et al., 2018), I was able to demonstrate that frailty predicts future pain with a small to moderate effect. Such a bidirectional relationship implies that pain and frailty could act together in a vicious cycle in which each accelerates the development of the other. These findings are of clinical importance given the strength of these predictive relationships and the fact that almost all (99%) participants in this study classified as frail rated their pain at a level regarded as unacceptable.

These findings are of importance given expert opinion (Marcucci et al., 2019) and current advice provided by NHS England (NHS England, 2022c) and NICE guidelines (NICE, 2015) about frailty prevention do not mention the role of pain. Exercise and nutrition have, to date, been the primary interventions employed in studies aiming to prevent or reverse frailty (Teh et al., 2022, Serra-Prat et al., 2017, Travers et al., 2019). The sparsity of available of interventions to effectively address pain could partly explain why the prevention and management of frailty remains a challenge. These findings justify the inclusion of pain-reducing strategies within randomised control trial

interventions designed to prevent, delay, or manage frailty. Furthermore, pain is not widely recognised as a feature or complication of frailty (NHS England, 2022a)nor widely used as an outcome measure in frailty studies (Teh et al., 2022, Serra-Prat et al., 2017, Travers et al., 2019). These findings justify the inclusion of pain as an outcome of importance in frailty studies.

Whilst musculoskeletal conditions are linked with pain, fatigue, physical activity, obesity, and morbidities (Versus Arthritis, 2021), many of which are included in frailty measures, frailty is rarely mentioned as a long-term outcome of musculoskeletal conditions. The NICE guidelines for the treatment and management of chronic pain make no mention of frailty (NICE, 2021). The only reference to frailty from the Core Standards for Pain Management Services in the UK (British Pain Society, 2021) is in terms of specialist palliative care. These findings suggest that raised awareness of the risks associated with pain and frailty could benefit public health interventions and the management of these conditions by medical professionals and social care. Identifying people at risk of frailty, for example, because they have chronic pain, alongside those who may benefit from an intervention is key to addressing future health challenges.

This study had several strengths and some weaknesses. In the analysis, I included the co-variables such as age, sex, and BMI previously linked to both pain and frailty, which could otherwise have introduced confounding.

The IMH&W cohort was not an epidemiologically representative sample of the population, and the relatively high prevalence of joint pain and frailty in this sample reflects the recruitment processes and limits the ability to say pain is part of the frailty construct. Whilst this means this study cannot derive the population prevalence of pain or frailty, this sampling issue would not affect the validity of or analysis of the relationships between pain and frailty.

This study explored the relationship with joint pain, and it may be that this aspect of pain has a stronger relationship with frailty than those previously tested due to its relationship with weight-bearing and mobility. Previous studies exploring the relationship between pain and frailty have been limited

by using categorical indicators of pain (yes/no). In contrast, I used a validated, continuous measure which enabled us to identify a dose-response (e.g., greater pain, greater risk of frailty). As a unidimensional measure of pain, NRS has limitations. However, pain management focuses on the overall reduction in pain rather than dimensional aspects. Other covariables, for example, cognitive impairment, may be related to frailty and pain but were not measured in this study. Polypharmacy may also be associated with frailty and pain but will be too closely correlated to the morbidities count to be an independent variable.

My crossed-lagged path analysis used two-time points, and the findings could, in the future, be strengthened with additional time points, which could potentially add to the findings. The advantage of cross-lagged methods is that they take account of baseline and 1-year factors within the same model. While path analysis is regarded as indicative of directional pathways, it cannot definitively conclude causality in observed non-experimental data. One year is a relatively short period of time to observe changes in frailty: stronger relationships between pain and frailty might have been observed had I used a longer period of follow-up. However, I did observe a change over one year, which supports the findings of other longitudinal studies (Romero-Ortuno et al., 2021).

Further research should identify pain mechanisms through which pain predicts frailty to identify people at risk of frailty and develop interventions to reduce the risk of future frailty while addressing current pain. Interventional studies are needed to assess feasibility, acceptability, and efficacy. My findings suggest that frailty is potentially reversible, at least to an extent, raising hope to enable people to age well.

In conclusion, there is a bidirectional relationship between pain and frailty, which could lead to a vicious cycle in which each accelerates the other's progression. This justifies attempts to prevent frailty by addressing pain, and to include pain measures as outcomes in frailty studies.

CHAPTER 5 THE ASSOCIATION OF PAINFUL AND NON-PAINFUL MORBIDITIES WITH FRAILTY.

5.1 Introduction

Frailty, whether classified according to cumulative deficit or phenotype models or the hybrid FRAIL (Chaplin et al., 2023), was associated with chronic pain as described in the introduction (Chapter 1). Musculoskeletal conditions are the most common causes of chronic pain, affecting over a third of the UK population (Versus Arthritis, 2021, Havelin and King, 2018). An estimated 8.5 million people in the UK have osteoarthritis (Versus Arthritis, 2021).

Frailty has been associated with multi-morbidity (two or more long-term health conditions) (Barnett et al., 2012). In fact, multi-morbidity is an integral part of frailty identification tools based on the cumulative deficit model (Rockwood and Mitnitski, 2007) and FRAIL (Morley et al., 2012). Accumulated deficits, including those from morbidities, represent a multi-organ decline and were associated with frailty classification (Rockwood and Mitnitski, 2007, Havelin and King, 2018).

An association between chronic pain and frailty has been identified both using the Fried phenotype model of frailty (which does not directly include morbidities) (Fried et al., 2001) and using the cumulative deficit models of frailty (Rockwood and Mitnitski, 2007). This suggests that the association of pain with frailty is not purely a statistical phenomenon resulting from the inclusion of morbidity counts in frailty identification tools. This raises the possibility that chronic pain might itself contribute to the frailty state. If so, chronic pain would be an additional variable that could be used to identify, predict, and measure frailty. Furthermore, attempts to ameliorate or manage chronic pain could potentially prevent or reverse frailty states. Current frailty interventions focus on other aspects, such as exercise and nutrition (Travers et al., 2019).

This study aims to examine the extent to which the association of chronic pain with frailty might be attributed to morbidities.

The study objectives were:

- to examine the association between pain and 'any' comorbidity count with frailty.
- to examine the association between pain and painful and non-painful morbidities with frailty.

5.2 Methods

The methods were described in Chapter 2, and the following relates to any particular methods or adaptations for this cross-sectional study.

5.2.1 Participants and data sources

Participants were from the Investigating Musculoskeletal Health and Wellbeing (IMH&W) study.

The Inclusion criteria:

- Baseline IMH&W completion including the five questions required for the FRAIL questionnaire.
- aged ≥60 years.

5.2.2 Variables

5.2.2.1 Frailty

The IMH&W survey included the 5 self-report FRAIL items described in Chapter 2. In the current study, to remove the overlap between FRAIL and morbidities, I modified FRAIL ("mFRAIL"). This omission of the illnesses (morbidity) item permitted examination of the contribution of morbidities to a frailty classification that approximates the phenotype model. Participants were classified using mFRAIL as non-frail (0 to 2 items) or frail (3 to 4 items).

5.2.2.2 Morbidities

I generated an 'any' morbidity count variable, which comprised the 11 conditions included in the illnesses item in the original FRAIL questionnaire (as above), plus 8 morbidities from the Charlson Comorbidity Index (CCI)

(Charlson et al., 1987) and 7 from the Functional Comorbidity Index (FCI) (Groll, 2004).

I ascertained these morbidities from the following:

1. A checklist of conditions prefaced with the question, 'has a doctor told you that you have any of these conditions or problems,' including the 11 FRAIL conditions and 7 other conditions.
2. Free text for "other conditions," classified using criteria developed by consensus between myself and my supervisors. Table 2-9 shows the criteria for classifying "other" morbidities from free text. Two reviewers (myself and Dr Shahtaheri) independently checked a sample of 100 participants and confirmed its reliability [ICC=0.94, (95%CI 0.91 to 0.96), p<0.001].
3. Participants' self-reported medications by free text and/or prescriptions, as described in Section 2.1.8.1.

Each morbidity was counted once, drawing first from the morbidity checklist, secondly from free text and finally by inference from medication lists.

I and Mr Harrison Lewis classified the 26 morbidities as either 'painful' or 'non-painful' morbidities according to the International Association for the Study of Pain, Classification of Chronic Pain list of conditions. This was used to indicate conditions in which pain management is routinely considered part of appropriate treatment (International Association for the Study of Pain, 1994) (Table 10.4). Diabetes without complications is classified as non-painful; However, diabetes is classified as painful if the participant reports complications such as neuropathy, Charcot foot, or retinopathy.

5.2.2.3 Pain

In my primary analysis, pain was measured using the McGill Pain Rating Index (Melzack, 1975, Melzack and Torgerson, 1971) to represent pain of any type or source. This bodily pain measure was selected as an alternative to joint pain, which may be related to specific morbidities; it is described in Chapter 2.

Confirmatory analysis was performed using standardised Numerical Rating Scale (0-10) (NRS) joint pain intensity previously described in Chapter 2. This part of the analysis included only participants who reported both types of pain measures.

5.2.2.4 Other variables

I used the previously identified co-variables of age, sex and BMI class as having an association with pain and frailty, and these were included in this analysis.

5.3 Statistical analysis

Data were summarised, and normality was assessed in the manner previously described in Section 2.3.1. Correlations were assessed using Spearman's rho and bootstrapped (10,000) to derive confidence intervals. Cases with any missing data were excluded from the regression analysis.

I validated the mFRAIL threshold (non-frail (0 to 2 items) or frail (3 or 4 items) by exploring the internal structure of FRAIL using Cronbach's alpha and Receiver Operator Curve (ROC) analysis of mFRAIL scores against the original FRAIL classification.

Multivariable logistic regression analyses were used to examine the extent to which association of chronic pain with frailty can be attributed to morbidities. Change between models was assessed by comparing the association of chronic pain with frailty alongside when 'any' morbidity count was added to the model. Standardised coefficients permitted the comparison of variables with different scales. They represent the change in the dependent variable's standard deviation associated with a one-standard-deviation increase in the predictor variable. I investigated associations between painful and non-painful morbidity count with frailty.

Age, sex, and BMI class were selected *a priori*; other co-variables were included if $p<0.05$ in prior bivariate analysis.

Categorical variables were classified as binary outcomes (absent/present) in all logistic regression models. Coefficients were standardised by generating z scores ((value-mean)/ standard deviation) to permit a direct comparison of the magnitude and impact of different variables on the dependent variable. Z-tests were used to compare the strengths of regression coefficients or the changes between coefficients in separate models (Clogg et al., 1995). Z values ≥±2 were interpreted as representing a significant difference.

5.4 Results

There were 7,074 baseline data records checked for eligibility; with 2,185 participants whose data met the eligibility criteria for this study. Their characteristics are shown in Table 5-1. Median age was 73 (range 60 to 96) years, and 1,202 (55%) were female. Participants were classified as frail using FRAIL and mFRAIL, respectively, 430 (20%) and 418 (19%). The use of 4-item mFRAIL led to a re-classification of only 12/430 (3%) participants classified by FRAIL. The median (IQR) Pain Rating Index was 13 (7 to 22). A flow diagram with details of missing data which were excluded from the analysis is shown in Figure 5-1.

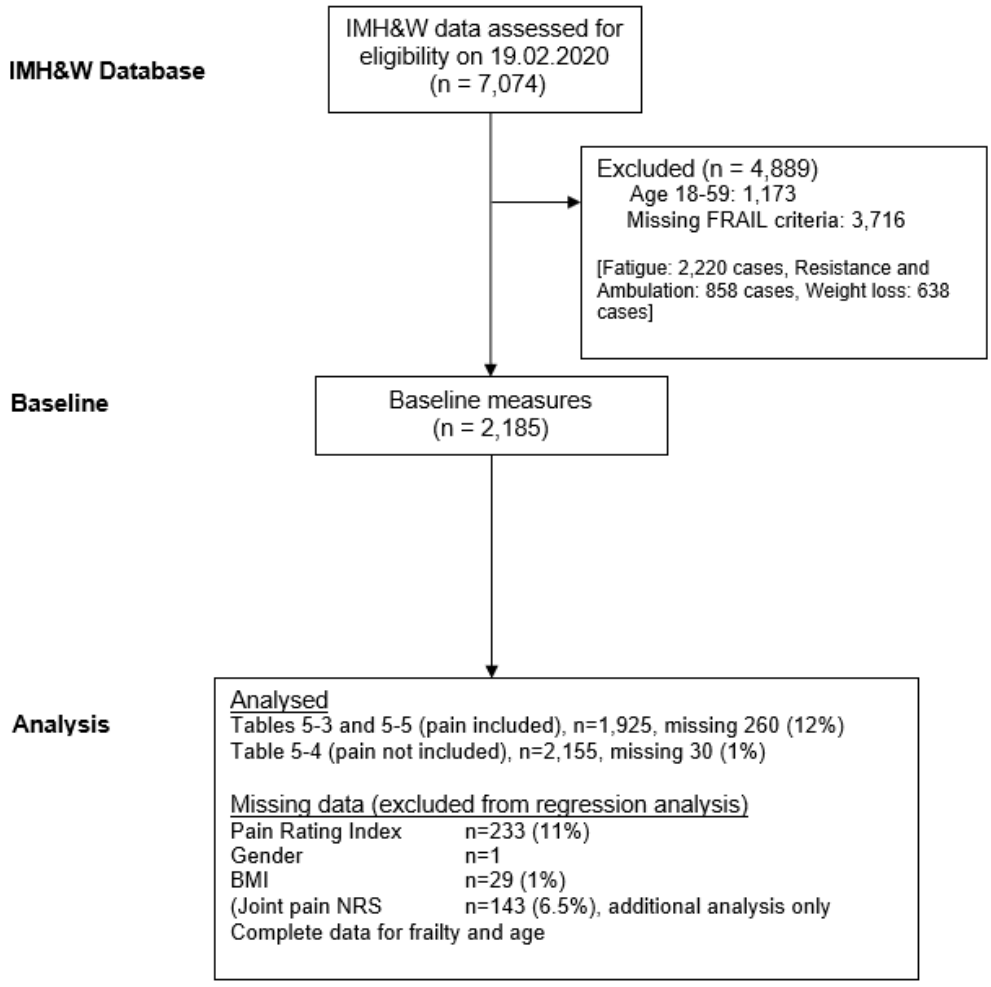

Figure 5-1 IMH&W flow Diagram with missing data.

Table 5-1 Participant characteristics

Variable	All participants N = 2185	≥1 painful morbidities	≥1 non-painful morbidities
Sex:			
Male, n (%)	982 (45)	833 (85)	677 (45)
Female, n (%)	1202 (55)	1,056 (88)	818 (55)
Age (years), median (range)	73 (60 to 96)	73 (60 to 96)	73 (60 to 96)
Ethnicity:			
White, n (%)	2,152 (99)	1865 (98)	1,468 (98)
Non-white	13 (1)	23 (1)	28 (2)
Socioeconomic Status, median (IQR) Indices of Multiple Deprivation (1-10 most deprived to least deprived)	8 (5-9)	8 (5-9)	8 (5-9)
BMI Classes[#], n (%)			
Underweight	30 (1)	27 (1)	20 (1)
Normal	653 (32)	540 (29)	417 (28)
Pre-obese	831 (39)	723 (39)	552 (38)
Obese	642 (30)	573 (31)	482 (33)
FRAIL classification			
Frail	430 (20)	414 (22)	343 (23)
Non-frail	1,755 (80)	1,476 (78)	1,153 (77)
Pain Rating Index (1-78) median (IQR)	13 (7-22)	14 (7-22)	14 (7-22)
FRAIL illness item (≥5/11), n (%)	58 (2.7)	58 (2.7)	58 (2.7)
Morbidity count			
All, median (range)	3 (0 to 12)	3 (2-4)	3 (2-4)
Painful, median (range)	2 (0 to 8)	2 (1-3)	2 (1-3)
Non-painful, median (range)	1 (0 to 5)	1 (0-1)	2 (1-2)
Recruitment Route n (%)			
GP	1,972 (90)	1697 (90)	1372 (92)
Previous studies	191 (9)	173 (9)	110 (7)
Other	22 (1)	18 (1)	12 (1)

Abbreviations: SD – standard deviation; BMI – body mass index; FRAIL (unmodified);
The number of observations for each variable varies; 2185 relates to complete FRAIL and age data.
[#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

Note: the ≥1 painful and non-painful categories are just for descriptive purposes; participants may have both a painful and non-painful morbidity.

5.4.1 Morbidities

Participants reported median (range) 3 (0 to 12) 'any' morbidities, 2 (0 to 8) painful morbidities, and 1 (0 to 5) non-painful morbidity. Only 96 (4%) participants reported no morbidities, and 1,297 (59%) participants had at least one painful plus one non-painful morbidity. The frequencies of morbidity counts are shown in Table 5-2. Figure 5-2 showed how the frequency of morbidities was reported by the three comorbidity classifications.

The most frequently reported painful and non-painful morbidities were arthritis 1,477 (68%) and hypertension 856 (39%), respectively. Higher 'any' morbidity count was associated with being female, pre-obese or obese. Higher painful morbidity count was associated with being female, older, or obese. A higher non-painful morbidity count was associated with obesity (Table 5-3).

In bivariate analyses, the Pain Rating Index was positively correlated with the count of 'any' morbidities (r_s= 0.24, 95% CI 0.19 to 0.28), p<0.001). Painful morbidity counts were positively correlated with non-painful morbidity counts (r_s= 0.10, 95% CI 0.06 to 0.15, p<0.001). Pain rating index was more strongly correlated with painful morbidity count (r_s= 0.26, 95% CI 0.22 to 0.31, p<0.001) than with non-painful morbidity count (r_s= 0.07 95% CI 0.02 to 0.11, p=0.003).

Table 5-2 IMH&W morbidity frequency by painful/non-painful classification (N=2185)

Morbidity	Painful	Check-list 1	Free text 2	Medications 3	Total
	Yes/No	n	n	n	n, (%)
Arthritis*	Yes	1447	21	9	1477 (68)
Hypertension *	No	779	42	35	856 (39)
Degenerative disc disease	Yes	767	24	0	791 (36)
Upper gastro-intestinal	Yes	0	26	658	684 (31)
Asthma*	No	325	7	81	413 (19)
Diabetes without complications*	No	349	12	25	386 (18)
Osteoporosis	Yes	218	4	29	247 (11)
Cancer*	Yes	201	30	6	237 (11)
Angina*	Yes	197	14	17	228 (10)
Lung disease*	No	139	38	8	185 (8)
Myocardial Infarction*	Yes	150	0	0	150 (7)
Stroke*	No	126	19	0	145 (7)
Kidney disease*	No	116	10	0	124 (6)
Depression	Yes	0	23	81	104 (5)
Visual impairment	No	0	34	57	91 (4)
Chronic Heart Failure*	Yes	60	2	1	63 (3)
Neurological	No	0	35	21	56 (3)
Anxiety	No	0	18	22	40 (2)
Lower Gastro-intestinal	Yes	0	29	0	29 (1)
Hearing impairment	No	0	12	0	12 (0.5)
Diabetes with complications	Yes	0	12	0	12 (0.5)
Dementia	No	9	0	0	9 (0.4)
Liver disease	Yes	0	7	0	7 (0.3)
Peripheral vascular disease	Yes	0	6	0	6 (0.3)
Hemiplegia	No	0	1	0	1 (<0.1)
AIDS	No	0	1	0	1 (<0.1)
Subtotal illnesses in FRAIL (11)		3,889	196	182	4,264
Subtotal illnesses not in FRAIL (15)		994	220	868	2,078
Total morbidities identified		4,883	413	1,050	6,342

Abbreviations: AIDS – Acquired immune deficiency syndrome. *Items are included in FRAIL; non-frail illnesses are extra morbidities from Charlson and Functional Comorbidity Indices.
Diabetes is classified as painful if the participant reports complications such as neuropathy (Charcot foot) and retinopathy.
1 - morbidity appeared in the checklist. This included all FRAIL illnesses plus degenerative disc disease, osteoporosis, and dementia. 2 - morbidity appeared in free text only. 3 - morbidity is inferred from medication only.

Note: there is an order of precedence to columns; the morbidity is counted as present in the following order: 1) checklist, 2) free text, 3) medication, and counted once even though it may be originally reported in all three ways.
1159 (53%) of participants reported free text morbidities, and 2088 (96%) reported medications.

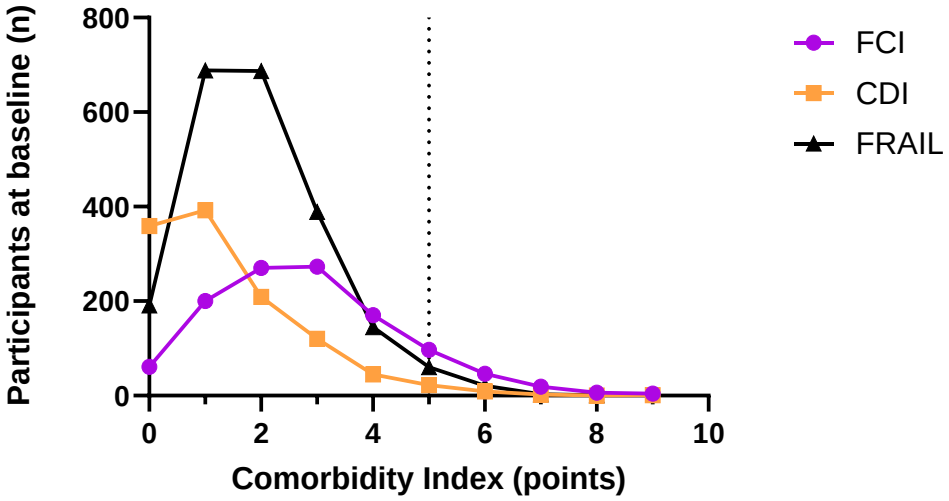

Figure 5-2 The comparison of comorbidity indices.
The dotted line indicates the FRAIL criteria for the illness item. Abbreviations: FCI – Functional Comorbidity Index; CDI – Charlson-Deyo Index. The CDI is weighted, whereas FCI and FRAIL are unweighted.

The three indices are similar at the threshold for FRAIL's illness criteria. These indices have different focuses with CDI predicting mortality and FCI predicting function.

Table 5-3 Bivariate associations between morbidity count and covariables.

Variable	'Any' morbidities	Bivariate association β Coef. (95%CI)	Painful morbidities	Bivariate association β Coef. (95%CI)	Non-painful morbidities	Bivariate β Coef. (95%CI)
Sex:						
Male,	3 (2-4)	Ref	2 (1-2)	Ref	1 (1-1)	Ref
Female	3 (2-4)	0.14 (003, 0.29), p=0.045	2 (1-3)	0.17 (0.07, 0.28), p=0.001	1 (0-2)	-0.03 (-0.11, 0.05), p=0.455
Age (years)	73 (69-79) *	0.01 (-0.001, 0.02), p=0.064	73 (69-79) *	0.01 (0.001, 0.02), p=0.02	73 (69-79) *	0.001 (-0.005, 0.007), p=0.746
BMI Classes#						
Underweight	3 (1-4)	0.17 (-0.44, 0.78), p=0.582	2 (1-3)	0.25 (-0.21, 0.71), p=0.289	1 (0-1)	-0.09 (-0.44, 0.26), p=0.616
Normal	2 (1-4)	Ref	2 (1-3)	Ref	1 (0-1)	Ref
Pre-obese	3 (2-4)	0.20 (0.03, 0.37), p=0.021	2 (1-3)	0.13 (-0.003, 0.26), p=0.055	1 (0-2)	0.07 (-0.03, 0.17), p=0.134
Obese	3 (2-4)	0.52 (0.34, 0.71), p<0.001	2 (1-3)	0.27 (0.13, 0.41), p<0.001	1 (1-2)	0.26 (0.15, 0.36), p<0.001

*Median age of participants with ≥1 morbidity count. Data are from n=2,155 participants

Abbreviations: BMI – Body Mass Index; β Coef. –beta coefficient**;** CI – 95% confidence intervals; Ref - reference group. #WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

5.4.2 Bivariate associations of frailty with pain, morbidity, and covariates

Frailty (mFRAIL) was associated with pain, morbidity counts, and covariates. In those classified as frail, the median Pain Rating Index was 22 (IQR 13 to 33) compared to 11 (IQR 6 to 19) in those who were non-frail. Pain Rating Index was associated with mFRAIL (OR 2.23, 95% CI 2.00 to 2.50, p<0.001).

'Any' (OR 2.04, 95% CI 1.83 to 2.28, p<0.001), painful (OR 1.89, 95% CI 1.69, 2.10, p<0.001) and non-painful (OR 1.50, 95% CI 1.36 to 1.67, p<0.001) morbidity counts were each associated with mFRAIL frailty classification.

Age (OR 1.02, 95% CI 1.00 to 1.03, p=0.045), female sex (OR 1.91, 95% CI 1.52 to 2.39, p<0.001), and BMI class (underweight OR 3.21 95% CI 1.42 to 7.25, p=0.005, pre-obese OR 1.50 95% CI 1.11 to 2.03, p=0.008, obese OR 2.96 95% CI 2.21 to 3.97, p<0.001) also each was associated with mFRAIL frailty classification.

5.4.3 The extent to which association of chronic pain with frailty can be attributed to morbidities.

In multivariable analysis, higher pain was associated with mFRAIL frailty classification (aOR 2.21, (95%CI 1.96 to 2.49), p<0.001, when adjusted for age, sex, and BMI class (Table 5-4). When 'any' morbidity count was added to the model, there was a non-significant (Z=0.76) reduction in the contribution of pain to frailty classification (aOR 2.07, (95%CI 1.83 to 2.33), p<0.001). When painful (aOR 1.48, (95%CI 1.30 to 1.68), p<0.001) and non-painful (aOR 1.39, (95%CI 1.24 to 1.56), p<0.001) morbidity counts were together included in the model, the contribution of pain to frailty classification was similar (aOR 2.07, (95%CI 1.83 to 2.34), p<0.001), Z=-0.002) (Table 5-4).

Table 5-4 Associations of pain and other characteristics with frailty

Factor	Interval/category	Model		
		1. Pain	**2. Pain & 'any' morbidity count**	**3. Pain, painful and non-painful morbidity count**
Chronic Pain	Standardised Pain Rating Index	2.21 (1.96, 2.49), p<0.001	2.07 (1.83, 2.33), p<0.001	2.07 (1.83, 2.34), p<0.001
'Any' morbidity	Standardised count	Not included	1.74 (1.54, 1.97), p<0.001	Not included
Painful morbidity	Standardised count	Not included	Not included	1.48 (1.30,1.68), p<0.001
Non-painful morbidity	Standardised count	Not included	Not included	1.39 (1.24, 1.56), p<0.001
Sex	Male	Ref	Ref	Ref
	Female	1.56 (1.21, 2.00), p=0.001	1.55 (1.20, 2.01), p=0.001	1.56 (1.21, 2.02), p=0.001
Age	Years	1.05 (1.03, 1.07), p<0.001	1.04 (1.02, 1.06), p<0.001	1.04 (1.02, 1.06), p<0.001
BMI Class[#]	Underweight	2.54 (1.02, 6.37), p=0.046	2.80 (1.10, 7.12), p=0.031	2.82 (1.11, 7.18), p=0.030
	Normal	Ref	Ref	Ref
	Pre-obese	1.43 (1.03, 1.98), p=0.033	1.42 (1.01, 1.99), p=0.041	1.42 (1.02, 1.99), p=0.040
	Obese	2.37 (1.71, 3.29), p<0.001	2.25 (1.60, 3.14), p<0.001	2.24 (1.60, 3.13), p<0.001
Pseudo r^2		0.1412	0.1832	0.1822

The outcome in each multivariable model was frailty classification (binary), defined as mFRAIL score >2. Data are aOR (95%CI) from n=1925 participants. Standardised coefficients represent the change in the dependent variable's standard deviation associated with a one-standard-deviation increase in the predictor variable; they permit the comparison of the variables with different scales. The pain model is frailty adjusted for pain, age, sex, and BMI class. The pain and 'any' morbidity count model is adjusted for pain, 'any' morbidity count, age, sex, and BMI class. The pain & painful morbidity count model is adjusted for pain, painful and non-painful morbidity count, age, sex, and BMI class.

Abbreviations: BMI – Body Mass Index; aOR –adjusted odds ratio**;** CI – 95% confidence intervals; Ref - reference group. [#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

5.4.4 The extent to which association of morbidities with frailty can be attributed to pain.

Higher 'any' morbidity count (aOR 1.98, (95%CI 1.77 to 2.23), p<0.001); higher painful (aOR 1.84, (95% CI 1.65 to 2.06), p<0.001) and higher non-painful (aOR 1.49, (95% CI 1.34 to 1.66), p<0.001) morbidity counts were associated with mFRAIL frailty classification in separate multivariable regression models, each of which included age, sex, and BMI class as covariates (Table 5-5). Both painful and non-painful morbidity counts remained significantly associated with mFRAIL frailty classification when they were included in a single age-, sex-, and BMI- adjusted model (painful morbidity count aOR 1.67, (95%CI 1.49 to 1.88), p<0.001, non-painful morbidity count aOR 1.38, (95%CI 1.24 to 1.55), p<0.001). When the Pain Rating Index was added to this model, painful and non-painful morbidity counts remained significantly associated with mFRAIL frailty classification (Table 5-4). However, the effect of painful morbidity count was slightly reduced and became similar to that of non-painful morbidities.

Table 5-5 Associations of morbidity counts and other characteristics with frailty.

Factor	Interval/category	Model		
		Any morbidities	**Painful morbidities**	**Non-painful morbidities**
Any morbidity	Standardised count	1.98 (1.77, 2.23), p<0.001	Not included	Not included
Painful morbidity	Standardised count	Not included	1.84 (1.65, 2.06), p<0.001	Not included
Non-painful morbidity	Standardised count	Not included	Not included	1.49 (1.34, 1.66), p<0.001
Sex	Male	Ref	Ref	Ref
	Female	1.96 (1.54, 2.49) p<0.001	1.89 (1.49, 2.40), p<0.001	2.03 (1.61, 2.57), p<0.001
Age	Years	1.02 (1.01, 1.04), p=0.005	1.02 (1.01, 1.04), p=0.005	1.03 (1.01, 1.04), p=0.001
BMI Class[#]	Underweight	2.93 (1.24, 6.92), p=0.014	2.79 (1.19, 6.53), p=0.018	3.06 (1.33, 7.04), p=0.008
	Normal	Ref	Ref	Ref
	Pre-obese	1.60 (1.16, 2.19), p=0.004	1.63 (1.19, 2.22), p=0.002	1.66 (1.22, 2.26), p=0.001
	Obese	2.99 (2.18, 4.10), p<0.001	3.21 (2.35, 4.39), p<0.001	3.18 (2.34, 4.32), p<0.001
Pseudo r^2		0.1225	0.1076	0.0763

The outcome measure was frailty classification (binary), defined as mFRAIL score >2. Data are aOR (95%CI) from n=2155 participants. Standardised coefficients represent the change in the dependent variable's standard deviation associated with a one-standard-deviation increase in the predictor variable; they permit the comparison of the variables with different scales. The first multivariable model is frailty adjusted for 'any' morbidity count, age, sex, and BMI class; the second is adjusted for painful morbidity count, age, sex, and BMI class, and the third is adjusted for non-painful morbidity count, age, sex, and BMI class. Abbreviations: BMI – Body Mass Index; aOR –adjusted odds ratio**;** CI – 95% confidence intervals; Ref - reference group. [#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

5.4.5 Confirmatory analysis using a measure of joint pain.

Similar findings were found in confirmatory analyses using NRS joint pain scores instead of the Pain Rating Index: NRS pain (aOR 3.34 (2.80, 3.99), p<0.001), painful (aOR 1.37 (1.21, 1.57), p<0.001) and non-painful (aOR 1.39 (1.24, 1.57), p<0.001) morbidities were significantly associated with mFRAIL frailty classification (Table 5-6).

The Pain Rating Index was then added into the NRS & Pain Rating Index model: NRS pain (aOR 2.68 (2.22, 3.24)), Pain Rating Index (aOR 1.54 (1.35, 1,77)), painful (aOR 1.54 (1.16, 1.51)) and non-painful (aOR 1.40 (1.24, 1.58)). This indicated that both measures of pain and painful and non-painful comorbidity count were all significantly associated (p<0.001) with mFRAIL frailty classification (Table 5-6).

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Table 5-6 Associations of frailty with standardised NRS pain and other characteristics.

		Model	
Factor	**Interval/category**	**NRS**	**NRS &Pain Rating Index**
NRS pain	Standardised NRS pain	3.34 (2.80, 3.99), p<0.001	2.68 (2.22, 3.24), p<0.001
Pain Rating Index	Standardised Pain Rating Index	Not included	1.54 (1.35, 1.77), p<0.001
Painful comorbidities	Standardised count	1.37 (1.21, 1.57), p<0.001	1.33 (1.16, 1.51), p<0.001
Non-painful comorbidities	Standardised count	1.39 (1.24, 1.57), p<0.001	1.40 (1.24, 1.58), p<0.001
Sex	Male	Ref	Ref
	Female	1.32 (1.01, 1.73), p=0.039	1.26 (0.97, 1.66), p=0.088
Age	Years	1.03 (1.01, 1.05), p=0.001	1.04 (1.02, 1.06), p<0.001
BMI Class[#]	Underweight	3.56 (1.36, 9.32), p=0.01	3.44 (1.28, 9.23), p=0.014
	Normal	Ref	Ref
	Pre-obese	1.41 (1.00, 1.99), p=0.051	1.37 (0.97, 1.95), p=0.074
	Obese	2.15 (1.52, 3.03), p<0.001	2.01 (1.42, 2.86), p<0.001
Pseudo r^2		0.2224	0.2432

The outcome measure is binary frailty without morbidity (mFRAIL), defined as mFRAIL score >2. The NRS model is frailty with standardised painful and non-painful comorbidities adjusted for standardised NRS pain severity, age, sex, and BMI class. The NRS & Pain Rating Index model is frailty with standardised painful and non-painful comorbidities adjusted for standardised NRS pain severity and Pain Rating Index, age, sex, and BMI class. Data are from n=1,915 participants. Standardised coefficients represent the change in the dependent variable's standard deviation associated with a one-standard-deviation increase in the predictor variable; they permit the comparison of the variables with different scales. Abbreviations: NRS – numerical rating score; BMI – Body Mass Index; aOR –adjusted odds ratio**;** CI – 95% confidence intervals; Ref - reference group. NA - Not Applicable [#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

5.5 Discussion

I found that pain, painful and non-painful morbidity counts were all associated with frailty when included in a single multivariable model. The inclusion of morbidities in any model did not substantially reduce the relationship between chronic pain and frailty, indicating that this relationship is unlikely to be explained entirely by morbidities.

The findings confirm and help to elucidate the previously demonstrated association between pain and frailty (Saraiva et al., 2018, Wade et al., 2017, Megale et al., 2018, Bindawas et al., 2018, Rodríguez-Sánchez et al., 2019, Chaplin et al., 2023). Others have described the relationship between morbidities and frailty (Clegg et al., 2013, Fried et al., 2009, Villacampa-Fernandez et al., 2017, Morley, 2016, Theou et al., 2012, Dent et al., 2019b); however, they have not explored this in the context of the relationship between pain and frailty. This research confirms the relationship between morbidities and frailty, and, to my knowledge, this is the first study to explore morbidity classification by pain.

A clinical implication of the findings, given that chronic pain is highly prevalent (Versus Arthritis, 2021, Havelin and King, 2018), is that effective pain management might have great potential to prevent or reduce frailty in the community. Another implication for those who study frailty is that chronic pain might be a factor that could be used in the identification and classification of frailty.

This study has both strengths and limitations. Although different results might have been obtained in different populations, my sample was representative of the IMH&W cohort, was large and had a high prevalence of painful and non-painful morbidities, pain, and frailty, enabling detailed exploration of these relationships. The sample had an approximately equal male-to-female distribution and included people from a range of socioeconomic backgrounds. However, IMH&W itself selectively recruited people with or at risk of frailty or musculoskeletal problems and displayed little ethnic diversity.

Different results might have been obtained using different frailty classification tools, and future work should include other frailty classification tools to confirm my findings. IMH&W was a postal questionnaire survey, so it was not possible to use in-person measurements of gait speed and grip strength to classify frailty phenotype (Fried et al., 2001). I modified the FRAIL classification criteria by omitting the illness item in order to investigate the role of morbidities in the relationship between pain and frailty. However, mFRAIL and FRAIL only classified 12 (3%) participants differently, suggesting that mFRAIL and FRAIL have similar validity for frailty classification. FRAIL has previously been shown to be a valid tool for frailty classification (Morley et al., 2012, Susanto et al., 2018), which performs comparably with other frailty tools (Aprahamian et al., 2017, Ravindrarajah et al., 2013), but it was not possible to compare directly with other classifications such as Fried Phenotype. My findings, however, suggest that mFRAIL and FRAIL might not fully describe frailty, and other frailty classifications might give different results.

I obtained similar findings using two different pain measurement tools (Pain Rating Index and NRS). It remains possible that aspects of pain (e.g., lower limb joint pain) result in an overclassification of frailty due to the inclusion in frailty classification tools of physical activity.

A strength of this study is that I found an association between pain and frailty, even after using an extensive list of morbidities to measure morbidity counts. I acknowledge the imprecision of classifying morbidities as either painful or non-painful using IASP criteria for conditions where pain management should be considered. Pain may be reported in conditions such as stroke that were classified as non-painful. Future research might assess the effects of differentially weighting specific morbidities. However, the findings suggest that weighting painful and non-painful morbidities differently would be unlikely to substantially affect frailty classification, nor the association of pain with frailty.

I acknowledge the risk of residual confounding due to the inclusion of inter-correlated variables in my multivariable models.

Longitudinal and interventional study designs are required to determine the causality of the relationships I observed between pain, morbidities, and frailty. The change in morbidities may be difficult to observe over a 1-year period and a change over a longer time frame should be observed. Future research should explore mechanisms by which pain might lead to frailty, for example, by reducing physical activity, impairing appetite, and nutrition, or through neuro-endocrine dysregulation. Randomised controlled trials would be required to test whether interventions that improve pain (even if not directly addressing underlying morbidities) can prevent or reverse frailty. A range of interventions that can reduce chronic pain (e.g., psychological, pharmacological, surgical, physical) might be explored in populations with or at risk of frailty, aiming not only to reduce pain but also to facilitate transition to a non-frail state or prevent transition into frailty.

In conclusion, chronic pain and multi-morbidity are both associated with frailty. The relationship of pain with frailty cannot be explained by morbidities, and the relationship between morbidities and frailty is not explained solely by pain. Further research is required to understand the complex relationship between pain and frailty. Interventions to mitigate the effect of chronic pain upon frailty should not be focussed solely upon treating underlying morbidities but also manage chronic pain irrespective of its aetiology.

CHAPTER 6 THE CROSS-SECTIONAL AND LONGITUDINAL ASSOCIATION OF CENTRAL ASPECTS OF PAIN WITH FRAILTY IN PEOPLE WITH KNEE PAIN.

6.1 Introduction

Exploring the relationship between chronic pain and frailty is important, and identifying factors that impact this relationship is key to improving our understanding. This involves examining factors with links to both pain and frailty.

In the previous chapters, I confirmed the bidirectional association of pain with frailty. This raised questions about the pain mechanisms involved in the association of pain and frailty. I found that the relationship between pain and frailty could not be explained by morbidities alone.

It's important to consider why pain is linked to frailty. It's possible that central aspects of pain could be evidence of a dysfunctional central nervous system (CNS) (Woolf, 2011, Latremoliere and Woolf, 2009, Nijs et al., 2021).

Exposure to chronic pain may increase central sensitivity by amplifying pain signals in the CNS whilst simultaneously, the inhibitory system becomes less effective, resulting in an overall increase in pain sensitivity (Woolf, 2011, Arendt-Nielsen et al., 2018a). Central aspects of pain factor (CAPf) is considered to be associated with increased pain hypersensitivity and shown to predict future knee pain, as discussed in Section 2.1.3 (Akin-Akinyosoye et al., 2021, Akin-Akinyosoye et al., 2018b). There were 8 characteristics associated with underlying CAPf (anxiety, depression, catastrophising, pain distribution, neuropathic-like pain, cognitive impact, sleep, and fatigue) (Akin-Akinyosoye et al., 2021).

Several of the CAPf items have been associated with frailty, including fatigue (Knoop et al., 2019), depression (Wang et al., 2022) and pain (Chaplin et al., 2023). Fatigue is included in many frailty classifications, including FRAIL (Morley et al., 2012). Subsequently, the association of CAPf with frailty will be assessed with the 'fatigue-item' omitted to form a modified CAPf (mCAPf).

This study aimed to investigate whether central aspects of pain explain the association between chronic pain and frailty.

This study has three objectives:

- to examine the association of central aspects of pain with frailty.
- to investigate the association of central aspects of pain and NRS pain with frailty classification.
- to explore the longitudinal association of central aspects of pain with frailty at 1-year

6.2 Methods

6.2.1 Participants

Participants in the IMH&W study were evaluated for their CAPf using the CAP-Knee questionnaire at baseline and 1-year. At that time, CAP-Knee was only validated in people with knee pain. Therefore, only those participants who reported knee pain (with NRS score ≥1) and indicated the knee as their most bothersome joint were considered eligible for the work described in this chapter.

The inclusion criteria were:

- Age ≥60 years.
- Completed all FRAIL questions.
- Completed CAP-knee questions.
- NRS pain ≥1 in the last 4 weeks.
- Reported the knee as the most bothersome joint.

6.2.2 Variables

6.2.2.1 Frailty

Frailty was classified using FRAIL classification, as described in Section 2.2. Participants were classified as non-frail (0-2 items) or frail (3-5 items).

6.2.2.2 NRS Pain

The people in the knee pain subgroup reported the pain intensity in their knee as the most bothersome joint. Therefore, using a measure of joint pain (NRS pain intensity) was appropriate.

6.2.2.3 CAP-Knee Questionnaire.

In the current study, to remove the overlap of the fatigue-item, which was included in both CAPf and FRAIL, I modified CAPf ("mCAPf"). This omission of the fatigue item permitted examination of the contribution of Central Aspects of Pain to frailty classification.

Details of the CAP-Knee questionnaire and scoring are shown in Section 2.1.3.

The CAP-Knee items (questions 1-6) were scored using a Likert scale as follows: 'never' = 0, 'sometimes' =1, and 'always' or 'often' =2. The depression item (question 7) was reverse coded: 'never' or 'sometimes' =2, 'often' =1 and 'always' = 0. The manikin was scored 2 if the shaded areas included both (i) any knee region and (ii) any other site below the waist. Score = 0 if shaded areas on the manikin did not include both (i) any knee region and (ii) any other site below the waist (Akin-Akinyosoye et al., 2020).

The modified CAPf score was calculated as the sum of all CAP-Knee items without fatigue; scores ranged from 0 to 14. Rasch analysis of CAPf has shown that omitting a single item does not invalidate the CAPf measurement (Smith et al., 2024, McWilliams et al., 2024) (both unpublished).

6.2.2.4 Other variables

In this analysis, I used the previously identified co-variables age, sex, and BMI class, which were described in Section 2.1.4.

6.2.3 Statistical Analysis

Initial analysis was run to provide descriptive statistics, summarise the percentage of categorical data, and evaluate normality and frequency distributions in the continuous data. This included the calculation of standard deviation and range where appropriate and if data did not have a normal distribution using the median and interquartile range. The assumption of normality was assessed statistically for continuous variables using the Shapiro-Wilk test and visually using histograms (Kirkwood and Sterne, 2010).

The Knee pain subgroup was compared to the baseline IMH&W data (see Chapter 3). Two of the items included in FRAIL classification (resistance and ambulation) may be present in people with knee pain, and therefore, may predispose people with knee pain to be classified with pain.

A comparison was also conducted between those who provided data at baseline only and those who completed 1-year follow-up. A paired t-test was conducted to test whether NRS pain had changed in the year, in those participants who reported at both timepoints. A large dropout at follow-up

reduces the statistical power. Additionally, if those completing follow-up have different characteristics compared to those who completed baseline only, then this affects the interpretation of the results.

Bivariate associations were analysed using logistic regression to examine the association of CAPf and NRS pain with frailty.

The outcome in each cross-sectional multivariable model was frailty classification (binary) adjusted for mCAPf and /or NRS pain, age, sex, and BMI Class. Longitudinal multivariable models were 1-year frailty classification (binary) adjusted for baseline frailty, mCAPf and /or NRS pain, age, sex, and BMI class.

6.3 Results

At baseline there were 639 participants who met the eligibility criteria for this study, as shown in Figure 6-1. Their characteristics are shown in Table 6-1. The median age was 73 (range 60 to 95) years, and 340 (53%) were female. 164 (26%) participants were classified as frail. The mean (SD) NRS pain at baseline was 6.0 (2.1). Very few people were classified as underweight; therefore, in the analysis, the underweight and normal BMI classes were combined.

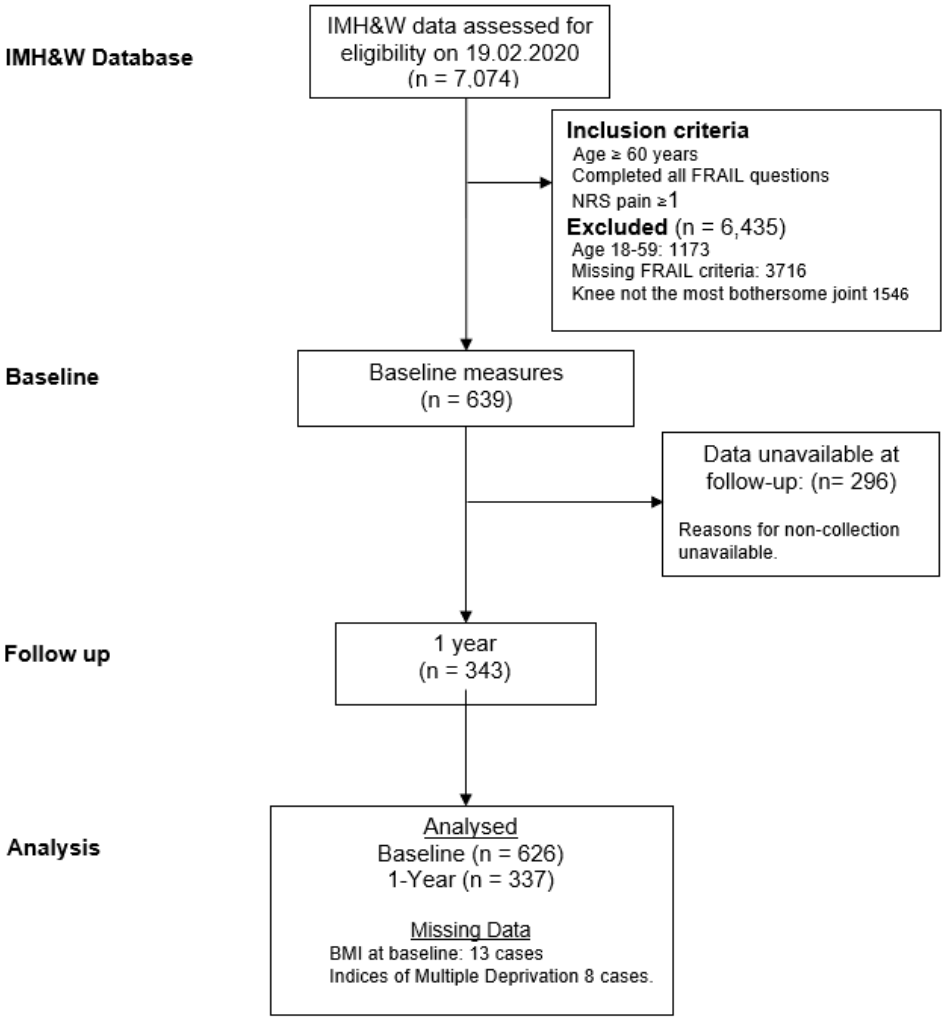

Figure 6-1 The IMH&W knee pain subgroup flow diagram with missing data.

Table 6-1 Participant characteristics of the IMH&W knee-pain subgroup at baseline.

Variable	All participants N = 639	Non-frail N= 475	Frail N=164
Sex:			
Male, n (%)	299 (47)	248 (52)	51 (32)
Female, n (%)	340 (53)	227 (48)	113 (68)
Age (years), median (IQR)	73 (68-78)	73 (68-78)	73 (68-80)
Ethnicity:			
White, n (%)	625 (96)	468 (99)	157 (96)
Non-white	14 (4)	7 (1)	7 (4)
Socioeconomic Status, median (IQR) Indices of Multiple Deprivation (1-10 most deprived to least deprived)	8 (5-9)	8 (5-9)	8 (5-9)
BMI Classes#, n (%)			
Underweight	4 (0.6)	3 (1)	1 (1)
Normal	166 (27)	136 (29)	30 (19)
Pre-obese	242 (39)	188 (40)	54 (34)
Obese	214 (34)	140 (30)	74 (47)
Joint pain (NRS 1-10)			
mean (SD)	5.95 (2.13)	5.38 (2.00)	7.58 (1.61)
Modified Central Aspects of Pain factor (mCAPf), median (IQR)	6 (4-9)	5 (4-7)	9 (8-11)

Abbreviations: SD – standard deviation; NRS – numerical rating scale; BMI – body mass index; IQR -Inter quartile range; mCAPf – modified Central Aspects of Pain factor.
The number of observations for each variable varies; it relates to complete FRAIL, pain, sex, age data, and ethnicity. Missing data BMI= 13 and SES=8
#WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

6.3.1 Comparison of the knee pain subgroup and those without knee pain at baseline.

There were some differences between the IMH&W baseline participants from who did not report having knee pain (see Chapter 3) and the knee pain subgroup (Table 6-2). The knee pain subgroup had a higher mean (SD) NRS pain of 5.95 (2.13) compared to those who did not report knee pain, with mean (SD) NRS pain of 5.22 (2.57), p<0.001. There was a higher proportion of the knee pain subgroup who were aged 60-69 years, obese and classified as frail compared to those who did not report knee pain. Those who reported at both time points NRS pain in people showed that the mean (SD) was higher at baseline 5.72 (2.12) than at 1-year with mean (SD) 5.48 (2.29), but this was not statistically significant (*t*=1.96 (327), p =0.05).

Table 6-2 Characteristics of IMH&W knee pain subgroup compared with participants who did not report knee pain at baseline.

Variable	KP subgroup participants N = 639	No knee pain. participants N=1,546	Chi-square value	P-value
Sex: n (%)			1.22	0.269
Male)	299 (47)	683 (44)		
Female	340 (53)	862 (56)		
Age group, n (%)			6.53	0.038
60-69 years	210 (33)	425 (27)		
70-79 years	293 (46)	779 (50)		
≥80 years	136 (21)	342 (23)		
Ethnicity: n (%)			3.84	0.05
White	625 (96)	1527 (99)		
Non-white	14 (4)	17 (1)		
Socioeconomic Status, median (IQR) Indices of Multiple Deprivation (1-10 most deprived to least deprived)	8 (5-9)	8 (5-9)	12.88	0.168
BMI Classes#, n (%)			13.49	0.004
Underweight	4 (0.6)	26 (2)		
Normal	166 (26)	487 (32)		
Pre-obese	242 (38)	589 (38)		
Obese	214 (33)	428 (28)		
FRAIL classification, n (%)			20.47	<0.001
Frail	164 (26)	266 (17)		
Non-frail	475 (74)	1280 (83)		

Abbreviations: BMI – body mass index; IQR Inter quartile range;
#WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

6.3.2 CAP factor in the IMH&W knee pain subgroup at baseline

All 639 participants completed the CAP-knee questionnaire at baseline. Modified scores ranged from 0 to 14. The distribution is shown in Figure 6-2.

The Shapiro-Wilk test was significant ($p<0.001$), indicating the mCAPf scores had a significantly different distribution from normal (skewness=0.18, and kurtosis=2.30). The median mCAPf was 6, with an interquartile range of 4 to 9.

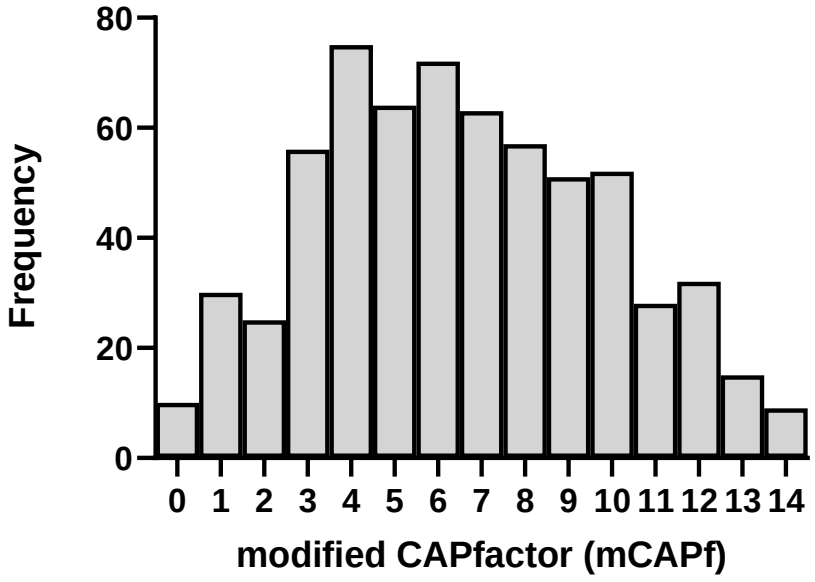

Figure 6-2 Histogram of mCAPf scores in IMH&W participants with knee pain.

Table 6-3 Contribution of Central Aspects of Pain of the Knee items towards mCAPf in IMH&W participants at baseline

CAP-Knee question	Aspect of pain	Contribution to mCAPf score (0-14)	Frequency, n (%)
Q1. Cold or heat (e.g. Bath water on my knee was painful	Neuropathic-like		
Always / Often		2	85 (13)
Sometimes		1	140 (22)
Never		0	414 (65)
Q3. Knee pain stopped me concentrating on what I was doing	Cognition		
Always / Often		2	155 (24)
Sometimes		1	305 (48)
Never		0	179 (28)
Q4. I kept thinking about how much my knee hurts	Catastrophising		
Always / Often		2	189 (30)
Sometimes		1	317 (50)
Never		0	133 (21)
Q5. In general, I got sudden feelings of panic	Anxiety		
Always / Often		2	38 (6)
Sometimes		1	123 (19)
Never		0	478 (75)
Q6. Knee pain affected my sleep	Sleep		
Always / Often		2	182 (28)
Sometimes		1	270 (42)
Never		0	187 (29)
Q7. I generally still enjoyed the things I used to enjoy	Depression		
Never / Sometimes		2	336 (53)
Often		1	180 (28)
Always		0	123 (19)
Q8. Pain manikin	Pain distribution		
Yes (one knee + one other area below the waist)		2	442 (69)
		0	197 (31)

Question 7 is reverse-coded so that 'Never / Sometimes' =2 and 'Always' =0. In this modified CAPf, Question 2, which referred to fatigue, was omitted.
Questions 1-7 are scored using a Likert scale. Question 8 was scored by interpreting a shaded manikin.

6.3.3 Cross-sectional associations

6.3.3.1 Bivariate associations of frailty with pain, mCAPf, and covariates in the knee pain subgroup at baseline.

Frailty was associated with NRS pain, mCAPf, and covariates. In those classified as frail, the mean (SD) NRS pain was 7.58 (1.61) compared to those who were classified as non-frail 5.38 (2.0), *t (637)* =-12.73, p <0.001. NRS pain was associated with frailty (OR 1.92, (95%CI 1.69 to 2.18, p<0.001). In participants classified as frail, the median (IQR) mCAPf was 9 (8 to 11) was higher compared to those classified as non-frail 5 (4 to 7), the bivariable association between mCAPf and frailty was (OR 1.55, (95%CI 1.43 to 1.68, p<0.001).

In bivariable associations, age was not significantly associated with frailty in people with knee pain (OR 1.00, (95%CI 0.98 to 1.03, p=0.721). However, female sex (OR 2.42, (95%CI 1.66 to 3.53), p<0.001) and the BMI class obese (OR 2.37, (95%CI 1.47 to 3.83), p<0.001) were each associated with frailty classification.

Higher NRS pain was not significantly associated with age (β=-0.02 95% CI -0.4 to 0.01, p=0.138). However, female sex (β=0.71 95% CI 0.38 to 1.04, p<0.001), and the BMI class obese (β=0.85 95% CI 0.42 to 1.27, p<0.001) were associated with higher NRS pain. Additionally, higher NRS pain was associated with higher mCAPf (β=0.39 95% CI 0.35 to 0.43, p<0.001).

Higher mCAPf scores were associated with younger age (β=-0.04 95% CI -0.07 to -0.002, p=0.037), female sex (β=1.26 95% CI 0.76 to 1.77, p<0.001), and the BMI class obese (β=1.52 95% CI 0.87 to 2.17, p<0.001).

6.3.3.2 Multivariable regression of mCAPf and pain with frailty classification.

In multivariable regression, higher mCAPf was associated with frailty classification (aOR 1.53, (95%CI 1.41 to 1.66), p<0.001), when adjusted for age, sex, and BMI class (Table 6-4). Higher NRS pain was also associated with frailty classification (aOR 1.87, (95%CI 1.64 to 2.13), p<0.001) adjusted for the same covariables (Table 6-4). When both mCAPf (aOR 1.37, (95%CI 1.26 to

1.50) and NRS pain (aOR 1.54, (95%CI 1.33 to 1.78) were included in the same model, they were both significantly associated with frailty classification, $p<0.001$ (Table 6-4).

Table 6-4 The association of mCAPf and other characteristics with frailty in the IMH&W knee pain subgroup at baseline.

		Frailty: mCAPf model	**Frailty: Pain model**	**Frailty: mCAPf & pain model**
Factor	Interval/Category			
mCAPf	(0-14)	1.53 (1.41, 1.66), p<0.001	Not included	1.37 (1.26, 1.50), p<0.001
NRS pain	NRS (1-10)	Not included	1.87 (1.64, 2.13), p<0.001	1.54 (1.33, 1.78), p<0.001
Sex	Male	Ref	Ref	Ref
	Female	1.87 (1.20, 2.91), p=0.006	1.88 (1.22, 2.90), p=0.004	1.65 (1.04, 2.61), p=0.034
Age				
	60-69 year	Ref	Ref	Ref
	70-79 years	1.35 (0.82, 2.23), p=0.239	1.00 (0.62, 1.62), p=0.989	1.29 (0.77, 2.16), p=0.335
	≥80years	1.75 (0.97, 3.18), p=0.065	1.57 (0.88, 2.78), p=0.124	1.76 (0.95, 3.26), p=0.072
BMI Class#	Underweight/Normal	Ref	Ref	Ref
	Pre-obese	1.30 (0.73, 2.30), p=0.378	1.29 (0.74, 2.26), p=0.373	1.24 (0.68, 2.26), p=0.478
	Obese	1.77 (1.00, 3.14), p=0.051	2.10 (1.21, 3.64), p=0.008	1.67 (0.92, 3.01), p=0.090
Pseudo r^2		*0.2616*	*0.2320*	*0.3140*

The outcome in each multivariable model was frailty classification (binary). Data are aOR (95%CI) from n=626 participants. The Frailty: mCAPf model is frailty adjusted for mCAPf and the co-variables age, sex, and BMI class. The Frailty: pain model is frailty adjusted for NRS pain, age, sex, and BMI class. The Frailty: mCAPf and pain model is frailty adjusted for mCAPf and NRS pain and the co-variables sex, age, and BMI class. Abbreviations: BMI – Body Mass Index; aOR –adjusted odds ratio; CI – 95% confidence intervals; Ref - reference group. #WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese. Underweight and normal were combined due to small numbers in the underweight class.

6.3.4 Participant Characteristics at 1-year

There were 343 participants who completed the IMH&W survey at both 1-year and baseline. Their characteristics are shown in Table 6-5. The participants who completed at both time points were less likely to be classified as frail at baseline. Additionally, baseline-only participants had a higher mean (SD) NRS pain at baseline 6.3 (2.01) compared to those who completed at both time points mean (SD) NRS pain 5.6 (2.1), *t* (637) =3.90, p<0.001. Baseline-only participants reported a higher mean (SD) mCAPf at baseline 7.0 (3.4) compared to those who completed at both time points mean (SD) 6.2 (3.2), t (637) =3.24, p=0.0013. However, other participant characteristics (sex, age, BMI) of those who completed 1-year compared to baseline-only were similar, as shown in Table 6-5.

Table 6-5 IMH&W knee pain subgroup participant characteristics at 1-year compared to those with baseline-only data.

Variable	1-year and baseline data N = 343	Baseline-only N = 296	Chi-square value	P-value
Sex: n (%)			0.77	0.382
Male)	166 (48)	133 (45)		
Female	177 (52)	163 (55)		
Age group, n (%)			5.41	0.067
60-69 years	174 (27)	210 (33)		
70-79 years	309 (48)	293 (46)		
≥80 years	156 (24)	136 (21)		
Ethnicity: n (%)			0.67	0.412
White	337 (98)	288 (97)		
Non-white	6 (2)	8 (3)		
BMI Classes[#], n (%)			1.06	0.786
Underweight	2 (0.6)	2 (0.6)		
Normal	94 (28)	72 (25)		
Pre-obese	131 (39)	111 (38)		
Obese	110 (33)	104 (36)		
FRAIL classification, n (%)			17.45	<0.001
Frail	67 (20)	101 (34)		
Non-frail	276 (80)	195 (66)		
NRS pain at baseline, mean (SD)	5.64 (2.12)	6.30 (2.01)		
mCAPf at baseline	6.17 (3.19)	7.01 (3.36)		

Abbreviations: BMI – body mass index; IQR Inter quartile range;
[#]WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese.

6.3.5 Longitudinal association of mCAPf, pain and baseline characteristics with 1-year frailty.

Multivariable regression models showed that baseline mCAPf did not predict 1-year frailty. However, NRS pain did predict future frailty (aOR 1.33, (95%CI 1.05 to 3.79), p =0.016). All models were adjusted for baseline frailty, sex, age, and BMI class (Table 6-6). In a model, that included mCAPf and NRS pain, NRS pain was significantly associated with 1-year frailty (aOR 1.29, (95%CI 1.00 to 1.65), p=0.047).

Table 6-6 The association of baseline mCAPf and pain and other characteristics with 1-year frailty in IMH&W participants with knee pain

Baseline factor	Interval/Category	Frailty: mCAPf model	Frailty: pain model	Frailty: mCAPf & pain model
Frailty	Absent/Present	17.25 (7.27, 40.91), p<0.001	15.15 (6.50, 35.32), p<0.001	13.23 (5.46, 32.08), p<0.001
mCAPf	mCAPf (0-14)	1.12 (0.98, 1.29), p=0.089	Not included	1.07 (0.93, 1.24), p=0.354
NRS pain	NRS (1-10)	Not included	1.33 (1.05, 3.79), p=0.016	1.29 (1.00, 1.65), p=0.047
Sex	Male	Ref	Ref	Ref
	Female	1.63 (0.71, 3.72), p=0.250	1.65 (0.72,3.79), p=0.235	1.59 (0.69, 3.66), p=0.277
Age				
	60-69 year	Ref	Ref	Ref
	70-79 years	0.82 (0.34, 2.00), p=0.663	0.78 (0.32, 1.91), p=0.592	0.82 (0.34, 2.02), p=0.671
	≥80years	2.91 (0.98, 8.59), p=0.054	3.48 (1.18, 10.27), p=0.024	3.39 (1.14, 10.12), p=0.028
BMI Class#	Underweight/Normal	Ref	Ref	Ref
	Pre-obese	0.90 (0.31, 2.61), p=0.848	0.86 (0.30, 2.49), p=0.785	0.85 (0.29, 2.46), p=0.764
	Obese	3.88 (1.43, 10.55), p=0.008	4.18 (1.54, 11.36), p=0.005	3.88 (1.42, 10.61), p=0.008
Pseudo r^2		*0.3872*	*0.3979*	*0.4007*

The outcome in each multivariable model was 1-year frailty classification (binary). Data are aOR (95%CI) from n=337 participants. The mCAPf model is 1-year frailty adjusted for baseline frailty, mCAPf and the co-variables age, sex, and BMI class. The pain model is 1-year frailty adjusted for baseline frailty, NRS pain, age, sex, and BMI class. The mCAPf and pain model is 1-year frailty adjusted for baseline frailty, mCAPf and NRS pain, and the co-variables sex, age, and BMI class.

Abbreviations: BMI – Body Mass Index; aOR –adjusted odds ratio; CI – 95% confidence intervals; Ref - reference group. #WHO classification for BMI (kg/m2), underweight <18.5, normal 18.5-24.9, pre-obese 25-29.9 and >30 obese. Underweight and normal were combined due to small numbers in the underweight class.

6.4 Discussion

In this study, I demonstrated that mCAPf and NRS pain were associated with frailty classification when included in the same model in a subgroup of knee pain participants drawn from the IMH&W cohort. Additionally, the study showed that knee joint pain is associated with current and future frailty.

Although mCAPf was not statistically significantly associated with 1-year frailty (aOR 1.12, (95%CI 0.98 to 1.29) p=0.089), the confidence intervals were close to 1. Therefore, I could not rule out that an association does exist, and this could be because so many people were lost to the study at 1-year. Those who dropped out reported higher NRS pain and mCAPf at baseline and were more likely to be classified as frail. These factors may have influenced the results, so the findings need to be interpreted cautiously. While the study could not demonstrate the association of future frailty with mCAPf, it is plausible that such an association exists. Further research is necessary to understand whether mCAPf is longitudinally associated with future frailty.

These findings confirm the previously demonstrated longitudinal association between knee pain and frailty (Bindawas et al., 2018) and my previous work exploring the association of joint pain with frailty (Chaplin et al., 2023).

The 8 characteristics associated with underlying CAPf are all interrelated and connected to fatigue. Even though fatigue was not included in the modified CAP factor, it is likely to be associated with the fatigue included in FRAIL. This limitation does not invalidate my findings and requires further investigation.

The CNS's dysfunction may increase pain sensitivity and increase the likelihood of other trauma, such as illness or falls. The mCAPf incorporates 8 underlying factors that have been independently linked to pain and also frailty and predict future pain. A deeper understanding of these factors and their collective impact could improve our understanding of the connection between pain and frailty. This requires clinical observations and examination of the underlying factors incorporated in CAPf. Each of the 8 characteristics associated with underlying CAPf (anxiety, depression, catastrophising, pain

distribution, neuropathic-like pain, cognitive impact, sleep, and fatigue) may be sub-threshold for clinical diagnosis but, in combination, may have a greater effect than any one characteristic. For example, an individual with subclinical threshold depression who tends to catastrophise may be more susceptible to pain and at a higher risk of developing frailty compared to someone experiencing depression alone. Understanding these associations will be the subject of the next chapter and the ACHING study.

The CAP-Knee questionnaire is just one way to measure central aspects of pain. Central sensitisation and associated terms are not a single entity. Research has shown that CAPf has a positive correlation with Quantitative Sensory Testing (QST) methods, although the correlation was not exceptionally strong (Akin-Akinyosoye et al., 2020). The QST methods measure different physiological processes:

- Pain Pressure Threshold assesses the sensitivity of deeper structures.
- Temporal Summation assesses spinal facilitation or wind-up.
- Conditioned pain modulation assesses descending modulation.

Central aspects of pain may indicate a dysfunctional CNS and impaired pain regulation, suggesting a system that is more vulnerable due to a loss of homeostatic reserve. Two competing models exist: one suggests that chronic pain causes central sensitisation, while the other proposes that central sensitisation causes chronic pain. However, both of these models may be valid, indicating a bidirectional relationship.

If central sensitisation exacerbates chronic pain, then addressing the central aspects of pain may be necessary to alleviate pain and prevent frailty. Some pain medications, such as duloxetine, also target central aspects of pain to enhance pain management (Skljarevski et al., 2011). The development of CAP-Knee (Akin-Akinyosoye et al., 2018a) aims to identify individuals who would benefit from such treatments. Additionally, therapies, such as cognitive behaviour therapy or exercise, may help people manage central aspects of pain, such as anxiety, depression and catastrophising. A comprehensive

intervention combining medication and other therapies may be necessary to address these factors, but further research is needed to determine if this approach would reduce pain and/or frailty.

In summary, the relationship between pain and frailty may be partially explained by central aspects of pain. I have previously identified a bidirectional link between chronic pain and frailty and suggested that improving pain management could potentially delay or ameliorate frailty. Understanding common mechanisms between pain and frailty is key to disrupting this vicious cycle. Further investigation is required to understand the different possible causes of pain and their relationship with frailty.

CHAPTER 7 THE DEVELOPMENT OF THE CASE-CONTROL ACHING STUDY: INVESTIGATING PAIN AND CHALLENGES TO FUTURE HEALTH AND WELLBEING STUDY.

7.1 Introduction

In this thesis, I have identified the bidirectional association between chronic pain and frailty and endeavoured to elucidate the underlying mechanisms of this association. Although, causes of pain have been investigated, for example, morbidities (Chapter 5) and Central Aspects of Pain (Chapter 6), neither has fully explained the strength of the pain-frailty association.

The ACHING study will examine multiple possible causes of pain and also provide newly collected data primarily aimed at addressing questions about pain and frailty.

So far, this thesis has relied on self-report questionnaire data. The ACHING study will be an observational case-control study and will include in-depth questionnaires and clinical observations. The study would provide data over a range of measures related to chronic pain, pain mechanisms and items associated with frailty, which could explain the relationship between chronic pain and frailty.

Frailty, chronic pain, and CAP factor are closely linked, but the underlying mechanisms are unclear. An in-depth assessment of each of these aspects in a case-control study in which people classified as frail are compared with people who are classified as ‘robust' may highlight what factors are involved. For example, it may be that there are different phenotypes of people with chronic pain that make some people more likely to become frail. An omics study of frailty with chronic widespread MSK pain identified shared neurological pathways between these conditions (Livshits et al., 2018a). They proposed a genetic correlation, also associated with depression and anxiety.

In this chapter, I will describe the design of this study, which aims to measure and explain the association of frailty with central pain mechanisms, alongside other potential causes of pain and pain severity in individuals with knee pain.

This study has four objectives:

- to design a study and select measures that could explore multiple causes of pain including peripheral indices and central aspects of pain.
- to design a study and select measures that could explore multiple possible causes of frailty including sarcopenia and low muscle mass.
- to write a protocol and prepare for collecting clinical observations.
- to obtain ethical approval from the Health Research Authority.

7.2 Development of the protocol

Within the protocol, there is mention of the Central Mechanism Trait. While the items measured by CAP-Knee (Section 2.1.3) remain the same, the total score is now referred to as CAP factor (CAPf). This modification was made due to the evolution of our understanding of this concept as more data has been gathered. The CAP-Knee score measures a state rather than the previously proposed trait. Studies have shown that CAPf can predict future knee pain and is associated with psychophysical evidence of pain hypersensitivity (Akin-Akinyosoye et al., 2020). It's important to note that these adjustments did not change the underlying objectives of my planned research, or the items being investigated.

This study was titled “Investigating pAin and Challenges to future Health and wellbeING study” but will be referred to using the acronym ACHING.

7.2.1 Background and rationale

Frailty, chronic pain, and CAP factor are closely linked, but the underlying mechanisms are unclear. An in-depth assessment of each of these aspects in a case-control study in which people classified as frail are compared with people who are classified as ‘robust' may highlight what factors are involved. For example, it may be that there are different phenotypes of people with chronic pain that make some people more likely to become frail. An omics study of frailty with chronic widespread MSK pain identified shared neurological pathways between these conditions (Livshits et al., 2018a). They proposed a genetic correlation, also associated with depression and anxiety.

Previously, I have shown an association between baseline NRS pain, mCAPf and frailty at baseline. A model adjusted for baseline factors showed that baseline NRS pain and frailty predicted 1-year frailty. Although mCAPf did not predict future frailty, this could be due to those who dropped out at 1-year. Those who did not complete their second time point were more likely to be classified as frail and report higher baseline NRS pain and mCAPf.

The criteria for classifying frailty typically focus on musculoskeletal aspects. However, I have demonstrated an association with the CAP factor. Having identified this association and recognising that psychophysical factors may be involved, it is necessary to carry out a mechanistic exploration to identify what explains the associations between pain and frailty. Whether it is CAP factor or one or more underlying characteristics that include depression, anxiety, catastrophising, cognitive impairment, sleep, neuropathic-like pain, pain distribution or fatigue. Additionally, whether indices of peripheral pain mechanisms or biomarkers of disease, e.g., inflammatory biomarkers, biomarkers of insulin resistance, gut microbiome measures, can explain most of the association between pain and frailty. I speculate that pain increases sedentary behaviour, which accelerates the ageing process, reducing physiological reserve, which leads to frailty. Higher central sensitisation may increase sensitivity to challenges both sensory and emotional. This increased sensitivity amplifies the response to pain and challenges such as illness or disability, and therefore, CAP factor might be a measure of vulnerability. While current frailty interventions focus on building muscle and dietary supplementation, investigating the contribution of central factors and pain may inform future novel interventions. This may include a biopsychosocial approach which addresses central factors to improve the health span.

7.3 ACHING study objectives and purpose

7.3.1 Hypothesis

I hypothesise that pain severity is associated with frailty due to central pain mechanisms in combination with other causes of pain.

7.3.2 Purpose

This study aims to measure and explain the association of frailty with central aspects of pain, potential causes of pain, and pain severity in individuals with knee pain.

The primary objective of the ACHING study is to identify which central pain mechanisms explain the association between pain intensity and FRAIL classification. The secondary objectives of the ACHING study are:

- to build a mechanistic model in which peripheral and central pain mechanisms explain the association between pain and FRAIL classification.
- to confirm primary analysis by examining alternative measures of peripheral and central pain mechanisms and frailty
- to explore the correlation between biomarkers of disease (for example, inflammatory biomarkers, biomarkers of insulin resistance, gut microbiome measures and physiological tests) and FRAIL classification.

7.4 Methods

This section will describe the decisions made and the selection of the variables and measures for the ACHING protocol and study. The protocol includes details of the procedure for collecting the measures.

7.4.1 Study design.

ACHING is a case-control study of people with knee pain who are classified as either frail or robust using FRAIL classification. This will provide as much separation as possible between the two classifications; thus, recruitment of people classified as prefrail will be avoided. All participants will have knee pain so that we can compare differences in those who are classified as frail with those who are classified as robust.

7.4.2 Participants

To explore which pain mechanisms might explain associations between pain intensity and FRAIL classification, I calculated that a cross-sectional study involving 122 people should be recruited from the Investigating Musculoskeletal Health and Wellbeing (IMH&W) cohort.

All ACHING participants will be at least 60 years old with moderate-to-severe knee pain and have previously participated in the IMH&W cohort; this will permit the establishment of previous pain and frailty classification and identify participants for recruitment. Robust controls will be age and sex-matched with cases who have been classified as frail. This will enable control of these variables as frailty is more prevalent in older people (>80 years) and the female sex.

All participants will be invited to provide written informed consent and to attend a single research visit at the University of Nottingham Clinical Sciences Building, City Hospital, Nottingham.

7.4.2.1 Recruitment

Potential participants who meet the eligibility criteria for this study and have previously consented to further research contact will be identified from the

IMH&W database. These people will be sent a letter of invitation, a Participant Information Sheet (PIS), and a reply slip with a pre-paid envelope.

7.4.2.1.1 Eligibility criteria

Inclusion criteria (all the following for all participants)

- Participants who have reported that their knee as their most bothersome joint, with a knee pain severity on most days of the last month of ≥4 on a 0–10-point numeric rating scale. This will be assessed using the following question: "Over the past 4 weeks, how intense was the average pain or aching in your knees on a 0-10 scale, where 0 is no pain, and 10 is pain as bad as could be?".
- Participants who have previously responded to IMH&W with a complete FRAIL scale.
- Adults aged 60 years and above, there is no maximum.
- Participants are able to stand from a seated position (with aids if required).

Exclusion criteria: (any of the following)

- Insufficient understanding of spoken or written English to comply with the requirements of the study protocol.
- Inability to meet the requirements of research assessments.
- Major active psychiatric condition, e.g., major depression
- Unable to give informed consent.
- Unstable angina or severe heart failure (class ≥3)
- Acute medical illness (for example, recent major operation or stroke, or any hospital admission) within three months
- Knee replacement in the index knee.
- A non-stable dose of glucocorticoid medication during the preceding three months, including dose changes of oral glucocorticoid or parenteral glucocorticoid; systemic or local administration.

7.4.3 Selection of Variables

The following describes the variables selected for inclusion in the ACHING study. Full details of how the variable is collected are described in the protocol document.

7.4.3.1 Frailty

The primary frailty classification is FRAIL. This will be used to classify the current FRAIL classification, which will be compared with previous entries for IMH&W. In selecting people already classified as frail in a previous IMH&W study, I will be able to confirm that they meet the FRAIL criteria. Additionally, I will examine variables associated with frailty, for example, fatigue, lean muscle mass, handgrip strength, and gait speed. These measures should permit a classification of frailty using the Fried Phenotype for confirmatory analysis.

7.4.3.2 Pain and associated measures

7.4.3.2.1 Joint pain NRS

The participants in this study will have knee pain as CAP-Knee has been validated in that population. An assessment of joint pain is, therefore, appropriate.

7.4.3.2.2 Knee pain measures

In addition to the NRS pain used in my previous work, I wanted to include a pain scale specifically designed for assessing knee pain. There are various options available, each with its advantages and disadvantages. These include the following three options.

The Intermittent and Constant Osteoarthritis Pain (ICOAP) questionnaire is designed to measure two distinct pain patterns. In a previous study, a separate association was identified between intermittent and constant pain and the CAP factor (Akin-Akinyosoye et al., 2018b). The ICOAP also asks about pain rather than how pain affects activities of daily living. The 11 items form

two subscales of pain intensity and the effect of pain on quality of life (Hawker et al., 2008).

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is a questionnaire for evaluating patients with knee OA. It includes 5 pain questions, 2 concerning stiffness of the joint, and 17 about activities of daily living (Bellamy et al., 1988). There is a charge to use WOMAC.

The Knee injury and Osteoarthritis Outcome Score (KOOS), the full measure, uses 42 items distributed across 5 subscales (Roos and Lohmander, 2003); however, the use of the Pain subscale has been validated in several populations and different knee complaints. Administered by questionnaire, KOOS has greater responsiveness to change than more generic instruments (Roos and Lohmander, 2003). There is no charge to use the KOOS.

The pain subscale KOOS was selected because it fulfilled the criteria for additional pain measures that were suitable for people with knee pain and did not add too many questions, which might burden patients. Additionally, its main focus was on pain rather than activities of daily living, which might be affected by frailty rather than pain. KOOS has been evaluated in a systematic review and meta-analysis (Collins et al., 2016). They found KOOS has 'adequate content validity, internal consistency, test-retest reliability, construct validity and responsiveness for age- and condition-relevant subscales.'

7.4.3.2.3 Central Aspects of Pain in Knee (CAP-Knee)

The questionnaire was presented and used in Chapter 6, which showed the association of CAP-Knee scores with frailty. CAP-Knee consists of 8 items associated with characteristics of: fatigue, sleep disturbance, cognitive impairment, anxiety, depression, neuropathic-like pain, pain distribution, and catastrophising (Akin-Akinyosoye et al., 2020). CAP-Knee predicts future knee pain and is associated with psychophysical evidence of central pain hypersensitivity.

The CAP-Knee asks a single question for each item. To explore the associated characteristics further, a specific measure for each item will be used, these are shown in Table 7-1. Understanding if there are underlying conditions that may be increasing the likelihood of frailty may indicate the pain and frailty mechanisms. I recognise that some aspects, such as depression, have previously been shown to be associated with frailty (Soysal et al., 2017a). However, when a number of sub-clinical factors are combined, they may be linked to increased vulnerability.

Table 7-1 Alternative measures to CAP-Knee items

Characteristic	Questionnaire	Administration method
Anxiety	Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983)	Questionnaire
Depression		Questionnaire
Concentration/ cognitive impairment	Cognitive ability tasks (described below) (Batty et al., 2016)	In-person clinical assessment
Catastrophising	The Pain Catastrophising Scale (PCS) (Sullivan et al., 1995)	Questionnaire
Neuropathic like pain	modified Pain Detect (mPDQ) (Hochman et al., 2013)	Questionnaire
Sleep disturbance	Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1991)	Questionnaire
Fatigue	Bristol Rheumatoid Arthritis Fatigue scale (BRAFs),	Questionnaire

7.4.3.2.4 Cognitive ability tasks

English Longitudinal Study of Ageing (ELSA) used a battery of nurse-led cognition tests waves 2-8. At Wave 9, they introduced a much longer protocol with a focus on dementia. ELSA has an established methodology for assessing cognition developed over many years. ELSA data is publicly available, and they have also classified frailty using Fried Phenotype. This permits comparisons with the IMH&W cohort.

Batty and colleagues analysed the ELSA data. They found the tests below gave a good range of scores (0-103) from a maximum of 144, with no ceiling or floor effects, and could be used as a continuous measure (Batty et al., 2016). These memory and executive function tests were also used in SHARE with frailty (Romero-Ortuno et al., 2010). They are neither too long or complicated to administer and are indicated in Table 7-2.

Memory will be measured using a word-list learning test, in which 10 words are presented orally to study participants. They will be asked to recall as many as possible immediately after the list is read to them. The recall request will be repeated again after a 5-minute delay, during which the participant completes other survey questions. The overall memory score (range,0–20) uses both the immediate and delayed recall results.

Executive function will be ascertained using a word-finding task (semantic verbal fluency) in which we tally the number of different animals that participants could name in 1 minute (range, 0–60).

Processing speed will be measured using a letter-cancellation test; the participant will be handed a page of randomly generated letters of the alphabet set out in rows and columns and asked to cross out as many of the target letters ("P" and "W") as possible within 1 minute. The total number of correct letters identified will provide a measure of the speed of processing (range, 0–64).

The four task scores will be added together.

Table 7-2 Cognitive ability tasks

Test	**Score Range**	**Time (mins)**
Memory	0-20	
10-item recall test: Immediate	10	1
10 item recall test: delayed (5 mins)	10	1
Exec function		
Name as many animals as possible	0-60	1
Processing speed		
letter cancellation test	0-64	1
Find in a grid W and P.		
Maximum score	144	

7.4.3.2.5 Quantitative Sensory Testing (QST

Quantitative Sensory Testing, or QST, is a non-invasive method of assessing pain sensitivity in individuals. These tests involve recording a person's pain response to a standardised physical stimulus. Pain sensitivity can indicate sensitisation of nociceptive neuronal pathways, whether in the peripheral or

central nervous system. QST is a psychophysical test that includes both subjective and objective components. The results of QST are influenced by various psychosocial factors, such as the participant's anxiety levels, comfort and confidence in the testing environment, and the gender of the researcher. The physical stimulus and testing environment also significantly impact the measurements obtained, including the rate of pressure increase, test modality sequence, anatomical test site, and room temperature.

The QST measurements will be (1) pressure pain detection thresholds (PPT), (2) temporal summation (TS), and (3) conditioned pain modulation
Radiological assessment

All participants will undergo radiography of the knees. A trained rater will score radiograms, grading of radiograms for changes of osteoarthritis will include (Guermazi et al., 2012) the Nottingham Logically Devised line drawing Atlas (NLDA) for individual scoring of osteophyte (0–5) and joint space width (−1 to +5, using sex-specific atlases) for each medial tibio-femoral (TF), lateral TF and patello-femoral (PF) compartment similar to previous published epidemiological studies (Ingham et al., 2011).

7.4.3.3 Measures of Sarcopenia

Sarcopenia is closely allied to frailty; it is viewed as an age-related loss of muscle mass associated with a decrease in function (Dent et al., 2021). There is no gold standard measure, and different organisations use different measures. The most common tool is that of the European Working Group for Sarcopenia. They use below-norm performance from the following measures to indicate sarcopenia: bioelectrical impedance analysis, calf circumference, and physical performance measured with a short physical performance battery. The reason I included these criteria in ACHING is that given all participants have knee pain; it might be assumed that they are more likely to have sarcopenia rather than frailty. The difference between the two conditions is arguable, and there may be overlap. However, it is important to understand whether people with knee pain would be considered to have sarcopenia, as this may influence future invention pathways.

There are measures included in the table below that are also included in their own right. For example, waist-hip ratio (WHR) will also be assessed if it is significantly different from BMI. Studies on obesity have shown mixed results, with some studies finding little difference between the performance of BMI and WHR, whilst other epidemiological studies have found that WHR is a better predictor of obesity-related morbidity than BMI as it accounts for central adiposity, which carries more risk to health (World Health Organization, 2011).

Table 7-3 Other clinical measures included in the classification of sarcopenia.

Measure	In-person clinical assessment	Calculations	Fried Phenotype measure
Body measurements	Height Weight Waist (standing) Hip (standing) Calf (supine)	BMI, Hip waist ratio	Yes
Bio Impedance Analysis (BIA)	Using measures of height and weight and BIA equipment	Lean body mass	No
Hand grip strength (kg)	Dynamometer measurement	Hand strength	Yes
Short Physical Performance Battery (SPPB)	In-person assessment of strength, gait speed and balance	Leg strength, gait speed and balance	Yes

The procedures are described in full in the protocol.

7.4.3.4 Sleep disturbance and physical activity levels.

All participants will be issued with an accelerometer (a watch-like device) that monitors their activity and sleep levels. The participants will be asked to wear it continuously for 1 week. The device is water resistant up to 1 metre, so it can be worn whilst bathing but should be removed for swimming. During this period, participants will be asked to record if they removed the device for any period of time and to make a daily record of their pain and fatigue levels on two NRS scales, in which 0 is none and 10 is extreme. At the end of this period, the participant puts the records and device in a prepaid post-box. This permits return with minimum inconvenience to participants.

7.4.3.4.1 Other measures

7.4.3.4.1.1 Blood samples

This will be used primarily to measure biomarkers of high sensitivity C-Reactive Protein measurement(hs-CRP) (a measure of inflammation) and Tartrate resistant acid phosphatase 5b (TRAcP5b) (a measure of bone

turnover). These are biomarkers associated with OA (Jin et al., 2015) and (Liu et al., 2016). Higher CRP has been associated with frailty (Soysal et al., 2016).

7.4.3.4.1.2 Saliva, urine, and faecal samples - optional

These may be collected for the purpose of identifying inflammatory biomarkers, biomarkers of insulin resistance, and gut microbiome measures. This is optional. Total genomic DNA extraction and processing may be done from whole blood samples by a specialist company in accordance with standard protocols and agreements. Extraction of bacterial DNA from faecal samples may also be done for the purpose of identifying bacterial species associated with inflammation and pain. Recent studies show clear evidence for microbiome composition being involved in OA-related knee pain (Boer et al., 2019). Other observational and interventional studies suggest that the gut microbiome is involved in pain intensity, progression, and sensitivity, including neuropathic pain. At least in animal models, these effects are mediated by the gut microbiome's role in modulating inflammation. Cortisol will be extracted from saliva samples. Protein and inflammatory markers will be extracted from urine samples. Participants will be asked if they wish to donate a faecal sample, and if they agree, they will be given a collection kit and the food frequency questionnaire to take home, which will be sent back by prepaid post. The University of Nottingham may store samples for use in future studies. Participants who do not agree to provide blood, saliva, urine, or faecal samples will not be excluded from the study.

7.4.3.4.1.3 Food Frequency Questionnaire (FFQ) - optional

Research is being conducted to link the microbiome with inflammatory markers. The FFQ will assist with understanding the eating habits of the participants. Nutritional status is also associated with frailty; insights into the dietary habits of participants may highlight areas for further exploratory analysis. This was developed by Dr Amrita Vijay.

7.4.4 Data collection regimen

Prior to the visit, participants will be asked to complete a questionnaire booklet either online or on paper, as they prefer. This is to reduce the burden on participants. At the visit, participants will be issued with a wrist accelerometer for one week whilst keeping a daily record of pain and fatigue. Participation is expected to be two weeks. The research visit is likely to last approximately 2 hours and no longer than 3 hours.

The study flow diagram is shown in Figure 7-1.

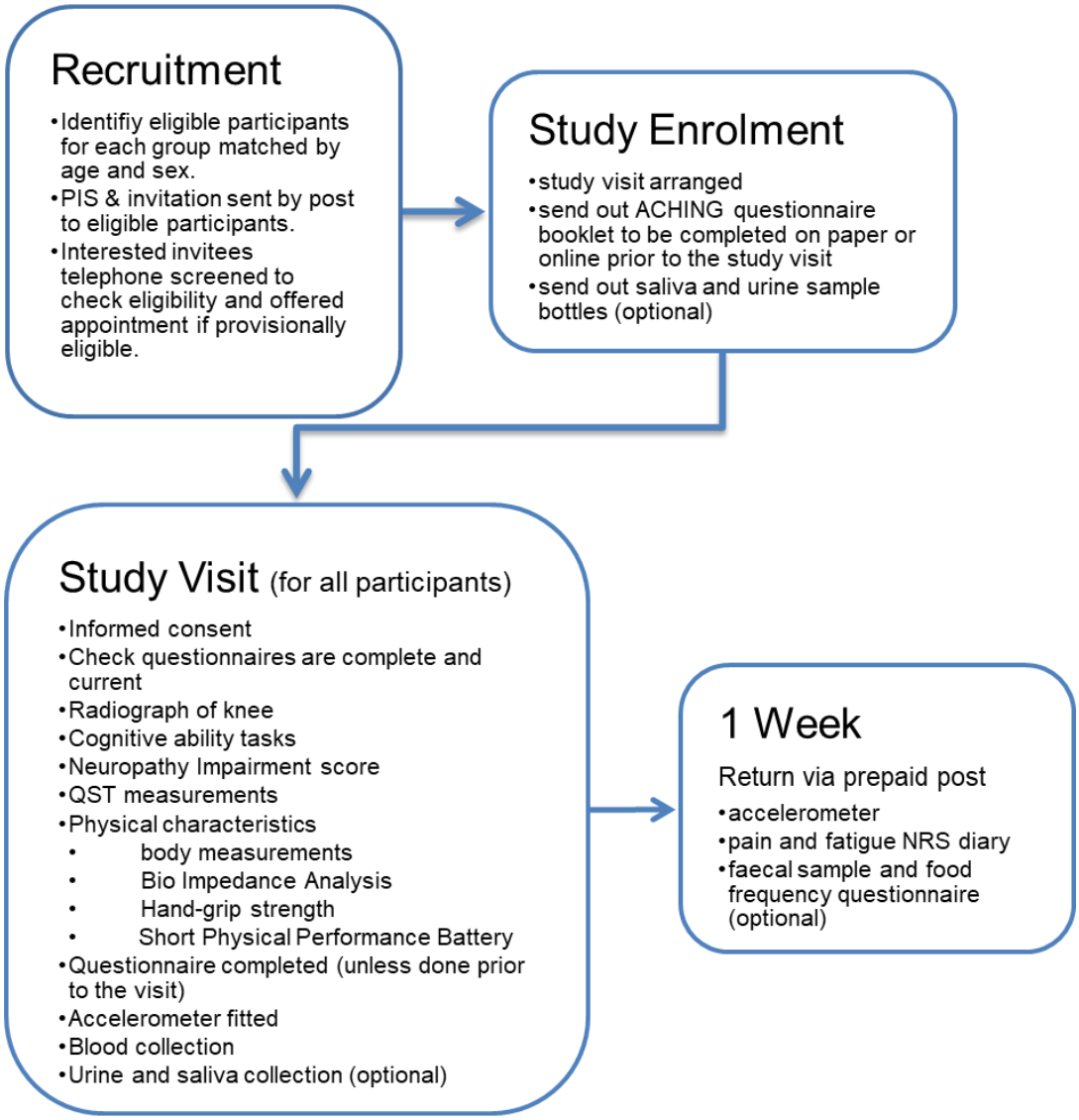

Figure 7-1 ACHING study workflow.

7.4.4.1 Compliance

Compliance is not applicable because this is an observational study, and there is no intervention. However, in order to contribute data to the study, participants should attend the study visit. Those who do not provide data cannot be included in the analysis. All study measurements are important. However, participants who are unable to complete all measurements and questionnaires can continue in the study provided they complete the FRAIL questionnaire and at least one QST measure. Participants will not be excluded if they do not wear the accelerometer or provide blood, saliva, urine, or faecal samples.

7.4.5 Study management.

Professor David Walsh (Chief Investigator) has overall responsibility for the study and oversees all study management. A central coordinating centre at Academic Rheumatology, University of Nottingham, will manage the study.

I was the designated researcher responsible for day-to-day study coordination. I coordinated ethical approvals, study design, data collection, data cleaning and preparation, validation of outcome measurement, assistance in recruitment, report writing and final data analyses.

7.4.5.1 Ethics committee and regulatory approvals

The study will not be initiated before receiving approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) are required.

The study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996, the Principles of Good Clinical Practice and the UK Department of Health Policy Framework for Health and Social Care, 2017.

7.4.5.2 Ethical considerations

Detailed information on the transport of tissues and samples and their laboratory analysis are included in the protocol.

The protocol also contains information about which adverse events and serious events I could anticipate, alongside any measures I included to mitigate any risks. Whilst no serious adverse events are anticipated, inviting older people classified as frail to a clinical observation could mean that they require frequent rest breaks. To reduce the likelihood of dehydration and to make easier to obtain a blood sample, participants will be offered refreshments.

Furthermore, how participants' data will be pseudonymised and stored needs consideration. I created a data management plan for the study. This covers details of how data is collected and treated within the study. It is important for any study that participant data is collected and kept securely. It is important to consider why data is being collected and how it will be used. All studies should adhere to The Data Protection Act 1998 and the General Data Protection Regulation (GDPR) (Data Protection Act 2018).

7.4.6 Statistics analysis plan

7.4.6.1 Primary objective analysis

- Descriptives and heterogeneity will be reported.
- Associations will be confirmed using correlation and regression analysis to account for covariables. The outcome variable is FRAIL classification, with CAP factor and pain as the predictor variables, with age, sex, and BMI class as covariables.

7.4.6.2 Secondary objective analysis

Secondary analyses will include predictors or covariables.

- Each of the 8 characteristics associated with underlying CAP factor (anxiety, depression, catastrophising, pain distribution, neuropathic-like pain, cognitive impact, sleep, and fatigue).

- Indices of peripheral pain mechanisms, including radiographs and neurological assessments by testing reflexes and Neuropathy Impairment Score in Lower Limbs (NIS-LL).
- QST measurements (PPT, TS, and CPM).
- Biomarkers of disease (e.g., inflammatory biomarkers, biomarkers of insulin resistance, gut microbiome measures and physiological tests.
- Exploratory models will assess the association of the above variables with pain as the outcome variable.
- Confirmatory analysis using the Fried Frailty Phenotype classification instead of the FRAIL.

7.4.6.3 Procedures for missing unused and spurious data.

Missing data will not be imputed. Should any data be missing, the reasons for this may be sought.

7.4.6.4 Reporting and significance

The odds ratio (OR) and 95% confidence interval (CI) will be reported for associations. Statistical significance will be inferred when the P-value is less than 0.05 or when the 95% confidence interval (CI) does not include unity.

7.4.6.5 Sample size and justification.

I calculated the sample size, using the G*Power 3.1.9.4 software (Heinrich-Heine-Universität Düsseldorf; Düsseldorf, Germany) utilising the Enumeration method, Wald Test (Faul et al., 2009). I made the following assumptions in a logistic regression to test whether CAP factor, a continuous variable, influences frail classification using FRAIL (frail 1, robust 0); the hypothesis was two-tailed; a large effect size of 0.8 was used; the α error was taken to be 0.05, with a 95% confidence interval; the 1-β power analysis was taken to be 0.80 and a moderate association of 0.25 between CAP factor and the other covariables. The odds ratio was calculated to be 1.98. This is based on my previous work (Chaplin et al., 2021) and represents the value in an adjusted logistic regression model of FRAIL (frail 1, robust 0) adjusted for CAP factor age, sex, and BMI.

From this, a total sample size of 122 participants, with 61 in each group, was determined. Since participants will complete only one visit, dropout is not anticipated; if the accelerometer data is not collected, this will be treated as missing data.

7.4.7 Patient and Public Involvement (PPI)

This study was presented to the Pain Centre's MSK Patient and Public Involvement (PPI) group for their input. This group consists of key stakeholders (patients with various chronic musculoskeletal pain conditions). Members were asked to comment on and help develop information leaflets, the questionnaire, and the protocol. I met with several groups, the first of which was in November 2021 with Pain Centre PPI groups; these meetings were online due to pandemic restrictions. I met with small groups to help develop the project. They were particularly helpful in navigating the terminology for the study. 'Frailty' has negative connotations and can create an image of helplessness; whilst some did not initially agree, they all agreed on the reflection that they would not like to be labelled frail. Subsequently, in the study documentation and title, I referred to frailty as a future challenge to health.

Later, I met face-to-face with the Dementia, Frail Older People and Palliative Care PPI based at Queens Medical Centre, Nottingham. I outlined the research and the project and asked those present for their thoughts, and several offered to help test the study.

The study will include a steering group including at least one PPI member to advise on progress, recruitment, protocol changes, etc. I want PPI involvement to support the interpretation of results, placing them within the `patient' context. PPI involvement will help to develop the dissemination of findings to a lay audience.

7.5 Results

The ACHING study REC reference 22/NW/0242 received a favourable ethics opinion for the Integrated Research Application System (IRAS) project ID 31169, protocol number 22020, on 20 September 2022 (Figures 7-2 and 7-3).

In preparation for this study, training and reliability measures were collected. The details of this study are in Chapter 8.

7.6 Discussion of ACHING study progress and plans.

The ACHING study ethics took longer than initially anticipated, in part due to delays in the system since the pandemic. NHS ethics were required due to the planned X-rays, which required radiological reviews. The radiation risk assessment was submitted on 23 February 2022, and approval was received on 13 April 2022. At this stage, documents for sponsors' approval were submitted, and their approval for IRAS submission was received on 14 July 2022. The IRAS submission was made on 15 July 2022.

I met with the Greater Manchester Central Research Ethics Committee REC on 16 August 2022 and received a favourable opinion at first review with minor conditions. The approval was finalised on 20 September 2022.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

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20 September 2022

Dear Professor Walsh

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Investigating pAin and Challenges to future Health and wellbeING (ACHING) study.**
IRAS project ID:	311699
Protocol number:	22020
REC reference:	22/NW/0242
Sponsor	**University of Nottingham**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Figure 7-2 ACHING REC approval page 1

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **311699**. Please quote this on all correspondence.

Yours sincerely,
Rebecca Throup
Approvals Specialist

Email: approvals@hra.nhs.uk

Copy to: *Ms Angela Shone, University of Nottingham*

Figure 7-3 ACHING REC approval page 2

.

CHAPTER 8 INTER-RATER RELIABILITY TESTING OF PHYSIOLOGICAL MEASURES

8.1 Introduction

The purpose of this study was to check reliability, firstly to assess whether I, as the rater, have achieved sufficient skill to record the measurement accurately and secondly that the equipment and/or method being used provides repeatable measures. These reliability studies were conducted in preparation for the ACHING study (Chapter 7). Hand-grip strength and bio-impedance analysis (BIA) are associated with frailty, and Quantitative sensory testing (QST) is associated with pain.

This study aims to assess the reliability of collecting data for three measures. Additionally, to prepare the procedures required for the ACHING study.

8.2 Background

8.2.1 Handgrip reliability measures in healthy participants.

Low handgrip strength is used as an indicator of low muscle strength throughout the body. Handgrip strength is measured using a dynamometer and recorded in kilograms. Hand-grip strength is used as an objective measure for the classification of sarcopenia by the European Workgroup for Sarcopenia (EWGSOP).

Furthermore, it has been claimed that the handgrip setting and the size of the hand can influence results; a study showed that hand length had a moderate correlation with maximal grip strength (Neumann et al., 2017). However, they report other literature presenting the opposite results. Thus, conclusions were inconsistent. In this study, in addition to collecting data on hand-grip strength, I will record hand length to examine if there was a need to adjust the handgrip for different participants and to test inter-rater reliability.

8.2.2 Bio-impedance analysis method in healthy participants

BIA is indicative of body composition. Lean percentage represents the amount of muscle present in the body; in using the percentage rather than kilograms,

this should be an indicator of muscle mass regardless of body size. Low muscle mass is associated with frailty as it reduces strength (FRAIL resistance item). Low muscle mass may result from atrophy of the muscle; this may be more likely if an individual has chronic pain.

This study used the BodyStat 1500. A weak electrical signal is passed through the body tissues from the hand to the foot; the BIA measures the impedance. Body tissues conduct electricity at different rates; lean tissue, including muscle, bone, and water, has less resistance or impedance than body fat. The BodyStat 1500 provides the impedance for a frequency of 50kHz. This test indicated the amount of lean tissue. Individuals tend to lose muscle mass with age. BIA is used in the diagnostic criteria for sarcopenia by the European Workgroup for Sarcopenia (EWGSOP). It should be noted that the BIA is likely to overestimate the lean body mass in the cheaper models. The gold standard measurement is Dual-energy X-ray Absorptiometry (DXA); however, it is expensive and not portable. The BodyStat 1500 has been used in sarcopenia research; there were published articles with the European norms for BIA, and it should be noted that BIA varies with gender and ethnicity (McIntosh et al., 2013, Batterham et al., 2002). The measure is also subject to variation due to hydration levels, jewellery, and also in people with renal failure or taking diuretics.

8.2.3 Quantitative Sensory Testing (QST)

Three modalities were employed: Pressure Pain detection Thresholds (PPT), Temporal Summation (TS) and Conditioned Pain Modulation (CPM), these were introduced in Chapter 7. Each has been used as a putative index of central pain processing when the test site is distant or distal to the site of clinical pain (Georgopoulos et al., 2022).

8.3 Method

The inter-rater reliability testing methods are described in Section 2.3.3.4. All participants were healthy adult volunteers who were working in the Clinical Sciences Building, UoN. However, it should be noted that some were not naïve to the method being tested, in particular the QST. All read a volunteer information sheet.

8.3.1 Handgrip strength methods

In this study, I and another researcher measured handgrip strength using the same equipment and following the same protocol on the same day for each participant. Three handgrip measurements were made with each participant using a JAMAR hydraulic hand dynamometer (Lafayette Instruments, Model J00105). All measures of isometric grip force were made using a handgrip setting of 2/4 and recorded in kilograms (0-90) from a dual-scale readout. Data were recorded on a CRF. The following protocols were observed:

- The dynamometer grip setting was set on the second of four positions unless the participant's fingertips or nails were touching the palm of their hands, in which case the grip size was increased to a size that permitted the participant to squeeze the dynamometer without restriction.
- Rotate the peak-hold needle counter-clockwise to 0.
- Participants were positioned sitting upright on a stable four-legged chair (no armrests) with thighs horizontal and at 90 degrees. The assessed arm was bent with the upper arm vertical, the lower arm horizontal, the elbow tight into the waist, and the non-assessed arm relaxed in their lap. The dynamometer was placed into the participant’s hand, and they were asked to squeeze the device momentarily as hard as possible and then release their grip.
- The researcher used verbal encouragement to participants to engage maximum force.

- The peak-hold measurement was recorded in kg, and the needle reset to zero after each reading.
- A short period of recovery was given before each attempt.
- Measurement was repeated three times on their dominant hand, and the mean of the three readings was recorded. If the dominant hand was not able to operate the hand dynamometer, for example, because of injury, the non-dominant hand was used, but this was made clear in the notes.
- Hand length was calculated from the distal wrist crease on the palmar surface of the hand to the tip of the longest finger and rounded to the nearest 0.5cm.

8.3.2 Bio-impedance analysis method

Bio-impedance analysis was conducted by another researcher and me using the same equipment on the same day and >20 minutes apart. Both raters placed the electrodes independently, and then I connected the BodyStat 1500 and input the required data.

To calculate BIA, the researcher collected the height, weight, and age of the volunteer. The equipment should not be used in people with a pacemaker or similar electrical implant; participants were asked to remove any jewellery and watches. To achieve equilibrium for stable measurements, it is recommended that the participant remain in a supine position for 5-10 mins. Electrodes were placed on the dominant hand and ipsilateral foot at the following points: red lead 1 behind the knuckle of the middle finger, black lead 1 on the wrist next to the ulna head, red lead 2 behind the 2nd toe next to the big toe, black lead 2 on ankle between medial and lateral malleoli.

The leads were connected to the BodyStat device, and weight, height and age were entered. The participant remains still with hands and legs, not touching the body or each other. The process took between 3-5 seconds, and then a set of readings were created. Lean percentage was recorded and used for reliability analysis.

8.3.3 QST Method

QST was performed by a research fellow who has had the experience of using QST over a period of years, as well as myself. The tests used the same equipment in a private clinical space on the same day run consecutively. The raters took turns as to who went first. I marked-up the test sites for all participants. Most of the participants were not naive to the procedures as they work in Academic Rheumatology.

Pain Pressure Threshold (PPT) was measured three times at each test site: tibialis anterior (TA) and medial joint line (ML) on the most painful knee and the brachioradialis (BR) on the non-dominant arm. The healthy volunteers chose which knee they wanted to be tested if they did not have a painful knee. Data were recorded, and each used a verbal instructions sheet, so the same instructions were given by both raters.

Temporal Summation (TS) measures used wind-up difference (WUD) calculated as the rating for the average of the 10 repeated punctate stimuli minus the rating of the single stimulus at the start of the procedure. The test site was the dominant hand BR. Participants made a mark on the visual analogue pain scale, which was then recorded in centimetres.

Conditioned Pain Modulation (CPM) CPM-effect used the BR PPT collected earlier in the assessment as the unconditioned value. A manual blood pressure cuff was used for the conditioning stimulus. A single PPT at the same BR site was conducted during the application of the conditioning stimulus, which was used as the conditioned threshold.

8.3.4 Statistical analysis

Data were processed using R statistical software and using the package ‘epiR.’

Bland–Altman plots and analysis visually evaluated the agreement between measures and established 95% limits of agreement (LoA, the range within which 95% of the differences between two separate means are expected to lie).

For the interpretation of ICC and CCC results, the following criteria were used:<0.5 = poor, 0.5–0.74 = moderate, 0.75–0.9 = Good and >0.91 = Excellent (Middlebrook et al., 2020).

Concordance plots were used to demonstrate the CCC. The solid line represents perfect concordance, and the dashed line represents a line of best fit in rater observations. The closer the two lines are to each other, the higher the level of concordance.

8.4 Results

8.4.1 Handgrip inter-rater reliability results

Participants were 20 healthy volunteers from the Academic Rheumatology department or the Clinical Sciences Building.

Table 8-1 Handgrip test-retest results in healthy participants

Hand Measure	Median (CI) Rater 1	Median (CI) Rater 2	ICC3 (CI)	P value	CCC (CI)	P value
Strength (Kg)	34.3 (29.3, 43.0)	36.0 (28.8, 43.0)	0.97 (0.92, 0.99)	<0.001	0.94 (0.89, 1)	<0.001
Length (cm)	18.0 (17.5, 20.0)	18.0 (17.5, 20.0)	0.95(0.87, 0.98)	<0.001	0.94 (0.89, 1)	<0.001

Abbreviations: CI – 95% confidence interval.

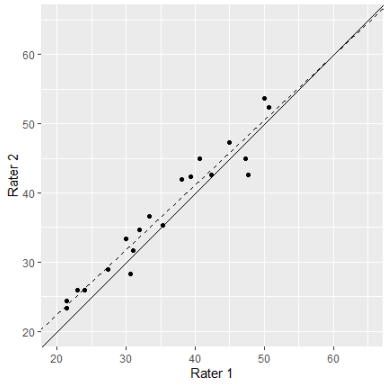

Figure 8-1 CCC of test-retest on healthy participants for handgrip strength.

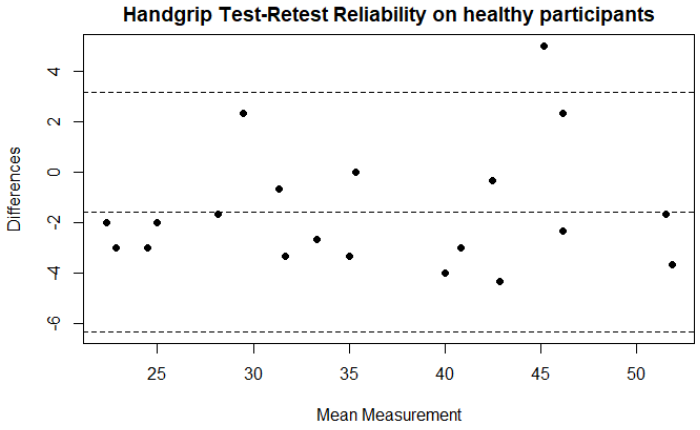

Figure 8-2 Handgrip Test-Retest in healthy participants.

Hand grip was measured in Kilograms.

The upper limit of agreement (LoA) = 3.17 (1.21, 5.13)

The lower LoA = -6.30 (-8.26, -4.34)

Mean difference =-1.57 (-2.70, -0.44)

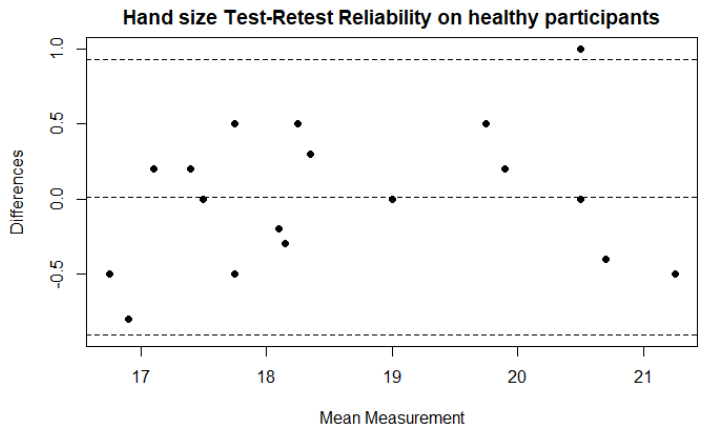

Figure 8-3 Hand-size test-retest reliability in healthy participants.

Hand length was calculated in centimetres.

The upper LoA = 0.92 (0.55, 1.30)

The lower LoA = -0.90 (-1.28, -0.53)

Mean difference = 0.01 (-0.21, 0.23)

8.4.2 Bio-impedance analysis results

Participants were 20 healthy volunteers from the Academic Rheumatology department or the Clinical Sciences Building. Data was incomplete on one participant due to equipment failure; therefore, data was collected from 19 volunteers by two raters.

Table 8-2Test-retest results of bio-impedance analysis in 19 healthy participants,

Hand Measure	Median (CI) Rater 1	Median (CI) Rater 2	ICC3 (CI)	P value	CCC (CI)	P value
Lean (%)	73.8 (68.7, 75.9)	72.9 (69.4, 75.9)	0.99 (0.98, 0.997)	<0.001	0.97 (0.91, 1)	<0.001

Abbreviations: CI – 95% confidence interval.

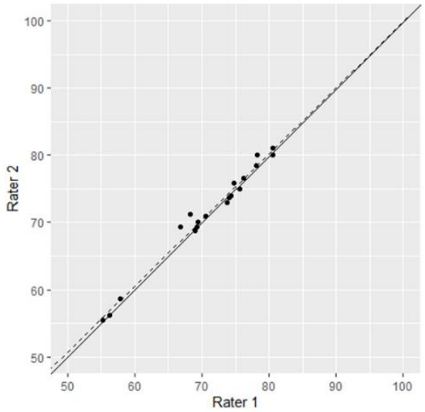

Figure 8-4 CCC of test-retest on healthy participants for BIA.

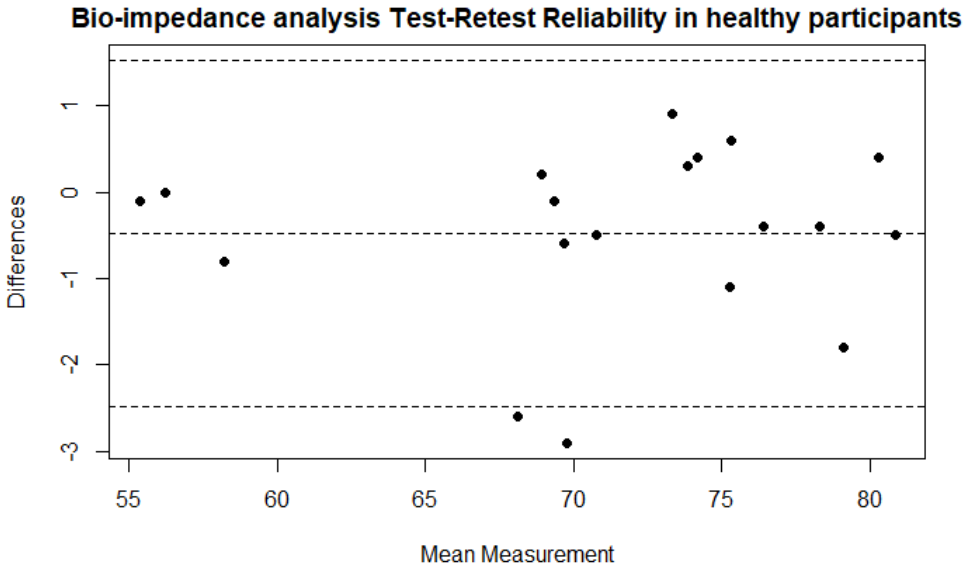

Figure 8-5 Bio-impedance test-retest reliability in healthy participants.

The upper LoA = 1.53 (0.68, 2.38)

The lower LoA = -2.48 (-3.33, -1.62)

Mean difference =-0.47 (-0.97, 0.02)

8.4.3 QST Results (N=20)

Participants were 20 healthy volunteers from the Academic Rheumatology department or the Clinical Sciences Building. The results are shown in Table 8-3

8.4.3.1 Transformation of data

The TA and ML PPTs were normally distributed, and the BR PPTs were log-transformed for the calculation of the ICC. Some temporal summation (TS) measures were recorded as 0; to avoid missing data, 0.1 was added to all scores. The 0.1 represented the lowest reading (apart from those marked as 0). The TS scores were not normally distributed, but the differences between raters were normally distributed; log-transformation did not improve the distribution. The CPM-Conditioned score was normally distributed in one rater only. For these reasons, the ICC was performed on untransformed scores. Some CPM-effect scores were negative and some positive, so they cannot be transformed; they had a normal distribution in one rater but not the other; for this reason, the non-parametric CCC should be used.

Table 8-3 QST Test retest and inter-rater Interclass Correlation Coefficients with associated Concordance Correlation Coefficients in healthy participants (N=20)

QST Measure	Median (CI) Rater 1	Median (CI) Rater 2	t/w	t/w P	ICC3 (CI)	P value	CCC (CI)	P value
TA	317 (273, 390)	363 (277, 499)	-2.35	0.030	0.81 (0.58, 0.92)	<0.001	0.765 (0.60,0.93)	<0.001
ML	258 (231, 308)	285 (233, 364)	-1.85	0.079	0.78 (0.53, 0.91)	<0.001	0.75 (0.565,0.94)	<0.001
BR*	152 (121, 171)	147 (134, 210)		0.114	0.65 (0.30, 0.85)	0.001	0.62 (0.29, 0.82)	0.001
TS $^{(WUD)}$*	0.50 (0.4,1.4)	0.80 (0.5, 1.5)	-0.38	0.711	0.87 (0.70, 0.95)	<0.001	0.86 (0.74,0.98)	<0.001
CPM ^{Cond}	162 (111, 221)	206 (171, 250)	-2.53	0.021	0.77 (0.51, 0.90)	<0.001	0.72 (0.51, 0.92)	<0.001
CPM effect	-8 (-22, 44) *	40 (-5, 57)		0.143	NA		-0.11(-0.54,0.31)	0.600

*Not normally distributed. Abbreviations: CI – 95% confidence interval; TA Tibialis anterior, ML – Medial joint line, BR – brachioradialis; TS (WUD) – Temporal summation wind-up difference; CPM – conditioned pain modulation. Cond – the conditioned measurement; CPM- effect = the conditioned measure – the unconditioned measure. t/w paired t-test or paired Wilcoxon signed-rank test.

8.4.3.2 Concordance plots for QST.

The plots below were used to demonstrate the CCC.

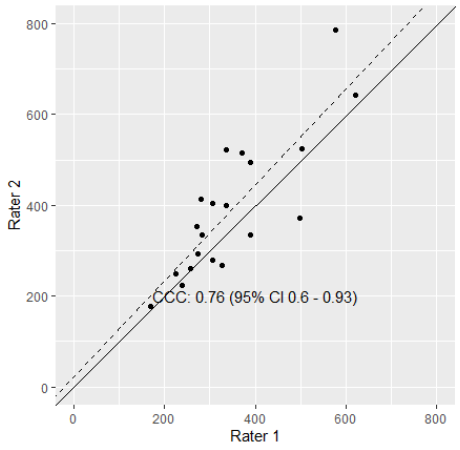

Figure 8-6 CCC of test-retest on healthy participants for PPT-TA

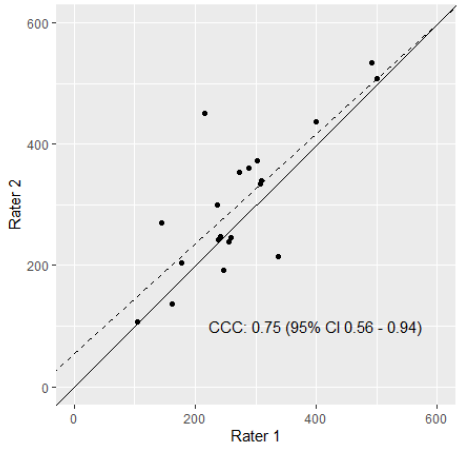

Figure 8-7 CCC of test-retest on healthy participants for PPT-ML

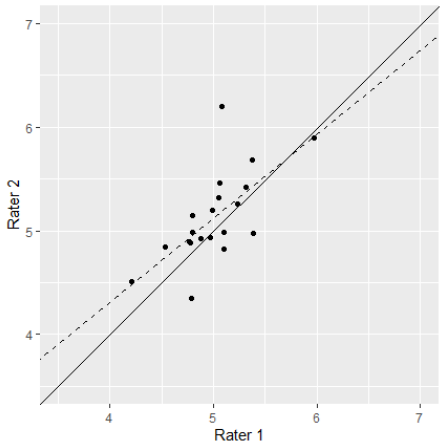

Figure 8-8 CCC of test-retest on healthy participants for PPT-BR transformed.

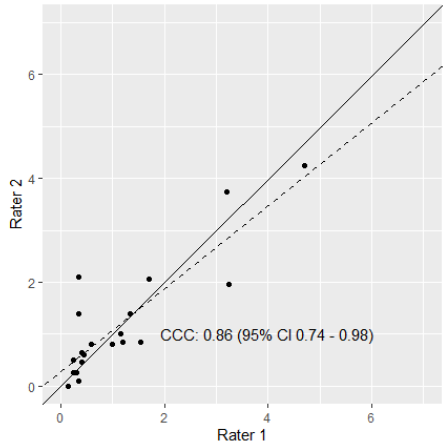

Figure 8-9 CCC of test-retest on healthy participants for TS-WUD

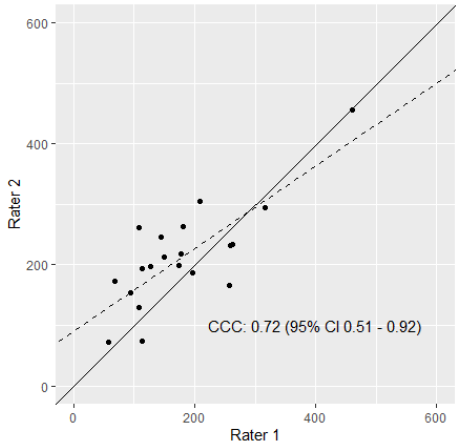

Figure 8-10 CCC of test-retest on healthy participants for CPM Conditioned BR

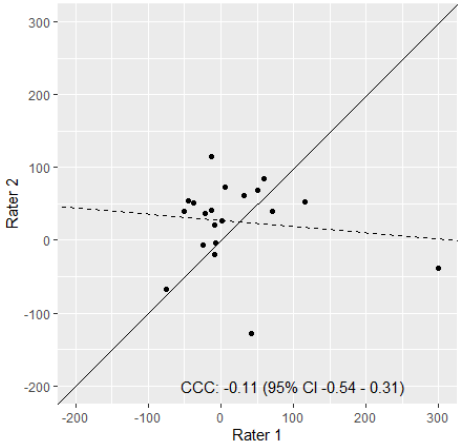

Figure 8-11 CCC of test-retest on healthy participants for CPM Effect BR

8.4.3.3 QST Bland-Altman plots

The following plots show the Bland-Altman plots for each QST site and modality. There was one outlier in every plot. If that individual's data was removed, the ICC and CCC were improved. This person became desensitised as the tests progressed, so there was a large difference between earlier measures and later measures; this was seen for each rater and between the raters.

8.4.3.4 Tibialis anterior

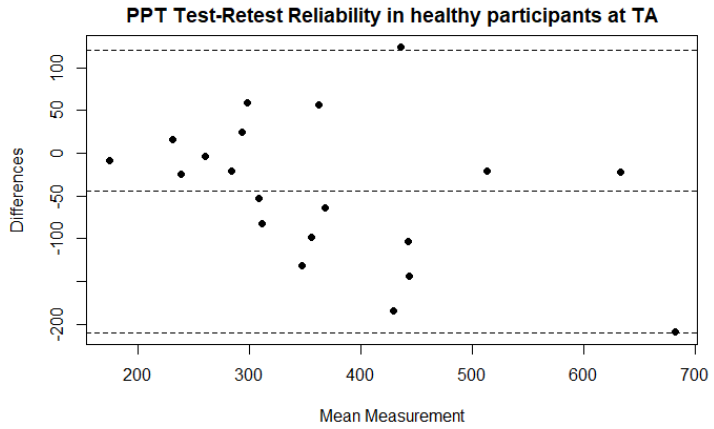

Figure 8-12 PPT test-retest reliability in healthy participants at TA.

The upper LoA = is 121.69 (52.77, 189.73)

The lower LoA = -209.89 (-278.37, -141.42)

Mean difference =-44.32 (-83.86, -4.79)

8.4.3.5 Medial Joint Line

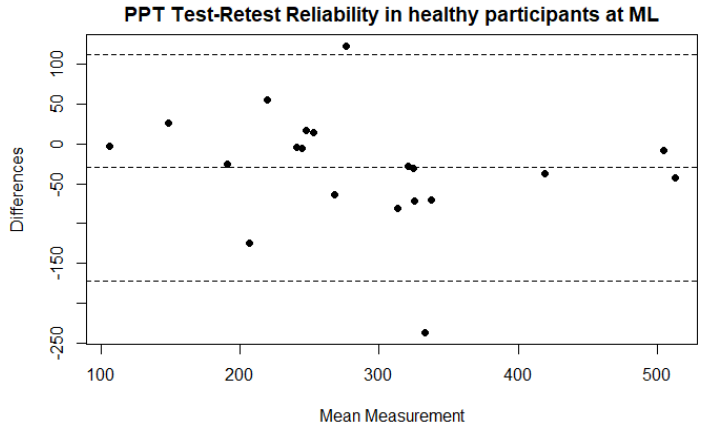

Figure 8-13 PPT test-retest reliability in healthy participants at ML.

The upper LoA = 111.73 (53.13, 170.33)

The lower LoA = -171.66 (-230.26, -113.06)

Mean difference =-29.96 (-63.80, 3.87)

8.4.3.6 Brachioradialis (non-dominant)

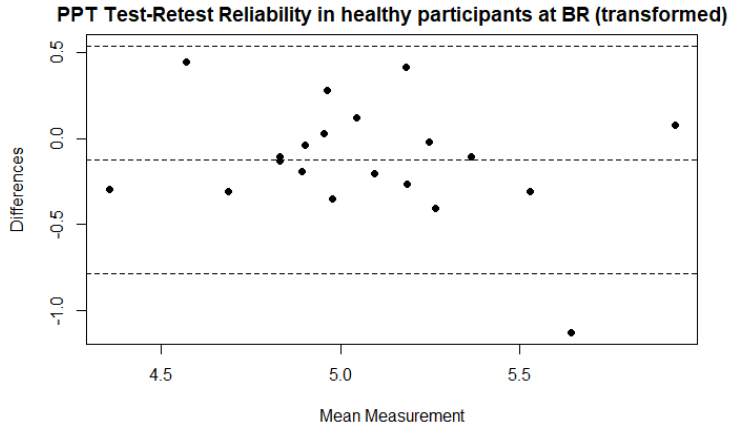

Figure 8-14 PPT test-retest reliability in healthy participants at BR.

These were log-transformed, as neither the measurements nor the differences between measures were normally distributed.

The upper LoA = -0.54 (0.26, 0.82)

The lower LoA = –0.79 (-1.06, -0.51)

Mean difference =-0.12 (-0.28, -0.03)

8.4.3.7 Temporal Summation (wind-up difference)

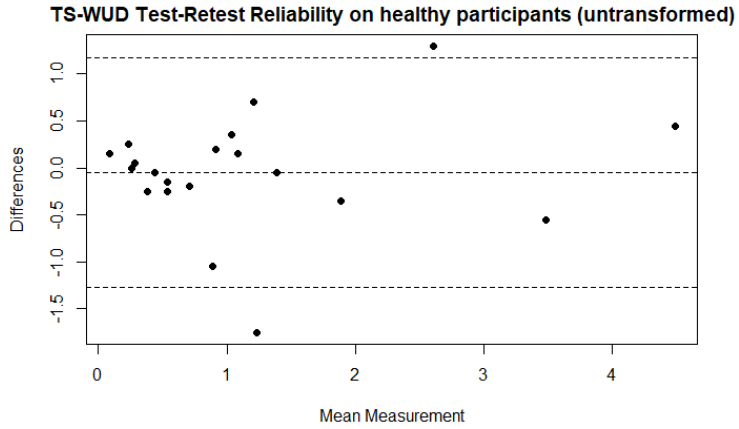

Figure 8-15 TS test-retest reliability in healthy participants.

These measurements were skewed, but the measurement differences were normally distributed, so the data were not transformed.

The upper LoA = 1.17 (0.66, 1.67)

The lower LoA = -1.27 (-1.78, -0.77)

Mean difference =-0.05 (-0.34, 0.24)

8.4.3.8 Condition Pain Modulation

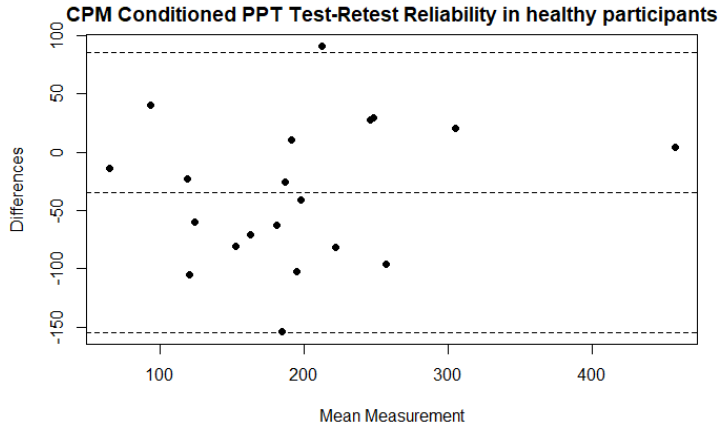

Figure 8-16 CPM test-retest reliability in healthy participants at BR.

This is the conditioned PPT measurement used in the CPM effect calculations. These measurements were skewed, but the measurement differences were normally distributed, so the data were not transformed.

The upper LoA = 85.36 (35.76, 134.95)

The lower LoA = -154.46 (-204.05, -104.87)

Mean difference =-34.55 (-63.18, -5.92)

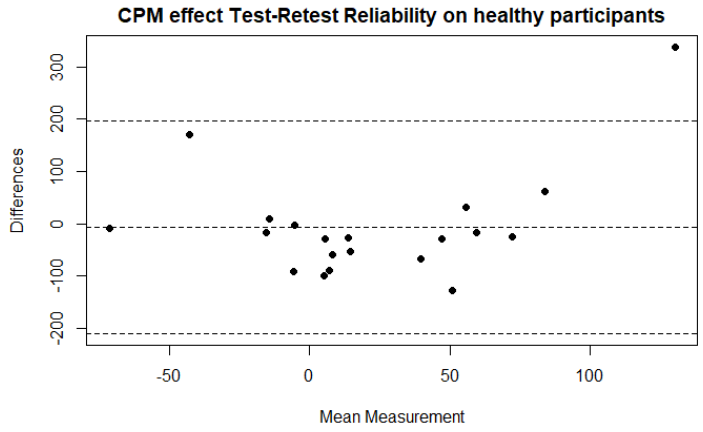

Figure 8-17 CPM effect test-retest reliability in healthy participants at BR.

The upper LoA = 196.61 (112.55,280.68)

The lower LoA = –209.91 (-293.97, -125.84)

Mean difference =-6.65 (-55.18, 41.89)

8.5 Discussion

In handgrip and bio-impedance analysis, inter-rater reliability using ICC and CCC were considered excellent. There were only very small differences between the two raters. In the case of handgrip strength, there were minor differences between the raters.

In the ICC and CCCs for the PPT sites of TA, ML, and the TS-WUD. The ICC for CPM-Conditioned measures was regarded as good, and the CCC as moderate. Both the ICC and CCC at the BR were regarded as showing moderate agreement.

The measures of CPM-effect were not normally distributed in one rater and could not be transformed, nor were the differences between measures normally distributed. Therefore, a parametric test such as ICC was unsuitable for CPM-effect, and the CCC method was used; this indicated a CCC of -0.11 (95%ci -0.54 to 0.31), which indicated no agreement.

The CPM-effect reliability agreement was poor, which can be seen clearly in the data. Some values were similar, but others were widely disparate. The CPM unconditioned measure was the mean BR-PPT measure; this was the PPT site with the lowest agreement of any PPT measure (ICC 0.65, (95%CI 0.30 to 0.85)). I think this could be due to the repetition of the measure over such a short period of time and sensitisation caused by repeated PPT measures in the same location in a short time period. The CPM-Conditioned was taken at the non-dominant BR, the same place as the PPT measures. This site was used for three PPT measures and one CPM-Conditioned measure by each rater. A total of 8 sets of data were obtained in this location in approximately 30 minutes. This affected the readings for both PPT (3 x2) and CPM (1x2) and should be considered going forward. As a reliability study, this was double the number normally experienced by a participant. But CPM in a less reliable location seems to decrease the chance of a reliable CPM-effect. It should be noted that CPM-Conditioned did have good ICC (0.77, (95%CI 0.51 to 0.91)); this suggests that the measure was being taken consistently by both raters at

tests 4 and 8. Middlebrook et al. proposed a two-hour gap between raters; this may be desirable, but it would cause some logistical problems when using this protocol (Middlebrook et al., 2020).

If, as in this study, the aim was inter-rater reliability, then comparing the CPM-Conditioned measures between raters may be a more reliable way of comparing raters than the CPM-effect. Others have shown that the CPM-effect was a less reliable measure in healthy volunteers (Kovacevic et al., 2021).

Some individuals became sensitised to the PPT process, while others became desensitised, consistent with random variation. The inter-rater reliability testing requires numerous tests, so an increase or decrease in sensitisation may be unsurprising. The recommendation for QST inter-rater reliability sample size was >19 (Middlebrook et al., 2020). Having seen how much one outlier can affect these results, I think, if possible, the sample size should be larger.

It should also be noted that most volunteers were not naïve to the testing procedure; several performed the testing regularly as researchers. As a psychophysical regimen, it should be noted that this was likely to influence the results. This was not possible to control. The other factor was that the two raters for the QST had different characteristics, and it is not possible to know whether this altered the results. In hindsight, I think the characteristics of the raters should be matched as closely as possible, although it may not always be practical.

In summary, the handgrip and bio-impedance testing indicated excellent reliability. The QST reliability was acceptable for most modalities, but caution needs to be exhibited when interpreting the CPM-effect reliability results.

CHAPTER 9 DISCUSSION

9.1 Overview

This thesis explored the relationship between chronic pain and frailty in an ageing population. The research conducted in Chapters 3 and 4 of this thesis focused on exploring the cross-sectional and longitudinal association of chronic pain and frailty in the IMH&W cohort. Furthermore, the thesis aimed to determine if there is a dose-response relationship between pain and frailty (Chapter 4). The findings of this thesis provide new insight into this association, demonstrating a bidirectional relationship and a dose-response relationship that have implications for future interventions.

Within the classification instruments for frailty, certain criteria items, such as morbidities, and in particular painful morbidities (Chapter 5), and similarly, central aspects of pain (Chapter 6), could offer an explanation for the association of chronic pain and frailty. However, further examination demonstrated that the relationship between chronic pain and frailty was unlikely to be attributed to these factors alone (Chapters 5 and 6).

My research indicated that central factors which may amplify chronic pain are additionally associated with frailty. The single-item CAP factor has been shown to predict future pain (Akin-Akinyosoye et al., 2020). Determining if the CAP factor could signify a state of vulnerability could aid in identifying mechanisms that may clarify the association between chronic pain and frailty. It could also be that the same items are associated independently with the mechanisms of frailty.

The ACHING study protocol was developed to investigate the CAP factor and aspects associated with chronic pain and frailty, as outlined in Chapter 7. Even though the research itself could not be conducted, Chapter 8 describes the preparations that were made to prepare for data collection. The ACHING study aims to measure and explain the association of frailty with central pain mechanisms and pain severity in individuals with knee pain.

9.1.1 Key findings and implications and outline for future directions

9.1.2 Bidirectional association

In Chapter 3, I explored the cross-sectional association of chronic pain. This initial work confirmed the findings of others that chronic pain is associated with frailty. My findings suggested that baseline pain predicted future frailty and vice versa. This led to a novel analysis in Chapter 4 to assess the possible bidirectional association between pain and frailty.

The subsequent study employed advanced statistical modelling, namely cross-lagged path analysis, to account for baseline and 1-year factors within the same model. I demonstrated a strong association between joint pain with current and future frailty at 1-year, even after adjusting for baseline age, sex, BMI, and frailty status (Chapter 4). Furthermore, over one year, I observed a small to moderate association between frailty classification and future joint pain. Additionally, greater pain severity increased the risk of transitioning from a non-frail to a frail state over one year of follow-up. Still, it did not appear to be a significant barrier to the transition from a frail to a non-frail state over the same time. These findings support the hypothesis that the relationship between joint pain and frailty is bidirectional and that there is a dose-response relationship between pain severity and frailty. Additionally, I observed frailty change over one year, which confirms the findings of other longitudinal studies of the dynamic course of frailty (Romero-Ortuno et al., 2021).

9.1.3 Explanations for the association of chronic pain with frailty.

In common with cumulative deficit frailty models such as the Frailty Index, FRAIL incorporates an illness-item or morbidity count to determine frailty classification. I examined the effect of morbidities on frailty (Chapter 5). Furthermore, I categorised morbidities as either 'painful' or 'non-painful', depending on whether pain management was a part of standard treatment for that particular morbidity (International Association for the Study of Pain, 1994). My findings demonstrated that pain, painful and non-painful morbidity counts were all associated with frailty when included in a single multivariable model.

The inclusion of morbidities in any model did not substantially reduce the relationship between chronic pain and frailty, indicating that this relationship is unlikely to be explained entirely by morbidities.

In my research, I explored the association of CAP-Knee with frailty. The CAP-Knee questionnaire comprises eight single-question items that are associated with fatigue, anxiety, depression, sleep disturbance, neuropathic-like pain, cognitive impairment, catastrophising, and pain distribution. When these items are combined to measure the CAP factor, they have been found to be a reliable predictor of future knee pain (Akin-Akinyosoye et al., 2018b). The CAP factor is associated with increased pain sensitivity (Akin-Akinyosoye et al., 2021). This led to the development of the ACHING protocol (Chapter 7).

9.2 Strengths and limitations

This thesis comprises studies that have several strengths and weaknesses. The chapters explore the limitations and caveats associated with each study. I acknowledge that the one-year period is a relatively brief timeframe to detect frailty changes, and a more extended follow-up might have enhanced the cross-lagged path analysis. Nevertheless, change was observed.

While other populations may yield different findings, the sample I studied was representative of the IMH&W cohort, featuring many participants with a complete range of pain scores and frailty classifications. This allowed my research to explore the relationship in detail. The IMH&W cohort had an approximately equal distribution of male and female participants and represented a broad range of socioeconomic backgrounds as represented by the Indices of Multiple Deprivation (IMD).

In UK research, there is often a higher representation of white females from a middle-class background, which can reduce the generalisability of findings (Smart and Harrison, 2017). The IMH&W tried to recruit participants from various sources, including via GPs, which may have increased the number of male participants who may be less likely to participate in research. The proportion of females in the IMH&W (55%) was comparable to both the UK

Biobank (56%) (Macfarlane et al., 2020) and ELSA Waves 2-6 (57%)(Wade et al., 2017). The East Midlands population comprises 51% females (Office for National Statistics, 2022b).

Despite the East Midlands population being 86% white (Office for National Statistics, 2021), the IMH&W cohort was 95% white, and the thesis studies were 99% white. This may be because those from ethnic minorities were younger than the 60-year inclusion criteria. This lack of ethnic diversity is regrettable and disappointing. However, I do not believe my findings are invalid. I think that a biological link between pain severity and frailty could be retained across different subgroups of society. If cultural differences alter pain reporting, then the estimates from my models might be altered when the cultural/ ethnic structure of the study population changes. It might indicate problems in completing a long questionnaire in English, which could cause bias by preventing non-white older people with lower English language abilities from participating.

To make the IMH&W more inclusive, it could have been offered in multiple languages, although this would increase costs. Anecdotes from collaborators suggest that people with poor written skills in English also have poor written skills in their first language. Collaborators have used a verbal translation service called Word360, which could be costed into future research applications. Conducting the survey electronically might simplify the inclusion of additional languages and allow people to use Google Translate to help them. However, this could also raise issues, such as those experienced with the McGill Pain Rating Index Questionnaire, which uses pain descriptors which may not be present in other languages. Additionally, some questionnaires' validity may not have been tested in other languages, although we would expect non-validated questionnaire responses to be preferable to missing data. An electronic survey might also introduce bias, as not everyone has equal access to technology, particularly older individuals and those in low-income households (Serafino, 2019). However, offering an electronic survey could include those with difficulty writing due to disability or chronic pain.

Trials with electronic forms of the IMH&W survey showed it was a valid method for capturing data, so having both paper and electronic versions could potentially increase accessibility. In recent years, IMH&W has been collected from both paper and electronic versions.

Other methods to enhance ethnic diversity include utilising researchers from ethnic minorities and distributing surveys in non-medical community environments, such as places of worship or community gatherings. The Born in Bradford project exemplifies good practice (www.borninbradford.nhs.uk). Some of these methods were planned for the IMH&W but were thwarted by the COVID pandemic. The data included in this thesis were collected immediately before this time.

Epidemiological research conducted in the UK is embedded in its cultural context. The FRAIL scale was originally developed with an African American cohort (Morley et al., 2012) and has been used globally, indicating its suitability for different ethnicities (Blyth et al., 2008, Susanto et al., 2018, Merchant et al., 2017). However, different regions of the world may experience frailty in different ways and at younger ages, partly dependent on lifespan (Swain and Chandra Mishra, 2019).

In deciding upon a cut-off of >60 years for the studies in this thesis, this aligns with most research in this field in Europe. Nevertheless, frailty may be experienced at a younger age. It is well-established that the prevalence and severity of frailty increase with age, particularly in those aged 80 years and over (O'Caoimh et al., 2018).

Pain may also be influenced by social context. Different cultures have unique ways of expressing, experiencing and managing pain shaped by social norms, gender, education and historical factors (Campbell and Edwards, 2012, Orhan et al., 2018). A comparison of work disability in rheumatoid arthritis compared two cohorts, one from Finland and the other from the USA (Chung et al., 2006). The Finnish cohort had greater work disability than the American cohort despite having lower disease activity. Some cultures encourage the open expression of pain, for example, in the southern Mediterranean and

Middle East, whereas others suppress expressions of pain (Sussex, 2015). Chronic pain perception is influenced by contextual, cognitive, emotional, and social factors alongside biological factors (Crofford, 2015, Gatchel et al., 2007, Manchikanti et al., 2002, Turk et al., 2016). These in turn affect the success of pain interventions by influencing patients' beliefs and behaviours leading to changes in pain intensity (Jensen et al., 2001, Nieto et al., 2012, Ryum and Stiles, 2023). In some countries, analgesia is relatively cheap and readily available and is accompanied by the belief that medication can block or remove the pain. However, whilst medications may be effective for controlling acute pain, they may be less effective for the treatment of long-term chronic pain. Whilst in other cultures herbal remedies and traditional methods may be utilised alongside a belief that pain should be endured and is 'normal' for older people, although this may also be due to economic considerations, such as household income and whether medical treatment is free at source, such as the NHS or privately run.

In conducting the analysis, I considered important covariables such as age, sex, and BMI class that have been previously associated with both chronic pain and frailty, which could otherwise have introduced confounding. It is worth noting that previous research has often focused on single-sex cohorts, which may limit the generalisability of their findings; most studies report that the female sex is usually associated with frailty, so single-sex (Megale et al., 2018).

9.3 Novel findings and implications

The results support the existence of a bidirectional association between chronic pain and frailty. This implies that chronic pain and frailty can exacerbate each other, creating a vicious cycle in which each condition accelerates the progression of the other. This discovery holds significant clinical relevance due to the strength of these predictive relationships and the fact that almost all (99%) participants in this study classified as frail reported that their pain was at an unacceptable level. Understanding that the relationship is bidirectional justifies future attempts to delay or prevent frailty

by addressing pain management. Primary targets that address both conditions include exercise and Cognitive Behavioural Therapy. This is further supported by identifying the dose-response relationship between pain and frailty; this indicated that greater pain intensity increased the risk of transitioning from non-frail to frail. These findings imply that improved pain management may reduce pain severity, which in turn could reduce the risk of future frailty. While eliminating pain may not always be possible, reducing it to levels that patients find acceptable may be achievable. Any reduction in pain may even reduce the likelihood of frailty. According to research, the Patient Acceptable Symptom State threshold for pain is 0 to 3 on the 11-point NRS scale (Georgopoulos et al., 2021).

Identifying the association between pain and frailty prompts a question as to why pain on an NRS scale is not regularly incorporated into frailty classification tools or indices. It is worth noting that some tools, such as eFI and FRAIL, do include arthritis, a condition often accompanied by pain. Interestingly, three RCT interventions have demonstrated an improvement in pain in people with frailty (Park et al., 2020, De Vriendt et al., 2016, Hinkka et al., 2007)However, pain was not the primary focus of the latter two studies. In order to gain a better understanding of the relationship between chronic pain and frailty, future frailty studies should strive to include pain measures as one of their outcomes whenever possible.

9.4 Future directions

My research has revealed important insights that have not been addressed in the current advice provided by NHS England and NICE guidelines (NICE, 2015), as well as by experts in the field (Marcucci et al., 2019). It appears that pain, which is often associated with frailty, has not been given sufficient attention in interventions aimed at preventing or reversing frailty. Instead, exercise and nutrition have been the primary focus in previous studies (Teh et al., 2022, Travers et al., 2019, Serra-Prat et al., 2017). However, the low prevalence of pain management strategies could be a contributing factor to why frailty remains a challenge to prevent and manage. Based on my findings, the

inclusion of pain reduction strategies in interventions designed to prevent, delay, or manage frailty is highly desirable. Furthermore, pain is not widely recognised as a feature or complication of frailty (NHS England, 2022a), nor is it commonly used as an outcome measure in studies related to frailty (Teh et al., 2022, Travers et al., 2019, Serra-Prat et al., 2017).

Although musculoskeletal conditions are commonly associated with pain, fatigue, physical activity, obesity, and comorbidities (Versus Arthritis, 2021). Many of these conditions are included in frailty classification, but frailty is not often recognised as a complication. Notably, the NICE guidelines for managing chronic pain do not address frailty (NICE, 2021) and the Core Standards for Pain Management Services in the UK only mention frailty in the context of specialist palliative care (British Pain Society, 2021). Based on my research, increasing awareness of the potential risks of pain and frailty could positively impact public health interventions and the treatment of these conditions by healthcare professionals and social care providers. Identifying individuals who may be at risk of frailty, particularly those with chronic pain, and providing appropriate interventions is key for addressing future health challenges.

Emerging evidence shows that exercise improves immune regulation and protects against age-related dysfunction (Nieman and Wentz, 2019). Additionally, research into the gut microbiome, which has a role in modulating inflammation, muscle strength and energy metabolism, is linked to exercises such as stretching and mobilising (Vijay et al., 2021). Evidence indicates that exercise affects the gut microbiome independently of diet (Mailing et al., 2019). These types of interventions offer an alternative to traditional nutritional supplementation interventions that focus on protein and vitamin deficiencies (Travers et al., 2019). Research has shown a reduction in reported pain using a web-based exercise intervention in people with knee pain (Gohir et al., 2021). Further research is currently being conducted at UoN by Professor Ana Valdes using an RCT with both exercise and diet supplements; whilst at an early stage and not targeting frail individuals, there is some indication that the combination is effective. The

type of exercises employed are not particularly physically demanding as they focus on functional exercises to improve stability and range of movement. Some people with frailty may have some exercise limitations. However, chair exercise is a safe alternative and may also provide social stimulation. Low-level physical exercise, such as yoga, has shown improvements in frailty markers (Loewenthal et al., 2023).

It is crucial to identify factors that can be modified to develop effective treatments for the future. The ACHING study protocol has received a favourable ethical opinion, but funding is necessary for completion. This study can potentially establish factors that can be modified in future interventions. For instance, modifying pain medication that targets central pain mechanisms could enhance an individual's pain management. Combined with other therapies like CBT, this effect may be further amplified.

9.4.1 Clinical translation of findings

It is to be hoped that perhaps the most useful clinical implications of these findings would be an integrated approach to managing pain and frailty. This will combine the efforts of clinicians who are interested in older age medicine and those clinicians who have a role in managing chronic pain. Frailty and pain management have chiefly resided in different specialisms. Effective early pain management can potentially prevent the onset of frailty. Chronic pain is a significant risk factor for frailty, and managing it well can enhance the quality of life for older adults.

The immediate strategy of my published papers is to call on pain clinicians and researchers to consider frailty and for geriatricians to recognise that their patients may have high levels of poorly controlled chronic pain. The British Geriatric Society has several Special Interest Groups including sarcopenia and frailty research but unfortunately this does not extend to a pain group, these are a good way to push narratives to health care professionals. There also needs to be increased public awareness about chronic pain and its management. Initiatives like pain awareness forums can help educate the public about the importance of managing chronic pain early.

There needs to be a knowledge mobilisation strategy to include educational campaigns to inform both healthcare providers and the public about the relationship between pain and frailty. The public needs to know it is not 'normal' to be in chronic pain, and that it is acceptable to request from healthcare providers. Healthcare providers need to acknowledge the importance of pain in its own right and should not expect it to go away on its own. Strategies should target people working with the older population. This can include workshops, seminars, online resources and working with national charities to roll these out. To encourage and inspire collaboration between researchers and clinicians to explore new pain management strategies and their impact on frailty. Finally, to work with policy professionals to advocate for policies that develop and implement integrated care approaches and early pain management interventions.

In a world where the employment age is rising and the focus of the government is to keep people in work as long as possible, it will become increasingly vital for individuals to be 'fit to work' until their late sixties. Occupations that require a level of physical ability, such as nursing, until comparatively recently had a retirement age for the majority of 60; the age at which the participants for these studies were observed.

Public awareness about chronic pain management is often limited to medication and rest. Psychoeducation is needed to explain the pain management strategies beyond medication, such as physical therapy, lifestyle changes and psychological support. This extends to the media platforms to encourage good proactive pain management in the same manner as public health campaigns for nutrition. By addressing these areas, you can help shift the perception of chronic pain management and improve the quality of life for older adults.

9.5 Conclusion

In summary, frailty is a state of vulnerability that is observed in older individuals due to multi-organ age-associated decline and is characterised by

homeostatic failure in response to challenge (Clegg et al., 2013). The underlying causes of frailty are complex, and interventions aimed at reducing or delaying its onset are likely to be multifaceted. Focusing on pain management as an intervention could mitigate the effect of chronic pain upon frailty. Given the ageing population in many countries, it is increasingly important to address conditions that disproportionately affect older individuals, such as frailty, and to ensure that we manage chronic pain irrespective of its aetiology.

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APPENDICES

APPENDIX A IMH&W CLASSIFICATION OF ANALGESIA

A1. Classification of Analgesia Medication

a) Paracetamol

Alka-seltzer Tablet
Altridexamol tablets
Alvedon suppositories
Anadin extra
Anadin Paracetamol tablets
Benorilate 2g granules sachets sugar free
Benorilate tablets
Benylin Powder
Benylin with Codeine oral solution
Boots Paracetamol caplets
Boots Paracetamol capsules
Calpol Six Plus Fastmelts tablets
Cocodamol
Co-dyramol
Co-proxamol
Dextropropoxyphene HCl with paracetamol tablets
Disprol Oral suspension
Fortagesic Tablet
Galpamol Oral suspension
Headex extra
Hedex tablets
Infadrops liquid
Kapake
Lemsip cold and flu sachets
Mandanol caplets
Medinol I Oral suspension
Medised Liquid
Medocodene Tablet
Migraleve tablets
Nuromol tablets
Panadeine Effervescent tablet
Panadol ActiFast Soluble tablets
Panadol ActiFast tablets
Panadol Advance tablets
Panaleve plusOral suspension sugar free
Panasorb 500mg Tablet
Paracetamol tablets
Paracets 500mg capsules
Parahypon Tablet r
Paramax
Paramol
Paravict tablets
Remedeine tablets
Solpadeine tablets
Solpadol tablets
Sudafed non-drowsy dual relief Capsule
Tramacet
Tramil Capsule
Triogesic Tablet
Tylex
Tylex capsules
umark Paracetamol capsules
Veganin tablets
Zapain

Appendix Figure 1 Paracetamol classification

b) Neuropathic/central Pain

AMITRIPTYLINE HYDROCHLORIDE

Amitriptyline tablets

Amitriptylineoral solution

Tryptizol

Lentizol modified-release capsules

Elavil

Tryptomer

GABAPENTIN

Gabapentin tablets

Gabapentin capsules

Gabapentin oral solution

Neurontin

TRICYCLIC

Dosulepin

Dothiepin

Nortriptyline tablets

PREGABALIN

Alzain capsules

Axalid capsules

Lecaent capsules

Pregabalin capsules

Pregabalin oral solution

Lyrica capsules

Pregabalin

Appendix Figure 2 Neuropathic analgesic classification

c) Strong Opioid

MORPHINE

Sevredol tablets

MST continus tablets

Morphgesic SR tablets

Zomorph capsules

MXL capsules

MST Continus suspension

Morphine sulfate oral solution

Oramorph oral solution

Morphine sulfate ampoules

Hydromorphone capsules

Palladone SR capsules

Morcap sr Modified-release capsule

Morphine tartrate ampoules

Filnarine SR tablets

Ipecacuanha & Morphine

Rhotard Morphine tablets

Cyclizine tartrate with morphine tartrate injection

Ammonium Chlor & Morphine double strength Mixed

BUPRENORPHINE

Temgesic sublingual tablets

Tephine sublingual tablets

Buprenorphine sublingual tablets

Natzon sublingual tablets

Prefibin sublingual tablets

Subutex sublingual tablets

Temgesic sublingual tablets

Tephine sublingual table

Espranor lyophilisates

Temgesic ampoules

Buvidal prolonged-release solution for injection

BuTrans transdermal patches

Bunov transdermal patches

Butec transdermal patches

Panitaz transdermal patches

Reletrans transdermal patches

Sevodyne transdermal patches

Bupramyl transdermal patches

Buplast transdermal patches

Carlosafine transdermal patches

Hapoctasin r transdermal patches

Relevtec transdermal patches

Transtec transdermal patches

Bupeaze transdermal patches

Alfentanil ampoules

Rapifen ampoules

FENTANYL

Abstral sublingual tablets

Effentora buccal tablets

Actiq lozenges oromucosal applicator

Cynril oromucosal applicator

Fentanyl ampoules

Durogesic DTrans transdermal patches

Fencino transdermal patches

Matrifen transdermal patches

Mezolar transdermal patches

Opiodur transdermal patches

Victanyl transdermal patches

Yemex transdermal patches

Fentalis Reservoir transdermal patches

Matrifen transdermal patches

Instanyl nasal spray

PecFentnasal spray

Appendix Figure 3 Strong opioid classification

Remifentanil powder for concentrate for solution for injection vials

Ultiva powder for solution for injection vials

Tilofyl transdermal patches

Mylafent transdermal patches

Osmanil transdermal patches

METHADONE HYDROCHLORIDE

Physeptone tablets

Methadone oral solution

Metharose oral solution

Physeptone oral solution

Methadose oral solution

Physeptone ampoules

OXYCODONE HYDROCHLORIDE

Abtard tablets

Carexil tablets

Ixyldone tablets

Longtec tablets

Oxeltra tablet

OxyContin tablets

Oxylane tablets

Oxypro tablets

Reltebon tablets

Renocontin tablets

Onexila XL tablets

Leveraxo tablet

Lynlor capsules

OxyNorm capsules

Shortec capsules

Lynlor capsules

OxyNorm oral solution

Oxycodone oral solution

Shortec oral solution

Shortec ampoules

OxyNorm ampoules

Oxycodone ampoules

Oxylan modified-release tablets

Targinact modified-release tablets

PETHIDINE HYDROCHLORIDE

Pethidine tablets

Pethidine ampoules

TAPENTADOL

Palexia tablets

Palexia SR tablets

Palexia oral solution

TRAMADOL HYDROCHLORIDE

Zydol tablets

Zamadol tablets

Zydol SR tablets

Invodol SR tablets

Mabron tablets

Maneo tablets

Marol tablets

Tilodol tablets

Tradorec XL tablets

Tramulief SR tablets

Tilodol SR tablets

Zydol XL tablets

Invodol SR tablets

Tramadol capsules

Zamadol capsules

Zydol capsules

Maxitram SR capsules

Tramquel SR capsules

Tramadol oral drops

Tramadol ampoules

Appendix Figure 4 Strong opioid classification part 2

Zamadol ampoules

Zydol ampoules

Tramacet

Tramake capsules

Marol modified-release tablets

Zeridame tablets

Larapam tablets

Nobligan retard tablets

Tramake pachets

PENTAZOCINE

Pentazocine tablets

Pentazocine capsules

Fortral 30mg/ml Injection

Fortagesic Tablet

MEPTAZINOL

Meptid Isolution for injection ampoules

OTHERS

Narphen Tablet

Nalbuphine hc Injection

Paveretum 20 MG Inj

Dextromoramide ampoules

Omnopon 20 MG Inj

Appendix Figure 5 Strong opioid classification part 3

d) Weak Opioids

CODEINE PHOSPHATE

Codeine tablets

Codeine linctus

Galcodine linctus

Codeine oral solution

Codeine ampoules

Solpadol tablets

Tylex capsules

Migraleve tablets

Galcodine Oral solution

Codeine phosphate/Epedrine Hyd/Promethazine Lin

Veganin tablets

Parahypon Tablet

Panadeine Effervescent tablet

Acetylsalicylic acid / Codeine phosphate MG tablet

Hypon Tablet

Co-codaprin tablets

Benylin with Codeine oral solution

DIHYDROCODEINE TARTRATE

Dihydrocodeine tablets

DF 118 Forte tablets

DHC Continus tablets

Dihydrocodeine oral solution

Dihydrocodeine I ampoules

Remedeine tablets

DHC Continus tablets

MEPTAZINOL

Meptid tablets

Meptid ampoules

Cocodamol

Co-dyramol

Kapake

Zapain

Solpadine

Codipar

Codis

Tylex

Migraleve tablets

e) Systemic NSAIDs

IBUPROFEN

Advil Tablet

Anadin tablets

Anadin Ibuprofen tablets

Anadin Ultra capsules

Boots Rapid Ibuprofen lysine tablets

Brufen 400mg tablets

Brufen Retard tablets

Calprofen Oral suspension

Clinoril tablets

Cuprofen tablets

Dexibuprofen tablets

Feminax tablets

Feminax tablets

Flarin capsules

Flurbiprofen tablets

Froben tablets

Galpharm capsules

Ibucalm tablets

Ibucalm tablets

Ibular tablets

Appendix Figure 6 Weak opioids classification

Ibular tablets	Volraman gastro-resistant tablets
Ibuprofen tablets	Volsaid Retard tablets
Ibuprofen tablets	Voltarol ampoules
Ibuprofen caplets	Voltarol Ophtha eye drops
Ketoprofen capsules	INDOMETHACIN
Mandafen	Indocid capsules
Migrafen tablets	Indometacine tablets
Motrin tablets	Indolar SR capsules
Nurofen tablets	Pardelprin MR capsules
Nurofen caplets	MEFENAMIC ACID
Nurofen Meltlets tablets	Mefenamic acid capsules
Nuromol tablets	Ponstan capsules
Phorpain Gel	Dysman tablets
Tiaprofenic acid capsules	Dolobid tablets
DICLOFENAC SODIUM	Diflunisal tablets
Acoflam Retard tablets	NAPROXEN
Akis ampoules	Naproxen
Arthrotec tablets	Synflex tablets
Defanac Retard tablets	Naproxen and misoprostol Tablet
Dexomon tablets	Naproxen suppositories
Diclofenac sodium gastro-resistant tablets	NABUMETONE
Dicloflex SR tablets	Nabumetone tablets
Dicloflex tablets	Relifex tablets
Diclomax SR capsules	ETODOLAC
Diclovol SR tablets	Lodine tablet
Diclozip gastro-resistant tablets	Etodolac capsules
Econac suppositories	KETOPROFEN
Enstar XL tablets	Valket Retard capsules
Fenactol tablets	Oruvail capsules
Flamrase tablets	PIROXICAM
Motifene capsules	Piroxicam capsules
Rhumalgan capsules	Feldene capsules
Rhumalgan tablets	Brexidol tablets

Appendix Figure 7 Weak opioid classification

COXIBS

arcoxia

Celebrex

celecoxib

Etorcoxib

rofecoxib

Vioxx

Valecoxib

TENOXICAM

Tenoxicam tablets

Tenoxicam powder and solvent for solution for injection vials

Sulindac

Clinoril tablets

Sulindac tablets

OTHERS

Lofensaid tablets

Fenbufen Effervescent tablet

Tolfenamic acid Capsule

Dexketoprofen tablets

Disalcid Capsule

Tolectin Capsule

Flexin Continus tablets (Indocid tablets)

Hypon Tablet (Asprin, Codeine phosphate, Caffeine)

Tolmetin

Ramodar

Aceclofenac tablets

Acetylsalicylic acid / Codeine phosphate MG tablet

Butazolidin Tablet

Choline Mg trisalicylate tablets

Meloxicam

Benorilate tablets

Benzydam

Surgam tablets (tiaprofenic acid)

Tolfenamic acid Capsule

Anadin Extra (Asprin+Paracetamol)

Codis (Asprin+Codeine phosphate)

Appendix Figure 8 Weak opioid classification

f) Cream NSAIDs

IBUPROFEN

Boots Ibuprofen 5% gel

Ibugel 5% gel

Ibuleve 5% gel

Ibuprofen 5% gel

Nurofen 5% gel

Phorpain 5% gel

Fenbid Forte 10% gel

Ibugel Forte 10% gel

Ibuleve 10% gel

Ibuprofen 10% gel

Nurofen 10% gel

Phorpain 10% gel

Proflex 5% cream

Oruvail 2.5% gel

Powergel 2.5% gel

DICLOFENAC SODIUM

Diclofenac 1% gel

Voltarol Emulgel

Solacutan 3% gel

Generic Balmosa cream

Flexiseq

g) Capsaicin Cream

Solaraze 3% gel

Zacin cream

Axsain cream

Qutenza - cutaneous patch

h) Topical Other

Biofreeze gel

Fisiocream

Flexiser

Movelat gel

Mussel gel

Musselflex gel

Perskindol

i) Analgesic Other

Nefopam

Nefopam Hydrochloride

j) Non-MSK anti-neuropathic

Tegrotol

Carbamazapine

lidocaine

Lidocaine plasters

Appendix Figure 9 Other analgesic classifications

A2. IMH&W Analgesia Results

The cross-sectional number of analgesia medications per participant ate shown in Appendix Table 1. The distribution of analgesic medications by age and sex is shown in Appendix Table 2.

Appendix Table 1 The number of analgesic medications reported per participant.

Number of analgesia medications reported per participant	Frequency n (%)
0	1048 (40)
1	632 (24)
2	543 (21)
3	265 (10)
4	108 (4)
5	36 (1)
6	8 (0.3)
7	3 (0.1)
10	1 (0.04)

Appendix Table 2 Analgesia classification by sex and age group

		Sex			Age group			
Analgesia	Total	Female	Male	Undeclared	<60	60-69	70-79-	≥80
Participants, n (%)	2,644	1533 (58)	1113 (42)	4 (0.2)	319 (12)	660 (25)	1137 (43)	528 (20)
Paracetamol, n (%)	1258 (48)	869 (57)	387 (35)	2 (50)	137 (43)	306 (46)	523 (46)	292 (55)
Neuropathic/central, n (%)	340 (13)	247 (16)	93 (8)	0	64 (20)	109 (17)	116 (10)	51 (10)
Strong Opioid, n (%)	228 (9)	154 (10)	74 (7)	0	50 (16)	65 (10)	82 (7)	31 (6)
Weak Opioid, n (%)	535 (20)	364 (24)	170 (15)	1 (25)	78 (25)	135 (20)	218 (19)	104 (20)
Systemic NSAIDs, n (%)	466 (18)	328 (21)	138 (12)	0	97 (30)	139 (21)	176 (16)	54 (10)
Cream NSAIDs, n (%)	91 (3)	61 (4)	30 (3)	0	6 (2)	21 (3)	38 (3)	26 (5)
Capsaicin Cream, n (%)	6 (0.2)	4 (0.3)	2 (0.2)	0	2 (0.6)	2 (0.3)	0	2 (0.4
Analgesia other, n (%)	11 (0.4)	8 (0.5)	3 (0.3)	0	2 (0.6)	4 (0.6)	5 (0.4)	0
Non-MSK anti-neuropathic, n (%)	17 (0.6)	10 (0.7)	7 (0.6)	0	3 (0.9	7 (1.1)	3 (0.3)	4 (0.8)
Topical other, n (%)	15 (0.6)	10 (0.7)	5 (0.4)	0	2 (0.6)	4 (0.6)	5 (0.4)	4 (0.8)
Total Reported Medications	2967	2055	909	3	441	792	1166	568

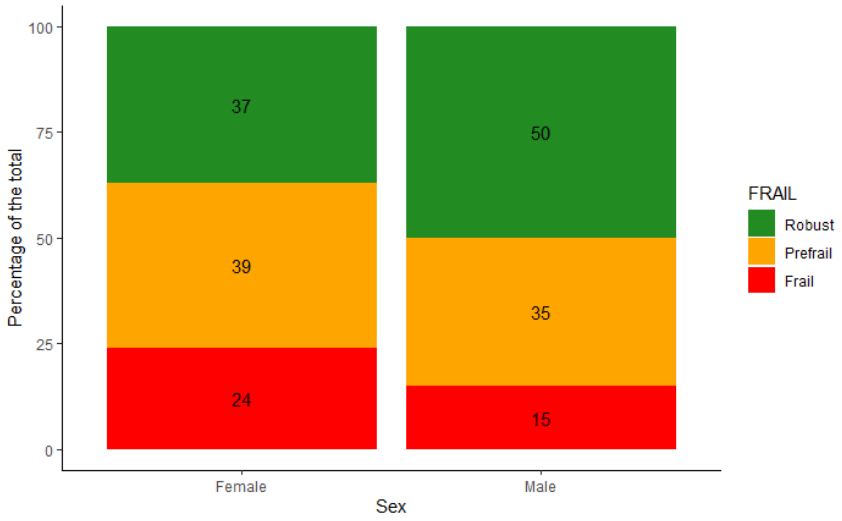
APPENDIX B IMH&W FRAIL CLASSIFICATION DATA USING ORIGINAL FRAIL.

B1. The association of covariables with FRAIL classification

The following shows the full frailty classification as described by Morley et., al (2012). The results for binary classification are shown in Chapter3.

B1.1a. FRAIL by sex classification

There was significant heterogeneity of FRAIL between sexes X^2 =49.38 p<0.001. In the IMH&W, 290 (24%) of females were classed as frail compared to 148 (15%) of males (Appendix Figure 10).

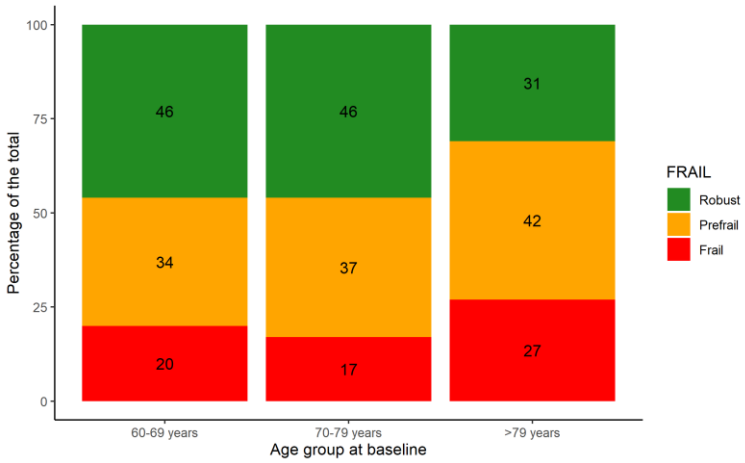


Appendix Figure 10 IMH&W FRAIL classification by sex

B1.1b. FRAIL by age group

In the IMH&W, participant ages ranged from 60 to 96 years; the median was 74, and IQR=69-79. When age was categorised, the relationship between age and frailty appeared to have significant heterogeneity (X^2 =42.36, p<0.001). There was a higher proportion of people aged ≥ 80 years who were classified frail (n=129, 27%) compared to those who were <80 years (Appendix Figure 11).

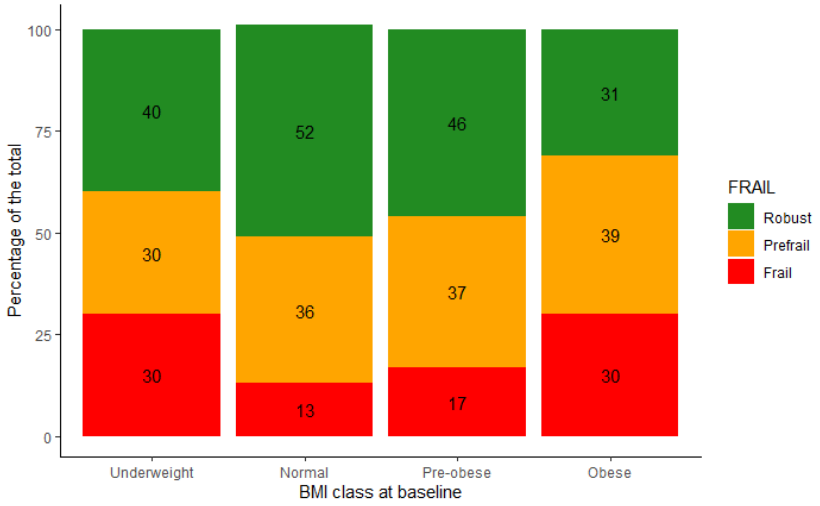
When age was treated as a continuous variable, the correlation between age and FRAIL was r_s= 0.09, p<0.001.



Appendix Figure 11 FRAIL classification by age group (n=2185).
The number refers to the percentage of the cohort of that age group in the frail category.

B1.1c. FRAIL with Body Mass Index

In the IMH&W cohort, the median BMI was 27.3, IQR=24-31. There was significant heterogeneity of frailty between BMI classes (X^2 =95.98 p<0.001). There was a greater proportion of people who were prefrail and frail increased in the participants classified as underweight, pre-obese and obese, compared to those with a normal BMI (Appendix Figure 12). However, it should be noted that only 30 participants were recorded as underweight. There appeared to be a U-shaped distribution; this was important for future analysis as it indicated that BMI should be categorised for future analyses rather than treated as ordinal or linear.

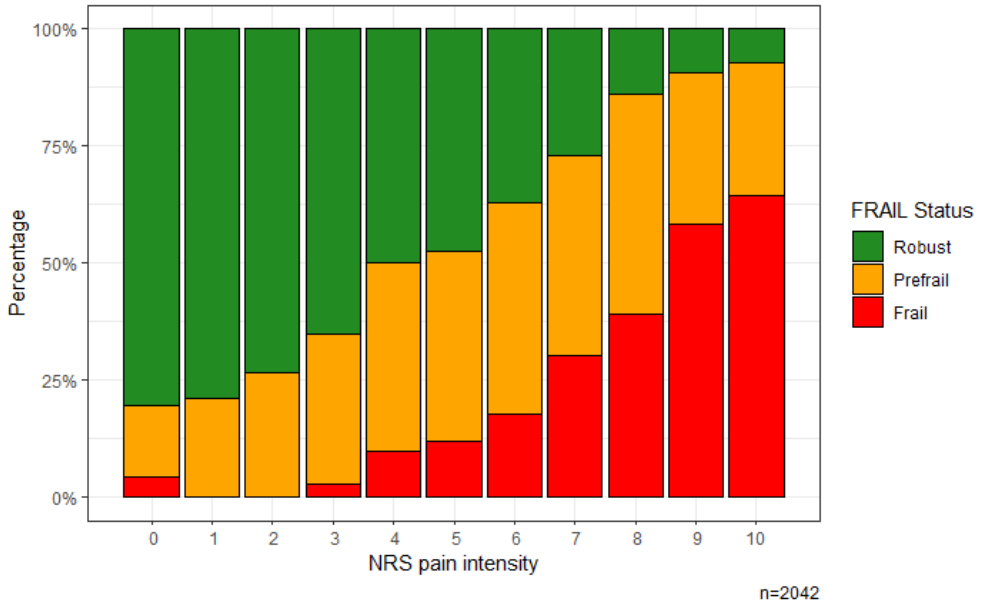


Appendix Figure 12 FRAIL classification by BMI class.

The number refers to the percentage of the cohort of that BMI class in the frail category.

B1.2a. The association of NRS pain with frailty

There is a significant, strong positive correlation between NRS pain and frailty (rs= 0.50 (95%ci 0.47, 0.53), p<0.001). Appendix Figure 13 indicates how the three FRAIL categories change between levels of pain. People who were robust had a lower range of NRS scores, whilst prefrail individuals had more NRS scores around the mid-scale. In contrast, those who were frail had pain in the higher NRS range.



Appendix Figure 13 Percentage of FRAIL classification by NRS pain scores

An ordinal logistic regression of FRAIL and NRS pain indicated the unadjusted odds ratio for a higher FRAIL category was 1.57 (95%CI 1.51, 1.64) per unit increase in NRS pain (p<0.001).

B1.3. Regression models using the ordinal frail classification.

The FRAIL odds ratios varied with each level (as discussed in Chapter 2). So, the odds ratio of increasing one level of FRAIL for people classified as robust was (aOR 1.49 (95%CI 1.42, 1.56), whereas for people classified as prefrail, it was (aOR 1.65 (95% 1.55, 1.76), per unit of NRS pain, as indicated in Appendix Table 3.

Appendix Table 3 Ordinal logistical regression model of FRAIL with pain and baseline characteristics

	Robust to Prefrail		**Prefrail to Frail**	
Variable	aOR (95%CI)	P-value	aOR (95%CI)	P-value
NRS pain (0-10)	1.49 (1.42, 1.56)	<0.001	1.65 (1.55, 1.76)	<0.001
Sex				
Female	1.53 (1.25, 1.87)	<0.001	1.16 (0.90, 1.48)	0.251
Age group				
60-69 years	Ref		Ref	
70-79 years	1.35 (1.08, 1.71)	0.010	0.95 (0.72, 1.26)	0.743
≥80 years	2.73 (2.03, 3.67)	<0.001	1.85 (1.34, 2.54)	<0.001
BMI class				
Underweight	1.74 (0.80, 3.78)	0.160	1.74 (0.80, 3.78)	0.160
Normal	Ref		Ref	
Pre-obese	1.21 (0.97, 1.50)	0.089	1.21 (0.97, 1.50)	0.089
Obese	2.02 (1.60, 2.55)	<0.001	2.02 (1.60, 2.55)	<0.001

Abbreviations: aOR adjusted odds ratio; 95%CI – 95% Confidence Intervals
BMI class = Body Mass Index categories <24.9, pre-obese 25-29.9, obese >30 kg/m