Association between pain and the frailty phenotype in older men: longitudinal results from the Concord Health and Ageing in Men Project (CHAMP)

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Abstract

Objectives: To determine whether pain increases the risk of developing the frailty phenotype and whether frailty increases the risk of developing chronic or intrusive pain, using longitudinal data.

Design/Setting: Longitudinal data from the Concord Health and Ageing in Men Project (CHAMP), a prospective population based cohort study.

Participants: A total of 1705 men aged 70 years or older, living in an urban area of New South Wales, Australia.

Measurements: Data on the presence of chronic pain (daily pain for at least 3 months), intrusive pain (pain causing moderate to severe interference with activities) and the criteria for the Cardiovascular Health Study (CHS) frailty phenotype were collected in three waves, from January, 2005 to October, 2013. Data on age, living arrangements, education, smoking status, alcohol consumption, body mass index, comorbidities, cognitive function, depressive symptoms and history of vertebral or hip fracture were also collected and included as covariates in the analyses.

Results: 1,705 participants were included at baseline, of whom 1,332 provided data at the 2-year follow-up and 940 at the 5-year follow-up. Non-frail (robust and pre-frail) men who reported chronic pain were 1.60 (95% confidence interval (CI): 1.02 to 2.51, p=0.039) times more likely to develop frailty at follow-up, compared to those with no pain. Intrusive pain did not significantly increase the risk of future frailty. Likewise, the frailty status was not associated with future chronic or intrusive pain in the adjusted analysis.

Conclusions: The presence of chronic pain increases the risk of developing the frailty phenotype in community-dwelling older men.

Key words: Ageing, Pain, Frailty, Male Health

Introduction

Chronic musculoskeletal pain is very common among older adults, affecting around one in four (1-5) people. Cross-sectional studies have shown an association between pain and disability in daily living activities (6-9) and between pain and frailty as measured using both the Frailty Index (FI) and Cardiovascular Health Study (CHS) frailty phenotype (10-16). Furthermore, two longitudinal studies have shown a causal association between pain and frailty assessed using the FI (17, 18). While it has been demonstrated that pain is associated with worsening frailty as assessed using the FI, it is still unclear whether pain is a risk factor for the development of the CHS frailty phenotype. Moreover, it is also possible that pain and the CHS frailty phenotype have a bidirectional risk relationship.

The CHS frailty phenotype differs from the FI because it distinguishes frailty from comorbidity and disability, defining a pre-disability syndrome based on specific clinical signs and symptoms (19). Therefore, CHS frailty criteria identify a group of frail older people sharing a common pathophysiological pathway (20), which provides a framework for identifying etiologic factors and interventions to prevent further functional decline. We aimed to explore the association between pain and CHS frailty phenotype using longitudinal data collected over 5 years. The objectives of this study were:

1. To establish whether chronic pain or intrusive pain at baseline would increase the risk of future frailty defined using the CHS criteria in older Australian men;
2. To establish whether frailty status at baseline would predict the occurrence of future chronic or intrusive pain.

Methods

Study design and sample population

The Concord Health and Ageing in Men Project (CHAMP) is a population-based cohort study of men aged 70 years or over, living in a defined geographical region near Concord Hospital in Sydney (21). The sampling frame used for the study was the New South Wales Electoral Roll. Eligible men in the study area were sent a letter describing the study and, if they had a listed telephone number, were contacted about one week later. Recruitment occurred sequentially across the geographic study area, with invitation letters being sent out each week during the recruitment period. The only exclusion criterion was living in a residential aged care facility.

Baseline data were collected between January 28, 2005 and June 4, 2007. Of the 2,815 eligible men with whom contact was made, 1,511 participated in the study (54%). An additional 194 eligible older men who lived in the study area heard about the study from friends or the media and asked to be in the study before receiving an invitation letter. Around half (49.8%) of the participants included in the CHAMP at the baseline were born in Australia, 19.6% in Italy, 4.6% in the Great Britain, 3.8% in Greece, 2.4% in China and 19.5% in other countries (21). Two-year follow-up assessments were conducted between January 2007 and October 2009, and the 5-year follow-up was conducted between January 2012 and October 2013.

Pain assessment

Chronic pain

The presence of chronic pain was assessed through the question: “In the last 6 months, have you experienced pain in any part of your body which has lasted for 3 months or more, that is pain experienced every day for at least 3 months?”; this question has been widely used in population studies (3). Data were collected at baseline and at 2 and 5-year follow-ups.

Intrusive pain

The following question from the SF-12 questionnaire (22) was used to assess the impact of pain on an individual’s life: “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?” Men who reported that their pain interfered “moderately”, “quite a bit” or “extremely” on normal work were classified as individuals with intrusive pain.

Frailty assessment

Frailty was assessed using the CHS frailty phenotype definition: weight loss/shrinking, weakness, exhaustion, slowness and low activity. The assessment of weakness and slowness used the standard CHS definition and cut-offs, but adapted criteria were used for weight loss/shrinking, exhaustion, and low activity. The following definitions were used: a) weight loss/shrinking: defined as current weight 15% or more less than self-reported heaviest weight; b) weakness: defined as being in the lowest CHS study quintile for grip strength, adjusted for BMI; c) exhaustion: defined according to responses to the following question from the SF12: ‘‘How much

of the time during the past 4 weeks did you have a lot of energy?"; d) slowness: defined as being in the lowest CHS study quintile for walking speed, adjusted for height; e) low physical activity: defined as being in the lowest quintile on the Physical Activity Scale for the Elderly (PASE) (cut-off score <73). Individuals who met 3 or more criteria were classified as frail. Those meeting less than 3 criteria were classified as pre-frail (1 or 2 criteria) or robust (0 criteria).

Socio-demographic and life-style factors

Age, living arrangements (living alone vs. living with others) and level of education (no post-school qualification vs. post-school qualification) were used to assess socio-demographic status of included participants.

Smoking status was classified as "never smoked" (those who smoked less than 100 cigarettes in their entire life), "ex-smokers" or "current smokers". Alcohol abuse was assessed through the CAGE questionnaire (23), with two or more positive answers in the questionnaire used to determine "alcohol abuse". Height and weight were measured, and body mass index (BMI) was calculated as kilograms per square metre.

Comorbidities

The comorbidity count was calculated for each participant by summing the presence of 18 self-reported, doctor-diagnosed conditions: diabetes; thyroid disease; osteoporosis; Paget's disease; stroke, blood clot in the brain or bleeding in the brain; Parkinson's disease; kidney stones; epilepsy or fits; hypertension or high blood pressure; heart attack, coronary or myocardial infarction; angina; congestive heart failure or enlarged heart; intermittent claudication or pain in

the legs from a blockage of the arteries; chronic obstructive lung disease, chronic bronchitis, asthma, emphysema or COPD; liver disease; chronic kidney disease or kidney failure; arthritis or gout; and cancer (excluding non-melanoma skin cancer).

Cognitive function and depressive symptoms

The mini-mental state exam (MMSE) (24) score was used as a continuous measure to assess cognitive function. Depressive symptoms were evaluated with the Geriatric Depression Scale (GDS) 15-item version (25). A total of five or more depressive symptoms were considered as indicating a possible depressed mood.

Statistical analysis

The statistical analysis was carried out using STATA v13 (Stata Corp, College Station, TX). Descriptive characteristics were expressed as means and standard deviation (SD) for continuous variables and absolute number and percentage for categorical variables. The statistical significance threshold was set at 0.05.

Generalised estimating equations (GEE) were used to explore the association between pain and frailty. GEE takes into account the time-varying nature of included variables allowing for the inclusion of all three waves of data collection in the analyses. The analyses were performed using a time lag model in which predictors were assessed in the previous wave, i.e. we tested in the GEE model whether chronic or intrusive pain would predict frailty in the next follow-up and whether the frailty status would predict chronic or intrusive pain in the next follow-up (Supplementary data, Figure 1). For the GEE models, exchangeable working correlation structure

and robust standard errors were used. Unadjusted, age-adjusted and multivariate analyses were carried out. Covariates selected for the multivariate analysis were those significantly associated with the outcome of interest ($p<0.1$) when included in the model. The results are expressed as odds ratios (OR) and 95% confidence intervals (95%CI).

Risk of developing frailty in participants with chronic pain or intrusive pain

To ascertain evidence of the role of chronic pain or intrusive pain in frailty development, individuals who were classified as frail at baseline were excluded from this analysis. The GEE model included data from baseline, 2- and 5-year follow-ups. Participants without chronic pain and participants without intrusive pain were considered the reference group.

Risk of developing chronic or intrusive pain in frail participants

To ascertain the role of frailty status as a risk factor for pain, men who reported chronic pain or intrusive pain at baseline (according to the outcome of interest) were excluded from the analysis. The GEE model included data from baseline, 2 and 5-year follow-up. Robust participants were considered the reference group.

Ethics approval and informed consent

All participants gave written informed consent. The study was approved by the Sydney Local Health District Human Research Ethics Committee, Concord Repatriation General Hospital, Sydney, Australia.

Results

1,705 patients were included in the baseline assessments. At the 2-year follow-up, frailty status

was assessed in 1,332 participants and at the 5-year follow-up in 940 participants. Death was the main reason for nonparticipation at 2 years and at 5 years. The other main reason for failure to attend the follow-up clinic visits was illness.

The mean (SD) age of the study population at baseline was 76.9 (5.5) years. Chronic pain was reported by 29.5% (n=501) of the participants and intrusive pain by 23.4% (n=392). There were significant differences in prevalence of chronic pain and intrusive pain between robust, pre-frail and frail participants at baseline. Other baseline characteristics of the participants are summarized in Table 1.

Longitudinal analysis

Risk of developing frailty in participants with chronic pain and intrusive pain

Of 1,508 robust and pre-frail participants included in this analysis, 422 reported chronic pain at baseline and 350 reported pain at the 2-year follow-up. Among participants reporting chronic pain at baseline who were also assessed for frailty status at the 2-years follow-up (n=350), 8.3% (n=29) developed frailty compared to 5.5% (n=49) of those without chronic pain (Supplementary data, Table 1). Among participants reporting chronic pain at 2-year follow-up who were also assessed for frailty status at the 5-years follow-up (n=234), 12.4% (n=29) developed frailty compared to 6.6% (n=40) of those without chronic pain (Supplementary data, Table 2). In GEE analyses presence of chronic pain in the previous wave was independently associated with increased odds of future frailty (OR 1.60, 95%CI 1.02-2.51, p=0.039) (Table 2).

Likewise, the GEE analyses suggested that the odds of developing frailty were higher in participants who reported intrusive pain (see Table 2). However, the association did not quite reach statistical significance in the fully adjusted model (OR 1.64, 95%CI 0.97-2.78, p=0.063).

Risk of developing chronic pain or intrusive pain in pre-frail and frail participants

Of 1,180 participants without chronic pain at baseline included in this analysis, 957 completed the 2-year follow-up and 660 completed the 5-year follow-up. Among participants classified as frail in the baseline who were also assessed for chronic pain at 2-year follow-up (n=47), 21.3% (n=10) had developed chronic pain compared to 18.4% (n=69) and 16.6% (n=89) of those classified as pre-frail and robust respectively (Supplementary data, Table 5). Among participants classified as frail at 2-year follow-up and who were also assessed for chronic pain at 5-year follow-up (n=20), 35% (n=7) had developed chronic pain compared to 28.5% (n=72) of the pre-frail and 25.1% (n=97) of robust participants (Supplementary data, Table 6).

Of the 1,277 participants without intrusive pain at the baseline, 1,049 completed the 2-year and 750 completed the 5-year follow-up. Participants who were frail were more likely to develop intrusive pain compared to robust participants (Table 3 and Supplementary data, tables 7 and 8).

After adjusting for covariates, however, pre-frail or frail individuals were not at a higher risk of reporting future chronic pain (Pre-frail: OR 1.07, 95%CI 0.80-1.44; p=0.649; Frail: OR 0.82, 95%CI 0.38-1.79; p=0.618) or intrusive pain (Pre-frail: OR 0.91, 95%CI 0.67-1.23; p=0.551; Frail: OR 1.38, 95%CI 0.70-2.74; p=0.356) at follow-up, compared to robust individuals (Table 3).

Discussion

This study has shown that chronic pain in older men is a risk factor for developing frailty, as assessed using the CHS frailty criteria. However, frailty status is not associated with increased risk of developing chronic or intrusive pain.

In 2008, Blyth et al. published one of the first studies exploring the relation between frailty and pain using baseline data from this same cohort study (10). The authors concluded that frailty was associated with intrusive pain at CHAMP's baseline. Since then, this association has been replicated by several studies, most of them cross-sectional studies (10-16). The causal association between chronic pain and frailty, however, have been demonstrated in only two cohort studies, the European Male Ageing Study (EMAS) (17) and the English Longitudinal Study of Ageing (ELSA) (19). Both EMAS and ELSA assessed frailty using the FI. Therefore, our study is the first study to show that chronic pain increases the risk of developing the CHS frailty phenotype.

The association between pain and the CHS frailty phenotype could be explained in several ways. The presence of pain might be acting as a persistent stressor, demanding continuous activation of stress-related systems, which would consume physiological reserves and increase the risk of frailty (13, 14). Alternatively, systemic inflammation and the hypothalamic-pituitary-adrenal axis dysfunction, often found in patients with chronic pain (26, 27), could contribute to frailty development (28, 29). Another interesting hypothesis to be tested in future research is that pain and frailty share some common determinants, such as genetic factors (16), age, comorbidity, cognitive function and depression. In that case, chronic pain could be a mediator variable in the relationship between these determinants and frailty. This theory is, in part, supported by the

finding that persistent pain may be a preclinical manifestation of phenotypic frailty (30).

As frailty-related brain changes might cause impairments in descendent inhibitory pain modulation (13), it was expected that frailty would be a risk factor for pain. However, our study has shown that frailty status is not independently associated with increased risk of developing chronic or intrusive pain.

The findings reported in this study have important clinical implications. If chronic pain increases the risk of frailty, then better pain management could reduce the frailty trajectory among older adults. However, randomised clinical trials are needed to test whether and which pain interventions have any effect on frailty progression.

Our study has a number of strengths: prospective data collection in this large cohort of older men (mean age 77 years) who were significantly older than the previous studies (17, 18); standardised criteria for frailty were used; longitudinal data collection up to 5 years. There are however limitations that must be pointed out. Our results cannot be extrapolated to women due to differences regarding pain (31) and frailty (32). Other important limitations are not including disease severity when examining comorbidities, not incorporating the ethnicity in the model as pain and pain management may vary in different ethnic populations (33), and the exclusion of information on pain medication from the analyses, given pain medication might mediate the association between pain and frailty (34).

This study represents a step forward understanding the influence of chronic pain, a common problem in aged populations, on frailty dynamics. However, many questions remain unanswered,

for example, the biological mechanisms responsible for this association, the influence of pain characteristics (such as origin and intensity) on frailty progression and the impact of pain management on vulnerable populations.

Conclusion

We have established that the presence of chronic pain increases the risk of developing physical frailty phenotype in community-dwelling older men, even after adjusting for potential confounders. Conversely, we found that frailty is not an independent risk factor for chronic or intrusive pain. Future studies should focus on the efficacy of different pain management strategies in reducing the risk of frailty.

Key Points

- Chronic pain is an independent risk factor for developing the CHS frailty phenotype among older men
- The frailty status does not independently increase the risk of developing chronic or intrusive pain among older men
- Future studies should focus on the role of pain management as a potential strategy to prevent frailty in older people

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Table 1. Baseline characteristics of population by frailty status (n=1705).

	Baseline			
	Robust (n=833)	Pre-frail (n=679)	Frail (n=158)	p
Demographic factors				
Age, mean (SD)	75.2 (4.4)	77.6 (5.2)	80.9 (6.5)	<.001
Living alone, n (%)	140 (16.8)	122 (18.0)	45 (28.5)	.004
Post-school qualification, n (%)	500 (60.3)	346 (51.5)	61 (38.9)	<.001
Alcohol abuse (CAGE>=2), n (%)	80 (9.5)	71 (10.4)	33 (20.9)	<.001
Cigarette-smoking status				
Never smoked, n (%)	316 (37.9)	246 (36.3)	56 (35.7)	.749
Ex-smoker, n (%)	463 (55.6)	394 (58.1)	92 (58.6)	.561
Current smoker, n (%)	54 (10.3)	38 (8.7)	9 (8.7)	.690
BMI, mean (SD)	27.7 (3.6)	28.0 (4.3)	27.7 (4.8)	.220
Mini-Mental, mean (SD)	27.6 (2.7)	26.9 (3.0)	25.7 (4.0)	<.001
Depressive mood (GDS>=5)	49 (5.9)	117 (7.3)	70 (44.9)	<.001
Hip or vertebral fracture, n (%)	27 (3.3)	14 (2.1)	5 (3.2)	.339
Comorbidity count, mean (SD)	1.2 (1.2)	1.5 (1.3)	2.3 (1.7)	<.001
Chronic pain, n (%)	215 (25.9)	207 (30.6)	62 (39.7)	.001
Intrusive pain, n (%)	138 (16.7)	177 (26.2)	67 (43.5)	<.001

Missing: living alone = 14, post-school qualification = 25, alcohol abuse = 14, smoking status = 18, BMI = 28, MMSE = 186, depression = 24, comorbidity count = 16, chronic pain = 8, intrusive pain = 30, frailty status = 35

Table 2. Unadjusted, age adjusted and multivariate OR for the association between chronic pain or intrusive pain and frailty using a time lag model[1] (N=1,512)

	Frailty	
	OR (95% CI)	**p**
Chronic pain in the previous wave		
Unadjusted model	1.71 (1.22-2.41)	0.002
Age-adjusted model	1.77 (1.24-2.53)	0.002
Multivariate model[2]	1.60 (1.02-2.51)	0. 039
Intrusive pain in the previous wave		
Unadjusted model	2.32 (1.59-3.38)	<0.001
Age-adjusted model	2.45 (1.65-3.63)	<0.001
Multivariate model[3]	1.64 (0.97-2.78)	0. 063

[1] Chronic pain and intrusive pain were assessed at baseline and 2-year follow-up and frailty at 2 and 5-year follow-up

[2] Adjusted for age (years), living alone, post-school qualification, BMI (kg/m2), Count of comorbidities (0-18), MMSE (0-30), Depression (see Supplementary data, Table 9, for the impact of covariates in the model)

[3] Adjusted for age (years), living alone, post-school qualification, BMI (kg/m2), Count of comorbidities (0-18), MMSE (0-30), Depression (see Supplementary data, Table 9, for the impact of covariates in the model)

Table 3. Unadjusted, age adjusted and multivariate OR for the association between frailty status and the development of chronic pain or intrusive pain using a time lag model[1].

	Chronic pain (N=1,196)		Intrusive pain (N=1,283)	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Frailty status in the previous wave				
Unadjusted model				
Robust	Reference	NA[2]	Reference	NA
Pre-frail	1.15 (0.89-1.49)	0.286	1.21 (0.91-1.60)	0.173
Frail	1.26 (0.70-2.27)	0.440	3.13 (1.85-5.27)	<0.001
Age-adjusted model				
Robust	Reference	NA	Reference	NA
Pre-frail	1.07 (0.82-1.40)	0.603	1.11 (0.83-1.48)	0.457
Frail	1.12 (0.62-2.04)	0.706	2.61 (1.49-4.56)	0.001
Multivariate model[3]				
Robust	Reference	NA	Reference	NA
Pre-frail	1.07 (0.80-1.44)	0.649	0.91 (0.67-1.23)	0.551
Frail	0.82 (0.38-1.79)	0.618	1.38 (0.70-2.74)	0.356

[1] Frailty status was assessed at baseline and 2-year follow-up and chronic pain or intrusive pain at 2 and 5-year follow-up

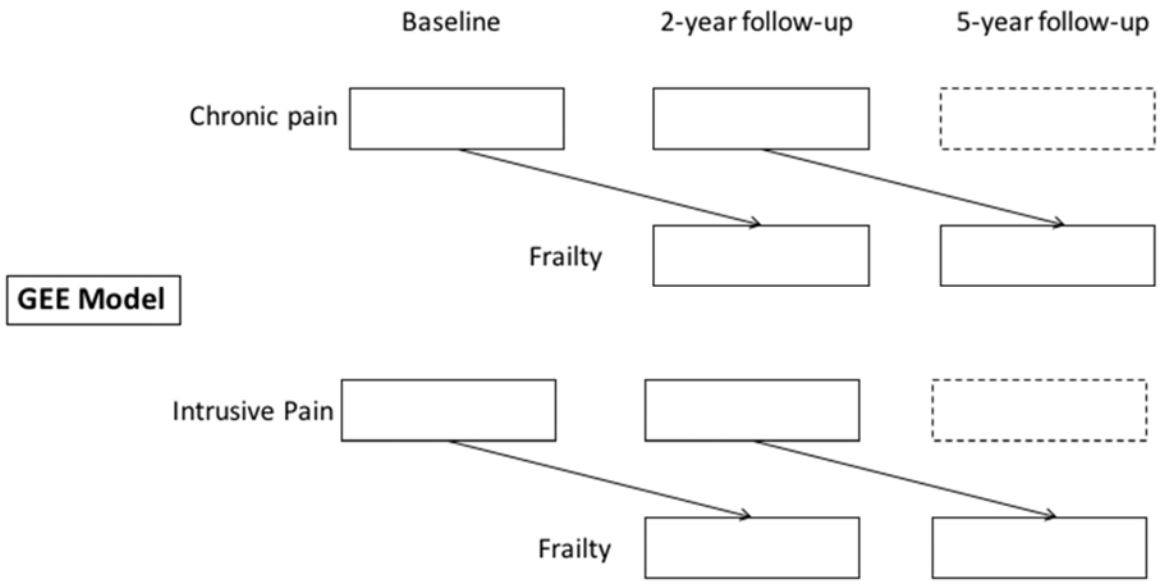
[2] Not applicable

[3] Adjusted for age (years), post-school qualification, smoking status, BMI (kg/m2), Count of comorbidities (0-18), MMSE (0-30), Depression (see Supplementary data, Table 10, for the impact of covariates in the model)

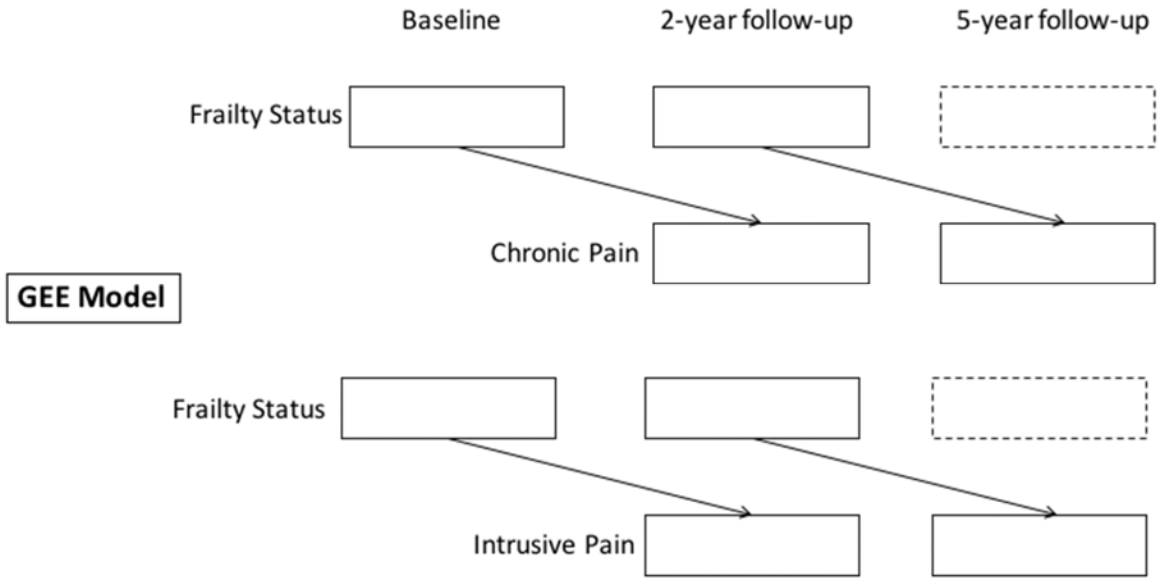
SUPPLEMENTARY DATA

Figure 1. Schematic diagram of the lag time model used in the GEE analysis

GEE analysis used in Table 2 (time lag model)



GEE analysis used in Table 3 (time lag model)



The statistical method used in this study, the generalised estimating equation (GEE), permits the analysis of repeated measurements of time dependent variables, taking into account an expected correlation between these measurements. Therefore, for the same individual, exposures were assessed at baseline and 2-years follow-up and outcomes at 2-years and 5-years follow-up. Data from an individual at a specified point in the study were included, regardless of whether data from this individual was missing at other points, under the assumption that the pattern of missing data is random. GEE models describe the average occurrence of the outcome for the group as a whole over time. We used the GEE method applied to logistic regression, estimating the odds ratio (OR) for each hypothesized association. The GEE model used in this study is also a time lag model, i.e. repeated measures of risk factors were associated with outcomes at the next follow-up. This model is particularly suitable considering the time-varying nature of risk factors and most covariates.

Table 1. Frequency data cross-classified according to chronic pain at baseline and frailty at 2-year follow-up (frail participants at baseline were excluded)

Chronic pain at baseline	Frailty at 2-year follow-up		Total
	No	Yes	
No	848 (94.5%)	49 (5.5%)	897 (100%)
Yes	321 (91.7%)	29 (8.3%)	350 (100%)
Total	1,169 (93.7%)	78 (6.3%)	1,247 (100%)

Pearson chi2(1) = 3.4218 Pr = 0.064

Table 2. Frequency data cross-classified according to chronic pain at 2-year follow-up and frailty at 5-year follow-up (frail participants at baseline were excluded)

Chronic pain at 2-year follow-up	Frailty at 5-year follow-up		Total
	No	Yes	
No	613 (93.5%)	43 (6.6%)	656 (100%)
Yes	205 (87.6%)	29 (12.4%)	234 (100%)
Total	818 (91.9%)	72 (8.1%)	890 (100%)

Pearson chi2(1) = 7.9067 Pr = 0.005

Table 3. Frequency data cross-classified according to intrusive pain at baseline and frailty at 2-year follow-up (frail participants at baseline were excluded)

Intrusive pain at baseline	Frailty at 2-year follow-up		Total
	No	Yes	
No	947 (95.7%)	43 (4.3%)	990 (100%)
Yes	213 (86.2%)	34 (13.8%)	247 (100%)
Total	1,160 (93.8%)	77 (6.2%)	1,237 (100%)

Pearson chi2(1) = 30.0619 Pr = 0.000

Table 4. Frequency data cross-classified according to intrusive pain at 2-year follow-up and frailty at 5-year follow-up (frail participants at baseline were excluded)

Intrusive pain at 2-year follow-up	Frailty at 5-year follow-up		Total
	No	Yes	
No	671 (92.6%)	54 (7.5%)	725 (100%)
Yes	136 (88.3%)	18 (11.7%)	154 (100%)
Total	807 (91.8%)	72 (8.2%)	879 (100%)

Pearson chi2(1) = 3.0366 Pr = 0.081

Table 5. Frequency data cross-classified according to frailty status at baseline and chronic pain at 2-year follow-up (participants reporting chronic pain at baseline were excluded)

Frailty status at baseline	Chronic pain at 2-year follow-up		Total
	No	Yes	
Robust	446 (83.4%)	89 (16.6%)	535 (100%)
Pre-frail	306 (81.6%)	69 (18.4%)	375 (100%)
Frail	37 (78.7%)	10 (21.3%)	47 (100%)
Total	789 (82.5%)	168 (17.6%)	957 (100%)

Pearson chi2(2) = 0.9473 Pr = 0.623

Table 6. Frequency data cross-classified according to frailty status at 2-year follow-up and chronic pain at 5-year follow-up (participants reporting chronic pain at baseline were excluded)

Frailty status at 2-year follow-up	Chronic pain at 5-year follow-up		Total
	No	Yes	
Robust	290 (79.9%)	97 (25.1%)	387 (100%)
Pre-frail	181 (71.5%)	72 (28.5%)	253 (100%)
Frail	13	7	20

	(65.0%)	(35.0%)	(100%)
Total	484 (73.3%)	176 (26.7%)	660 (100%)

Pearson chi2(2) = 1.6335 Pr = 0.442

Table 7. Frequency data cross-classified according to frailty status at baseline and intrusive pain at 2-year follow-up (participants reporting intrusive pain at baseline were excluded)

Frailty status at baseline	Intrusive pain at 2-year follow-up No	Yes	Total
Robust	528 (87.4%)	76 (12.6%)	604 (100%)
Pre-frail	338 (85.4%)	58 (14.7%)	396 (100%)
Frail	31 (78.7%)	18 (36.7%)	49 (100%)
Total	897 (85.5%)	152 (14.5%)	1,049 (100%)

Pearson chi2(2) = 21.3498 Pr = 0.000

Table 8. Frequency data cross-classified according to frailty status at 2-year follow-up and intrusive pain at 5-year follow-up (participants reporting intrusive pain at baseline were excluded)

Frailty status at 2-year follow-up	Intrusive pain at 5-year follow-up No	Yes	Total
Robust	374 (83.7%)	73 (16.3%)	447 (100%)
Pre-frail	220 (77.7%)	63 (22.3%)	283 (100%)
Frail	13 (65.0%)	7 (35.0%)	20 (100%)
Total	607 (80.9%)	143 (19.1%)	750 (100%)

Pearson chi2(2) = 7.3299 Pr = 0.026

Figure 2. Histogram of frailty score (number of CHS frailty criteria) at baseline, 2-year follow-up and 5-year follow-up

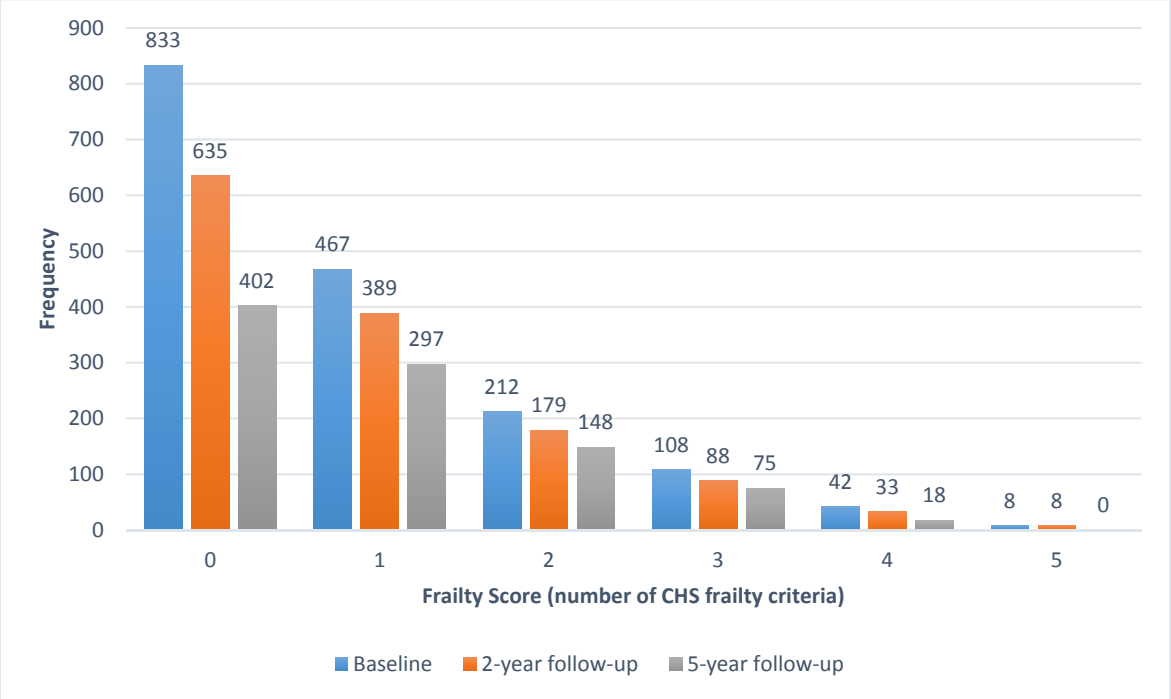


Table 9. Impact of each covariate in the multivariate GEE models assessing chronic or intrusive pain in previous wave as a risk factor for frailty development (n=1,512)

	Frailty	
	OR (95% CI)	**p**
Chronic pain	1.60 (1.02-2.51)	0. 039
Covariates[1]		
Age (years)	1.17 (1.12-1.22)	<0.001
Living alone	0.92 (0.52-1.64)	0.789
Post-school qualification	0.86 (0.54-1.37)	0.522
BMI (kg/m^2)	0.91 (0.87-0.96)	<0.001
Count of comorbidities (0-18)	1.40 (1.24-1.60)	<0.001
MMSE (0-30)	0.88 (0.83-0.94)	<0.001
Depression	4.20 (2.57-6.86)	<0.001
Intrusive pain	1.64 (0.97-2.78)	0. 063
Covariates[2]		
Age (years)	1.17 (1.12-1.23)	<0.001
Living alone	0.96 (0.54-1.69)	0.879
Post-school qualification	0.85 (0.53-1.34)	0.474
BMI (kg/m^2)	0.91 (0.87-0.96)	<0.001
Count of comorbidities (0-18)	1.38 (1.21-1.57)	<0.001
MMSE (0-30)	0.87 (0.82-0.93)	<0.001
Depression	3.99 (2.43-6.53)	<0.001

[1] Smoking status, alcohol abuse and history of hip/ vertebral fracture were not included because these variables were not significantly associated ($p<0.1$) with frailty when included in the GEE model.

[2] Smoking status, alcohol abuse and history of hip/ vertebral fracture were not included because these variables were not significantly associated ($p<0.1$) with frailty when included in the GEE model.

Table 10. Impact of each covariate in the multivariate GEE models assessing frailty status in the previous wave as a risk factor for development of chronic pain or intrusive pain.

	Chronic pain (n=1,196)		**Intrusive pain (n=1,283)**	
	OR (95% CI)	**p**	**OR (95% CI)**	**p**
Pre-frail	1.07 (0.80-1.44)	0.649	0.91 (0.67-1.23)	0.551
Frail	0.82 (0.38-1.79)	0.618	1.38 (0.70-2.74)	0.356
Covariates[1]				
Age (years)	1.03 (1.00-1.06)	0.021	1.04 (1.01-1.08)	0.012
Post-school qualification	0.74 (0.55-0.99)	0.042	0.83 (0.62-1.11)	0.209
Smoking status[2]	1.53 (1.17-2.00)	0.002	1.04 (0.79-1.36)	0.771
BMI (kg/m^2)	1.00 (0.97-1.04)	0.959	1.05 (1.01-1.09)	0.009
Count of comorbidities (0-18)	1.10 (1.01-1.20)	0.024	1.32 (1.21-1.45)	<0.001
MMSE score (0-30)[3]	1.06 (1.00-1.12)	0.060	N/A	N/A
Depression	1.63 (1.07-2.50)	<0.001	2.49 (1.66-3.73)	<0.001

[1] Living alone, alcohol abuse, and history of hip/vertebral fracture were not included because these variables were not significantly associated ($p<0.1$) with frailty when included in the GEE model.

[2] Smoking status: never smoked, ex-smokers and current smokers.

[3] MMSE score was not significantly associated ($p<0.1$) with intrusive pain when included in the GEE model.