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What factors mediate the inter-relationship between frailty and pain in cognitively and functionally sound older adults? A prospective longitudinal ageing cohort study in Taiwan

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ABSTRACT

Objectives The main aim was to investigate the complex inter-relationship between frailty and pain, and the mediating roles of cognitive function, morbidity and mood in this nexus.

Design A cross-sectional analysis.

Setting A prospective community-dwelling population-based cohort.

Participants 1682 adults age ≥50 years without evident cognitive or functional impairment, or history of cancer.

Primary and secondary outcome measures The mediating effect of depression, cognitive function and comorbidity on the nexus between pain and frailty among older and middle-aged adults.

Results The pain score among older subjects (≥65 years), increased with the degree of frailty (robust=0.96±0.82; pre-frail=1.13±0.86; frail=1.63±1.02; P<0.001); multivariate analysis gave the same result, while moderate pain was associated with frailty in older subjects (OR=3.00, 95% CI 1.30 to 6.60). Conversely, pain and frailty among middle-aged subjects (aged 50–64 years) did not appear to be significantly related; in mediation analysis, pain exerted an indirect effect on frailty via depression (indirect effect=0.03, 95% CI 0.01 to 0.07), while neither cognitive function nor comorbidity had any significant effect in mediating the relationship between pain and frailty.

Conclusion In cognitively and functionally sound community-dwelling adults aged ≥50 years, moderate pain was related to frailty in those older than 65 years, but not younger ones. Besides the direct influence of pain on frailty, depression partially mediated the pain–frailty nexus. The mechanism by which depression influences pain and frailty requires further investigation.

INTRODUCTION

Frailty is a common and well-known geriatric syndrome characterised by age-associated declines in the physiological functioning and capacity of multiple organ systems, which increases vulnerability to adverse sequelae of stressful events.[1] Frailty is usually operationally

Strengths and limitations of this study

► Using data excerpted from a large, well-characterised, longitudinal ageing cohort, we were able to apply a bootstrapping macro to ascertain putative direct and indirect mediators of the pain–frailty nexus in community-dwelling older adults.

► The cross-sectional design precluded the determination of causality in the relationship between mediators, pain and frailty nexus.

► Pain was defined as moderate pain during past 4 weeks and so could not be classified as either acute or chronic.

defined according to the Cardiovascular Health Study (CHS) criteria, which comprise five diagnostic elements: unintentional weight loss, exhaustion, slow walking speed, weak handgrip strength and diminished physical activity. People with at least three of these CHS components are defined as frail, and people with one or two, as prefrail.[2]

In previous studies, which used various operational definitions, the prevalence of frailty ranged from 4.0% to 59.1%: in a meta-analysis, the prevalence of frailty was 10.7%, and of prefrailty 41.6%.[3–5] Frailty in older adults may increase the risk of adverse health outcomes, the need for healthcare, vulnerability to stressful events and functional deterioration. Manifold risk factors for frailty have been reported, including among others, older age, female sex, lower educational level, multimorbidity and depressed mood.[6 7] Moreover, many risk factors are extensively intercorrelated, further complicating data analysis and interpretation.

Another common symptom that substantially impairs older adults' quality of life is pain; the prevalence of chronic pain among

community-dwelling older adults ranges from 24% to 72%, depending on the definitions used.[8 9] Maxwell *et al* found that 48% of older adults receiving home care services suffered from daily pain, 21.6% of whom did not take analgesic medications.[9] Others reported that bothersome pain was associated with female sex, obesity, musculoskeletal problems and depressive symptoms.[8]

Numerous studies have explored the association between pain and frailty in older adults, demonstrating that pain is associated with frailty, independent of other factors,[10–12] and that chronic widespread pain increases the incidence of frailty and may also worsen its severity.[13] A concept termed 'pain homeostenosis' has been proposed to explain the pain–frailty nexus,[12] and this inter-relationship might be mediated by mental and/or physical conditions, including cognitive and functional impairments, physical and mental illness, age-associated increased sensitivity to pain, social isolation and age-related brain structural changes. Several investigators have reported the associations of pain-cognition[14–16] and cognition-frailty,[17 18] which involved cognitive domains including working memory, visuospatial and executive function. However, the role of cognition in the pain–frailty nexus was not investigated. Similar evidence supports the associations between pain and depression,[19 20] pain and multicomorbidity[8 21] and depression, multimorbidity and frailty.[6 22] Weiner *et al* found that neuropsychological performance mediates the relationship between pain and physical performance,[23] despite the established inter-relationship between pain and frailty, the mechanism of pain-related frailty remains obscure. Therefore, we investigated the roles of cognitive function, multimorbidity and depressive symptoms in the development of pain-related frailty.

METHODS
Design and participants
Participants were recruited from the I-Lan Longitudinal Aging Study (ILAS) cohort, which was established to explore the complex inter-relationships between age-related frailty, sarcopenia and cognitive decline; the ILAS cohort comprises 1839 permanent residents of Yuanshan Township, Yilan County, Taiwan, aged ≥50 years, having excluded: (1) subjects who could not adequately communicate with the interviewer and complete the interview; (2) people whose physical function was too poor to evaluate, for example, the 6-metre walk test; (3) people with limited life expectancy due to major diseases or (4) residents of long-term care facilities. The protocol is described elsewhere.[24]

This cross-sectional study used the baseline data of 1682 ILAS participants, having excluded 93 with cognitive impairment, 37 with impaired activities of daily living/instrumental activities of daily living (ADL/IADL) and 27 with cancer, to avoid potential confounding effects.

The National Yang Ming University Institutional Review Board approved the whole study, and all participants provided informed written consent. The study was designed and conducted in accordance with the ethical standards of the Institutional Research Committee and the principles of the Declaration of Helsinki. The observational design and reporting format follow Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[25]

Functional assessments
All participants answered a questionnaire including age, sex, education duration, tobacco smoking and alcohol consumption history and comorbidities based on the Charlson Comorbidity Index (CCI).[26] Functional status was assessed using the Functional Autonomy Measurement System (SMAF), a 29-item questionnaire that includes ADL/IADL, mental function, mobility and communication: in SMAF-ADL and SMAF-IADL, a negative score indicates disability.[27] People with either ADL or IADL impairment, that is, SMAF-ADL <0 or SMAF-IADL <0, were excluded. The means of SMAF-ADL and SMAF-IADL were both zero. Mood and depressive symptoms were evaluated according to The Center for Epidemiologic Studies Depression Scale (CES-D).[28]

Definition of frailty
Frailty in ILAS was defined by adapted CHS criteria.[2] Weight loss was defined as unintentional weight loss >5% in the past year. Exhaustion was defined by agreement of either one of two statements from CES-D, that is, "I felt that everything I did was an effort" and "I could not 'get going'". Weakness was defined as low dominant handgrip strength measured by a dynameter (Smedlay Dynamo Meter, Tokyo, Japan). Slowness was measured by 6-metre walking test. Low physical activity was measured by International Physical Activity Questionnaire Score. Weakness, slowness and low activity were defined as lower than the gender-specific quintile of all participants. Participants fulfilling three or more of these criteria were defined as frail, those meeting one or two criteria as prefrail and those with no such conditions, as being robust.

Pain measurement
To assess pain, we adapted a question about pain from the Short Form 12 Health Survey[29]—"During the past one month, how severe was your bodily pain?"—which was measured on a five-point Linkert scale (0=no pain to 4=very severe pain). We divided the score into two categories for further analysis: score 2–4=moderate-to-severe pain and <2 =mild pain according to previous publication.[10]

Cognitive function measurement
The Chinese Mini-Mental State Examination (MMSE) is a valid tool to measure the global cognitive function and is extensively used in previous studies.[30 31] In addition, we evaluated specific cognitive domains: memory (Chinese Verbal Learning Test (CVVLT))[32]; speech/verbal recall (Boston Naming Test (BNT)) and Category (animal) Verbal Fluency Test (VFT)[33 34]; visuospatial ability (Taylor

Complex Figure Test (CFT))[35] and executive functions (digit backward (DB) and Clock Drawing Test (CDT)).[36 37] Participants with total MMSE score below 24 (educated ≥6 years), or 14 (educated <6 years), were deemed to be globally cognitively impaired.[31] Impairment in the other cognitive function domains assessed was defined as falling below 1.5 SD of the established norms for age and educational level.[31–37]

Statistical analysis

All statistical analyses were performed using SPSS Statistics for Microsoft Windows XP, V.16.0 (SPSS, Chicago, Illinois, USA). A two-tailed P value <0.05 was considered to be statistically significant.

In the univariate analysis, between-group differences in continuous variables such as age, education duration, body mass index, comorbidities (CCI), depressive symptoms (CES-D), physical activity (International Physical Activity Questionnaire - Short Form (IPAQ -SF)) and cognitive function (MMSE, CVVLT, BNT, VFT, CFT, DB and CDT) were analysed by analysis of variance. Categorical variables were compared by X^2 test, as appropriate. To investigate relationships between neuropsychological performance, frailty and pain, we cross-checked the Pearson's correlation coefficients of each neuropsychological test against the frailty and pain scores. Multivariate analysis applied multinomial logistic regression to explore the association between pain and frailty, by entering variables with a P value <0.1 in the adjusted univariate analysis.

In the mediation analysis, we applied an SPSS macroinstruction program (macro) to ascertain direct and indirect effects in the pain–frailty nexus. This macro used a bootstrapping strategy to test the validity of indirect effects[38]: each test was resampled 5000 times to estimate the bias-corrected and accelerated 95% CIs. In the single-step multiple mediator model, comorbidities (CCI), depressive symptoms (CES-D) and compound cognitive function (NP=the sum of CVVLT, BNT, VFT, CFT, DB and CDT scores) were hypothesised as possible mediators between pain and frailty. In the mediation analysis, CCI, CES-D and number of adapted frailty criteria fulfilled were designated as numerical variables for linear regression analysis. All tests were adjusted for age, sex and duration of education. If the 95% CI of the indirect effect does not span zero, the indirect effect is significantly different from zero at P<0.05 (two-tailed).[39]

RESULTS

Among 1682 ILAS participants without cognitive impairment, impaired ADL/IADL or known cancer, 41 (6.18%) subjects older than 65 years, and 16 (1.57%) aged 50–64 years met the criteria of frailty. Pain severity positively correlated to frailty severity in the older group (table 1), among whom age and female predominance significantly increased with the severity of frailty. Both CCI and CES-D scores also increased with the degree of frailty, suggesting that frailty was associated with more

multimorbidity and depressive symptoms. Impairment in global cognitive function and individual domains likewise increased with more severe frailty.

Conversely, the pain score in younger subjects was not associated with frailty. However, similar to the older group, the results of educational level, CCI, CES-D, MMSE and each cognitive function domain all differed significantly between frailty groups.

Table 2 shows the correlation coefficients between the frailty and pain scores, and between frailty and pain for each neuropsychological test; among subjects aged 65 years or older, neuropsychological test scores correlated negatively with frailty scores. In cognition-pain comparisons, only language (BNT), visuospatial (CFT) and executive function (DB and CDT) were significantly and negatively correlated with pain. However, pain correlated positively with frailty. Similarly, in younger subjects, all neuropsychological scores were negatively correlated with frailty scores. However, the cognition-pain relationship differed; only language (BNT and CVF), visuospatial (CFT) and executive function (DB) were significant associated with pain. Although the pain and frailty scores were negatively correlated, this association was not statistically significant.

Results of multinomial logistic regression to identify factors independently associated with frailty are shown in table 3. We found no statistically significant association between pain and frailty in subjects younger than 65 years, whereas moderate-to-severe pain was associated with frailty in the older group. Compared with subjects aged 65–74 years, those older than 75 were more than twice as likely to be prefrail and approximately seven times more likely to be frail. Women were also more likely to be prefrail or frail. Depressed mood (CES-D) was only associated with frailty relative to subjects without depressive symptoms. Prefrailty was associated with DB in the executive function domain. People with visuospatial impairment (CFT) were more likely to be frail, and those with moderate-to-severe pain were threefold more likely to be frail than people without.

Figure 1 shows the mediation analysis of the inter-relationships between cognition, multimorbidity and depressive symptoms in the pain–frailty nexus, adjusted for age, sex and education level. Pain score was associated with frailty score in the linear regression model: no significant indirect effect of BNT on the pain–frailty relationship was evident. Likewise, there were no significant mediation effects of CFT, DB and CDT on the pain–frailty relationship.

After controlling for mediation by comorbidity (CCI), depression (CES-D) and NP score and covariates (age, sex, educational level), the direct effect of pain on frailty was 0.076 (P=0.042); CES-D had a significant indirect effect in mediating the pain–frailty relationship, but the mediation effects of CCI and NP were not significant. Compared with the total direct effects after controlling for mediators, depressive symptoms contributed to an indirect effect of 29.1% on the pain–frailty relationship.

Table 1 Basic characteristics according to age and frailty status

	All (n=663)	Robust (n=341)	Prefrail (n=281)	Frail (n=41)	P value
Age ≥ 65 years					
Pain	1.07 (0.96)	0.96 (0.82)	1.13 (0.86)		<0.001
Age (years)	73.13 (5.11)	72.17 (4.91)	73.74 (5.00)	76.91 (5.30)	<0.001
Male sex (%)	354 (53.4)	232 (68.0)	114 (40.6)	8 (19.5)	<0.001
Body mass index	24.71 (3.44)	24.54 (3.04)	24.88 (3.77)	24.92 (4.04)	0.446
Education (years)	3.28 (4.32)	4.19 (4.71)	2.49 (3.75)	1.07 (2.17)	<0.001
Charlson Comorbidity Index	1.58 (1.33)	1.42 (1.25)	1.69 (1.39)	2.12 (1.29)	<0.001
CES Depression Scale	2.52 (4.43)	1.78 (2.93)	2.56 (4.13)	8.49 (9.57)	<0.001
Mini-Mental State Examination	23.91 (3.93)	24.95 (3.46)	23.17 (3.96)	20.34 (4.27)	<0.001
Chinese Version Verbal Learning Test	5.51 (2.30)	5.79 (2.17)	5.40 (2.37)	3.93 (2.31)	<0.001
Boston Naming Test	8.26 (2.83)	8.90 (2.79)	7.75 (2.72)	6.44 (2.36)	<0.001
Verbal Fluency Test	13.24 (4.35)	14.16 (4.54)	12.54 (3.75)	10.41 (4.48)	<0.001
Taylor Complex Figure Test	26.06 (9.01)	28.43 (6.94)	24.45 (9.62)	17.36 (11.91)	<0.001
Digit Backward Test	2.35 (1.87)	2.84 (1.79)	1.90 (1.82)	1.37 (1.62)	<0.001
Clock Drawing Test	6.05 (2.84)	6.71 (2.54)	5.59 (2.90)	3.78 (2.98)	<0.001
	(n=1019)	(n=668)	(n=335)	(n=16)	P value
Age 50 – 64 years					
Pain	0.92 (0.85)	0.95 (0.85)	0.86 (0.86)	1.06 (0.93)	0.210
Age (years)	57.21 (4.06)	56.88 (4.00)	57.77 (4.10)	59.15 (4.62)	0.001
Male sex (%)	452 (44.4)	294 (44.0)	150 (44.8)	8 (50.0)	0.877
Body mass index	24.97 (3.65)	24.82 (3.60)	25.05 (3.70)	25.35 (4.71)	0.785
Education (years)	8.36 (4.45)	8.63 (4.31)	7.95 (4.71)	5.88 (3.50)	0.006
Charlson Comorbidity Index	0.52 (0.86)	0.45 (0.77)	0.63 (0.95)	1.19 (1.33)	<0.001
CES Depression Scale	2.04 (4.16)	1.37 (2.57)	2.89 (4.83)	12.19 (14.64)	<0.001
Mini-Mental State Examination	27.49 (2.45)	27.66 (2.24)	27.23 (2.72)	25.63 (2.45)	<0.001
Chinese Version Verbal Learning Test	7.12 (1.66)	7.22 (1.57)	6.95 (1.75)	6.50 (2.56)	0.016
Boston Naming Test	11.25 (2.63)	11.54 (2.50)	10.76 (2.79)	9.38 (2.13)	<0.001
Verbal Fluency Test	15.55 (4.70)	15.82 (4.79)	15.12 (4.49)	13.25 (4.20)	0.012
Taylor Complex Figure Test	32.51 (4.85)	32.85 (4.39)	32.00 (5.31)	28.63 (9.43)	<0.001
Digit Backward Test	4.24 (1.69)	4.35 (1.67)	4.05 (1.73)	3.25 (1.53)	0.002
Clock Drawing Test	8.48 (1.90)	8.64 (1.78)	8.23 (2.05)	6.63 (2.50)	<0.001

All values show mean (SD), except sex, number (%).
CES, Center for Epidemiologic Studies.

DISCUSSION

This study shows that, in community-dwelling adults older than 50 years without cognitive or functional impairment, moderate-to-severe pain is associated with frailty in those older than 65 years, but not in those aged 50–64 years. Depressive symptoms partially mediate the pain–frailty nexus, whereas multimorbidity and cognitive function do not.

The mean age of subjects in prior cross-sectional studies of the association between pain and frailty ranged from 68 to 79.5 years.[10–12 40 41] In the longitudinal study by Wade et al, the mean age was 58.4 among people without frailty at baseline or follow-up, but 67.4 among those who became frail during the observation period[13]; the prevalence

and incidence of frailty were higher in older adults and increased among subjects with chronic widespread pain, implying that pain exerts a greater effect on frailty in older adults than younger ones. This may explain why the pain–frailty association in our study was only evident in older subjects.

Factors associated with frailty in previous studies include old age, female sex, low educational level, multimorbidity, depression and cognitive impairment.[6 7] Blyth et al described the relationship between intrusive pain and frailty in community-dwelling older adults; pain remained associated with prefrailty and frailty after controlling age, comorbidity, educational level, arthritis and depressive mood.[10 12] Likewise, among older adults

Table 2 Correlations between neuropsychological test scores and frailty/pain

Age ≥65 years	Frailty score		Pain score	
	Pearson's correlation coefficient	P value	Pearson's correlation coefficient	P value
Mini-Mental State Examination	−0.363	<0.001	−0.067	0.083
Chinese Version Verbal Learning Test	−0.196	<0.001	−0.055	0.154
Boston Naming Test	−0.275	<0.001	−0.079	0.042
Verbal Fluency Test	−0.261	<0.001	−0.024	0.542
Taylor Complex Figure Test	−0.352	<0.001	−0.080	0.041
Digit Backward Test	−0.291	<0.001	−0.109	0.005
Clock Drawing Test	−0.300	<0.001	−0.125	0.001
Pain score	0.193	<0.001		
Age 50–64 years				
Mini-Mental State Examination	−0.132	<0.001	−0.048	0.124
Chinese Version Verbal Learning Test	−0.097	0.002	−0.049	0.117
Boston Naming Test	−0.179	<0.001	−0.068	0.031
Verbal Fluency Test	−0.094	0.003	−0.079	0.011
Taylor Complex Figure Test	−0.127	<0.001	−0.103	0.001
Digit Backward Test	−0.119	<0.001	−0.111	<0.001
Clock Drawing Test	−0.159	<0.001	−0.052	0.096
Pain score	−0.029	0.350		

in the second wave of the Canadian Study of Health and Aging, Shega *et al* found pain to be independently associated with prefrailty and frailty.[12] In our study too, the association of pain and frailty was significant among older adults. Besides pain, older age, female sex, depression and impaired non-memory cognitive domains were also associated with frailty. These findings are congruent with previous studies. However, the cross-sectional design did not allow us to establish a causal relationship between pain and frailty. The European Male Ageing Study (EMAS) longitudinal study showed chronic widespread pain to be associated with increased risk of frailty in older men.[13] Although many models have been proposed to explain how pain affects frailty, further studies are needed to elucidate the mechanism.

Shega *et al* have proposed a concept of 'pain homeostenosis', which denotes declining biological, psychological and social capacity and function with advancing age, with reduced capacity to cope with stressors and consequent development of frailty.[12] Weiner *et al* found that neuropsychological performance mediates the relationship between pain and physical performance,[23] which prompted us to investigate the effect of cognitive function in mediating the pain–frailty nexus.

Patients suffering pain often have some degree of cognitive impairment; for example, 'fibro-fog' in fibromyalgia. The pain-cognition relationship has been widely studied[14–16]; a systemic review, summarised pain-related cognitive dysfunctions including attention, working memory, executive function, visuospatial and language.[16] Leurding *et al* also reported that structural changes in the frontal brain and anterior cingulate cortex were associated with impaired working memory and non-verbal long-term memory in fibromyalgia,[15] indicating that pain is associated with both cognitive function and cognition-related brain structure changes. In this study, the result of pain score being negatively associated with neuropsychological scores echoed this concept.

The relationship between frailty and cognitive function is bidirectional. Cross-sectional studies have reported that frail adults have proportionally more cognitive impairment than prefrail or robust older adults.[7 17 18] We found the risk of having one or more cognitive impairment to be higher among prefrail and frail older adults in the ILAS cohort, compared with robust ones.[17] The result is the same in the present study. In other longitudinal studies, frailty predicted cognitive decline and incident dementia.[42–44] On the other hand, cognitive impairment could also predict further frailty.[45]

To our knowledge, no previous reports have specifically discussed the associations between cognitive function, frailty and pain. Weiner *et al* investigated how pain, neuropsychological performance and physical performance are interrelated; pain was associated with memory, language, attention and executive function.[23] In a confirmatory regression analysis, the association of pain and physical performance disappeared after controlling for neuropsychological performance. Thus, Weiner *et al* concluded that neuropsychological performance mediates the effect of pain on physical performance.[23] Similarly, we found that pain was associated with language, visuospatial and executive function in

Table 3 Multinomial logistic regression of factors associated with different frail status in people older than 65 years

	Model 1†		Model 2‡		Model 3§	
	Prefrail OR (95% CI)	Frail OR (95% CI)	Prefrail OR (95% CI)	Frail OR (95% CI)	Prefrail OR (95% CI)	Frail OR (95% CI)
Age 50–64 years						
Moderate-to-severe pain	0.8 (0.6 to 1.1)	1.7 (0.6 to 4.7)				
Age ≥65 years						
Moderate-to-severe pain	1.4 (0.9 to 1.9)	4.4 (2.2 to 8.7)*	1.1 (0.8 to 1.6)	2.8 (1.3 to 5.9)*	1.1 (0.8 to 1.6)	3.0 (1.3 to 6.6)*
Age ≥75 years			2.2 (1.5 to 3.3)*	7.3 (3.2 to −17.1)*	2.2 (1.5 to 3.4)*	6.8 (2.8 to 16.5)*
Female sex			3.2 (2.2 to 4.6)*	9.0 (3.6 to 22.8)*	2.9 (2.0 to 4.2)*	6.0 (2.3 to 15.9)*
Education ≥6 years			0.7 (0.5 to 0.9)	0.3 (0.1 to 1.1)	0.8 (0.5 to 1.2)	0.3 (0.1 to 1.2)
Charlson Comorbidity Index ≥2			0.9 (0.6 to 1.3)	1.3 (0.5 to 3.1)	0.9 (0.6 to 1.3)	1.3 (0.5 to 3.1)
CES Depression Sale ≥16			3.5 (0.7 to 17.7)	40.1 (7.2 to 223.1)*	3.7 (0.7 to 18.3)	43.9 (7.2 to 265.9)*
Boston Naming Test					1.3 (0.7 to 2.3)	1.0 (0.3 to 2.9)
Taylor Complex Figure Test					1.7 (0.9 to 2.9)	5.1 (2.0 to 13.2)*
Digit Backward Test					1.7 (1.1 to 2.5)*	1.3 (0.6 to 3.1)
Clock Drawing Test					0.8 (0.4 to 1.6)	2.5 (0.9 to 6.8)

*P<0.05.
†Unadjusted.
‡Adjusted for age, gender, educational year, comorbidity and depressive mood.
§Adjusted for covariates in model 2 and plus cognitive functions significantly related to pain in Pearson's correlation tests.
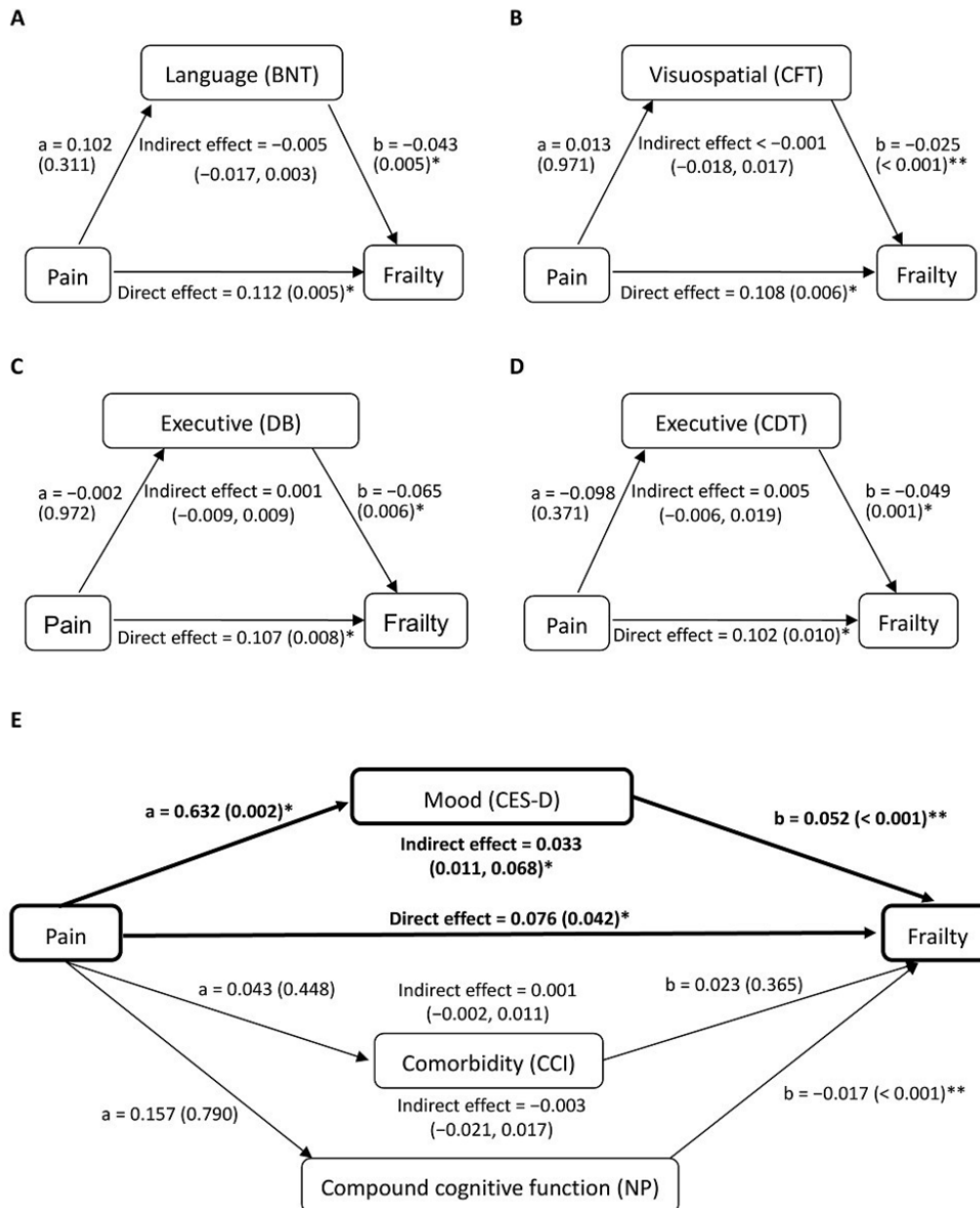CES, Center for Epidemiologic Studies.

Figure 1 Mediator analysis of cognitive function, comorbidity and depression in the pain–frailty nexus in people ≥65 years (n=663). Panels A to D show the single-step single mediator models of the Boston Naming Test (BNT), Taylor Complex Figure Test (CFT), Digit Backward Test (DB) and Clock Drawing Test (CDT), respectively on the pain–frailty nexus. Panel E shows the single-step multiple mediator model of multimorbidity (CCI), depressive symptoms (CES-D) and sum of neuropsychological scores (NP). All mediator analyses were adjusted for age, sex and educational level. Standard coefficients were shown along with their estimated P values: 'a' is the linear regression coefficient of the pain–moderator association; 'b' is that of the moderator–frailty association; 'c' is the total effect of pain on frailty. Bold lines denote significant association. CCI, Charlson Comorbidity Index; CES-D, Center for Epidemiologic Studies Depression Scale. *P<0.05, **P<0.001.

subjects older than 65 years. We used mediation analysis by the bootstrapping method to analyse the relationships between pain, frailty and cognitive function. Although unadjusted BNT, CFT, DB and CDT partially mediated pain–frailty, the mediator effect of all cognitive function domains disappeared after adjusting for age, sex and education level; the relationship between pain and cognitive functions also became non-significant after

adjustment. Therefore, we suppose that age influences both the pain–frailty and pain–cognition nexuses. By controlling for age, we have revealed the true relationship between pain, frailty and cognitive function.

Comorbidity is also associated with frailty. Chen *et al* reported higher incidence of comorbidity in frail older adults.[6] The Assessing frailty in elderly people in Lleida (FRALLE) Survey showed comorbidity to be an

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independent risk factor for frailty,[7] and in the Concord Health and Ageing in Men Project (CHAMP) study, older people with more than four cormobidities had a higher risk of intrusive pain than non-frail older adults with a low comorbid burden.[10] Because the ILAS participants in our study were relatively healthy, the association of comorbidity and frailty was not significant in either multivariate or mediation analysis.

Pain–depression and depression–frailty relationships have been extensively studied[46–48]; Landi *et al* reported higher risk of depressive symptoms in frail older adults with pain,[46] and Herrick *et al* found that moderate-to-severe hip pain following a fracture was associated with analgesics use, muscle weakness and depression.[47] A systemic review, correlated depressive symptoms and poorer depression outcome with moderate-to-severe pain, functional impairment and poor treatment response.[19]

Regarding depression–frailty, Parmelee *et al* followed 1245 older long-term care facility residents and discovered that depressive mood predicted further health deterioration.[48] Another study, of 1827 community-dwelling older adults, found that frail older adults without depression at baseline, had 3.75 times higher risk of developing depression during follow-up compared with non-frail older adults.[49] A systematic review of depression and frailty concluded that they had a bidirectional association: frailty and functional impairment were risk factors of depression, and depression was associated with incident frailty.[50]

Although we tried to explore possible mediators between pain and frailty, the cross-sectional study design precluded determination of any causal relationship between them; further longitudinal research is needed to answer this question. In addition, this study cohort comprised community-dwelling older adults without cognitive or functional impairment, who were relatively healthier subjects among their community; therefore, the findings may not apply to institutionalised older adults or those with cognitive impairments or disability. Mediators of the pain–frailty nexus may differ in elderly people with poor cognitive and/or physical function. Another limitation was that pain in this study was defined as moderate pain during the past 4 weeks; consequently, such pain was general, without a specific painful site, and could not be classified as either acute or chronic pain.

CONCLUSIONS

In cognitively and functionally sound community-dwelling adults aged 50 years or older, pain was only associated with frailty in people aged ≥65 years, and not in those aged 50–64 years. Pain had a direct effect on frailty, besides which, pain indirectly affected frailty via depression; however, the mechanism by which depression mediates the relationship between pain and frailty requires further research.

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