Retrospective Study

Chronic Pain Increases the Risk of Dementia: A Nationwide Population-Based Cohort Study

Pei-Hsin Kao, MD[1], Fong-Lin Jang, MD[1], Chung-Han Ho, PhD[2,3], Yi-Chen Chen, MS[2], Chien-Chin Hsu, MD, PhD[4,5], Hung-Jung Lin, MD, MBA[4,6], Jhi-Joung Wang, MD, PhD[7], and Chien-Cheng Huang, MD, PhD[4,8,9]

From: [1]Department of Psychiatry, Chi Mei Medical Center, Tainan, Taiwan; [2]Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan; [3]Department of Hospital and Health Care Administration, Chia Nan University of Pharmacy and Science, Tainan, Taiwan; [4]Department of Emergency Medicine, Chi Mei Medical Center, Tainan, Taiwan; [5]Department of Biotechnology, Southern Taiwan University of Science and Technology, Tainan, Taiwan; [6]Department of Emergency Medicine, Taipei Medical University, Taipei, Taiwan; [7]Department of Anesthesiology, Chi Mei Medical Center, Tainan, Taiwan; [8]Department of Senior Services, Southern Taiwan University of Science and Technology, Tainan, Taiwan; [9]Department of Environmental and Occupational Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan

Address Correspondence:
Chien-Cheng Huang, MD, PhD
Department of Emergency Medicine, Chi Mei Medical Center, 901 Zhonghua Road, Yongkang District, Tainan City 710, Taiwan
E-mail: chienchenghuang@yahoo.com.tw

Disclaimer: This study was supported by Grant CMHCR11051 from the Chi Mei Medical Center.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 03-08-2020
Revised manuscript received: 02-08-2021
Accepted for publication: 02-10-2021

Free full manuscript:
www.painphysicianjournal.com

Background: Chronic pain (CP) may increase the risk of cognitive impairment; however, the association between CP and dementia is still unclear.

Objectives: Therefore, we conducted this study to clarify the association between CP and dementia.

Study Design: Retrospective cohort study.

Settings: Nationwide population based.

Methods: This study recruited 27,792 patients (≥ 50 years) with CP from the Taiwan National Health Insurance Research Database between January 1, 2000, and December 31, 2015, as the study cohort. The comparison cohort consists of patients without CP who were matched 1:1 for age, gender, and index date with the study cohort. A comparison of the risk of dementia between the two cohorts was performed by following up until 2015.

Results: The prevalence of CP was 13.4% in the population aged ≥ 50 years. Patients with CP had a higher risk of dementia than those without CP (adjusted hazard ratio [AHR]: 1.21; 95% confidence interval [CI]: 1.15-1.26). Compared with the other age subgroups, the 50-64 years age group with CP had the highest risk of dementia (AHR: 1.28; 95% CI: 1.14-1.43). The impact of CP on the increased risk of dementia was more prominent in the younger age subgroup and decreased with aging. The increased risk of dementia in patients with CP was persistent, even following up for more than 5 years (AHR: 1.19; 95% CI: 1.12-1.26).

Limitations: Using "analgesics use at least 3 months" as the surrogate criteria of CP may underestimate the diagnosis of CP.

Conclusions: CP was associated with a higher risk of dementia, especially in the 50-64 years age group. Early treatment of CP for the prevention of dementia is suggested.

Key words: Chronic pain. cognitive impairment, dementia

Pain Physician 2021: 24:E849-E856

Chronic pain (CP) is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, which has persisted beyond normal tissue healing time, assumed to be 3 months (1). It is estimated that CP affects 31% of the adult population worldwide (2). CP

is more common in older adults, especially in women (3,4). Previous studies reported that CP was prevalent in 29.9%-36.2% of older Australians, 55% of older Swiss, and 69.8% of older German (5-7). In nursing home residents, CP is more common and estimated to comprise up to 82.9% (8). CP is usually underdiagnosed and undertreated, which leads to a significant mental burden on individuals and an economic burden on society (3,9).

The origins of CP are diverse because of its complex pathophysiology. It could be neuropathic pain (direct damage to the nervous system), inflammatory pain (peripheral inflammatory insults), cancer pain (tumor progression), and dysfunctional pain (unclear origins, e.g., fibromyalgia) (10). Common causes of CP include cancer, spinal disorders, osteoarthritis, fibromyalgia, migraine, postherpetic neuralgia, and diabetic neuropathy (11).

According to previous studies, CP is found to be associated with an increased risk of depression (12-16). Recent studies showed that pain may also have a negative impact on cognition. A cross-section study that enrolled 765 older patients in Boston showed that there was a significant relationship between pain interference and impaired general cognitive function (17). The study was to investigate "pain" (17), which is different from CP (i.e., a longer pain duration: ≥ 3 months). In addition, the causal relationship might not be clear in a cross-section study. Impaired cognitive function and memory are not equal to dementia. Another cohort study recruiting 10,065 American older adults reported that persistent pain was associated with memory decline (4). The study recruited patients ≥ 62 years (4); however, the onset of dementia may be more earlier (18). The pain severity in these studies (4,17) was evaluated by the patients' subjective feelings, which are not an objective outcome measurement. Furthermore, the subtypes of dementia, including Alzheimer's disease and vascular dementia, are not studied. Therefore, we conducted this nationwide population-based cohort study recruiting younger patients to delineate these issues.

Methods

Data Source

Taiwan's National Health Insurance (NHI), the country's compulsory social health insurance, was launched in March 1995. It includes more than 99% of 23.74 million residents in Taiwan. The National Health Research Institute (NHRI), a nonprofit foundation, published the National Health Research Database (NHIRD), which contained all the records of NHI from the start (19). NHRI used a systemic sampling method and issued a series of NHIRD subsets, called the Longitudinal Health Insurance Database (LHID), which contained complete data of all medical services offered to a million randomly sampled people from the national population. This study used the LHID 2000, which retrieved individuals from NHIRD enrollment files in 2000. After NHRI's conformation, there were no significant differences in age, gender, health care costs, geographic distribution, and annual turnover rate between the LHID 2000 and NHIRD.

Study Design, Setting, and Patients

We recruited all patients (aged ≥ 50 years) with CP between January 1, 2000, and December 31, 2015, from the LHID 2000 as the study cohort (Fig. 1). Those who were younger than 50 years were excluded because dementia rarely occurred in this age population. CP was defined as patients who used analgesics for at least 3 months (20-22). The analgesics mentioned in this study included nonsteroidal anti-inflammatory drugs (excluding aspirin), acetaminophen, and opioids. We recruited patients without CP as the comparison cohort by exactly matching them based on the same age, gender, and index date at a ratio of 1:1 with the study cohort. The index date was the date that the patient with CP fit the CP criteria. Patients with known dementia before the index date were excluded. Dementia was identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis classifications of 290, 294.1, 294.2, or 331 with at least one hospitalization or 3 outpatient clinic visits.

Definitions of the Variables

We classified patients into 4 age subgroups, including 50-64, 65-74, 75-84, and ≥ 85 years (23). Two major subtypes of dementia, Alzheimer's disease and vascular dementia, were also analyzed. Alzheimer's disease and vascular dementia were defined as ICD-9-CM of 331.0 and 290.4, respectively. We included comorbidities that were potential confounding factors for dementia in the analyses: hypertension (ICD-9-CM codes 401-405), diabetes (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), depression (ICD-9-CM codes 296.2, 296.3, and 311), coronary artery disease (ICD-9-CM codes 410-414), malignancy (ICD-9-CM codes 140-208), stroke (ICD-9-CM codes 436-438), congestive

heart failure (ICD-9-CM code 428), chronic obstructive pulmonary disease (ICD-9-CM code 496), liver disease (ICD-9-CM codes 570-576), renal disease (ICD-9-CM codes 580-593), alcoholism (ICD-9-CM codes 291, 303, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, and V113), and head injury (ICD-9-CM code 959.01). All the diseases were defined as having the diagnoses with at least one hospitalization or 3 outpatient clinic visits.

Main Outcome Measures

We compared the risk of dementia, including 2 major subtypes (Alzheimer's disease and vascular dementia), between the 2 cohorts by following up until 2015.

Ethical Statements

This study protocol was approved by the Institutional Review Board of Chi Mei Medical Center. Informed consent was waived because we used deidentified secondary data from the NHIRD. The waiver does not affect the rights and welfare of the patients.

Statistical Analyses

When comparing the demographic data between the 2 cohorts, we used an independent t test for continuous variables and Pearson χ^2 tests for categorical variables. We used competing risk survival analysis to compare the risk of dementia between the two cohorts. Kaplan-Meier analysis and the log-rank test for the risk of dementia were also done. SAS 9.4 statistical software (SAS Institute Inc., Cary, NC) was used for all statistical analyses. The significance level was set at 0.05 (2-tailed).

Results

A total of 27,792 patients with CP were recruited into this study (Fig. 1). In the age population of ≥ 50 years, the prevalence of CP was 13.4% (27,792/206,700). The mean age was 66.5 years, and most patients with CP were aged between 50 and 74 years (77.6%; Table 1). In patients with CP, women have a higher percentage than men. Patients with CP had a higher prevalence of all comorbidities than those without CP, including hypertension, diabetes, hyperlipidemia, depression, coronary artery disease, malignancy, stroke, congestive heart failure, chronic obstructive pulmonary disease, liver diseases, renal diseases, alcoholism, and head injury. Competing risk survival analysis showed that patients with CP had a higher risk of dementia than those without CP (adjusted hazard ratio [AHR]: 1.21; 95% confidence interval [CI]: 1.15-1.26) after adjusting for all the comorbidities (Table 2). The risk difference of Alzheimer's disease and vascular dementia between

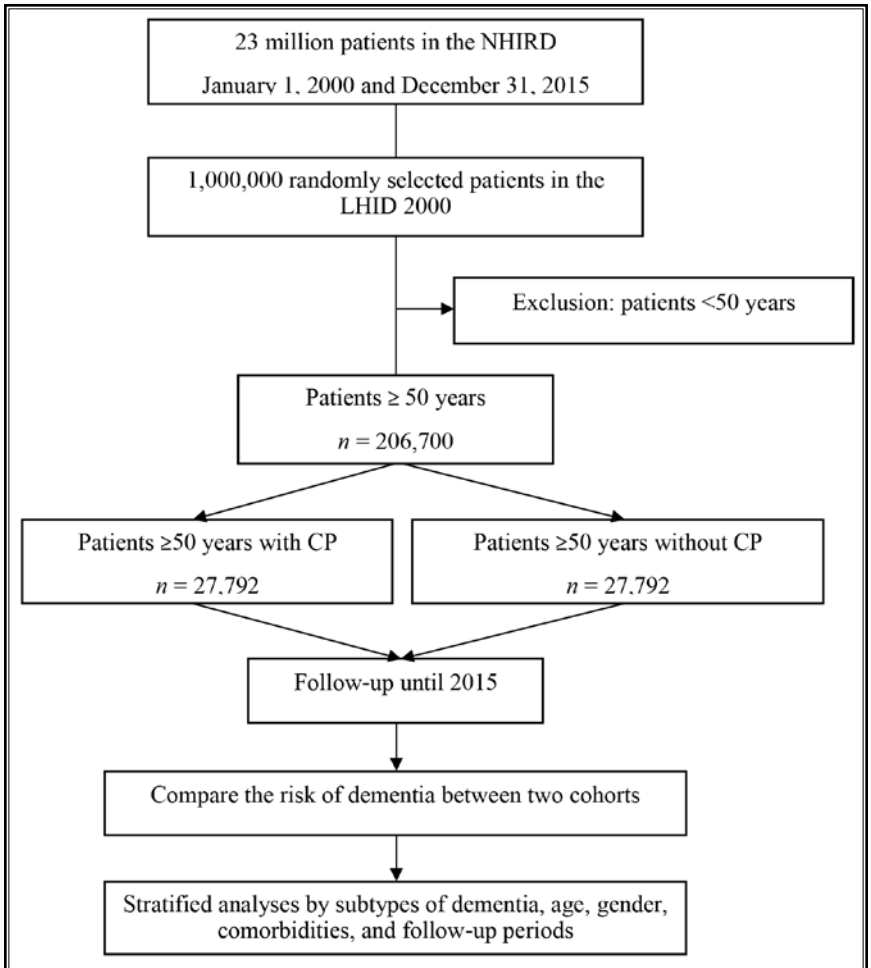

Fig. 1. *Study flowchart for comparing the risk of dementia between patients with and without CP. NHIRD, National Health Research Database; LHID, Longitudinal Health Insurance Database; CP, chronic pain.*

Table 1. *Comparison of demographic characteristics between patients with and without CP.*

Characteristics	With CP (n = 27,792) n (%)	Without CP (n = 27,792) n (%)	*P*-value
Age, years (mean ± SD)	66.5 ± 9.3	66.5 ± 9.3	> 0.999
Age subgroup (years)			
50-64	11,877 (42.7)	11,877 (42.7)	> 0.999
65-74	9,702 (34.9)	9,702 (34.9)	
75-84	5,613 (20.2)	5,613 (20.2)	
≥ 85	600 (2.2)	600 (2.2)	
Gender			
Male	12,087 (43.5)	12,087 (43.5)	> 0.999
Female	15,705 (56.5)	15,705 (56.5)	
Comorbidity			
Hypertension	13,589 (48.9)	8,256 (29.7)	< 0.001
Diabetes	5,875 (21.1)	3,551 (12.8)	< 0.001
Hyperlipidemia	3,698 (13.3)	2,150 (7.7)	< 0.001
Depression	666 (2.4)	262 (0.9)	< 0.001
Coronary artery disease	4,422 (15.9)	2,583 (9.3)	< 0.001
Malignancy	1,725 (6.2)	804 (2.9)	<0.001
Stroke	3,244 (11.7)	1,222 (4.4)	< 0.001
Congestive heart failure	2,858 (10.3)	1,656 (6.0)	< 0.001
Chronic obstructive pulmonary disease	4,233 (15.2)	2,167 (7.8)	< 0.001
Liver disease	2,951 (10.6)	1,704 (6.1)	< 0.001
Renal disease	2,154 (3.9)	1,165 (4.2)	< 0.001
Alcoholism	442 (1.6)	192 (0.7)	< 0.001
Head injury	54 (0.2)	28 (0.1)	0.004

Data are presented as number (percentage) or mean ± SD. CP, chronic pain; SD, standard deviation.

the 2 cohorts was not significant. The increased risk of dementia was significant between 50 and 84 years of age subgroups but not significant in the age subgroup of ≥ 85 years. The AHRs of 50-64, 65-74, and 75-84 years were 1.28 (95% CI: 1.14-1.43), 1.20 (95% CI: 1.12-1.28), and 1.17 (95% CI: 1.08-1.26), respectively. Stratified analyses showed that the increased risk was significant in the subgroups of both gender and comorbidities of hypertension, diabetes, hyperlipidemia, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, and liver disease. Patients with CP had an increased risk of dementia than those without CP during the entire follow-up period, even more than 5 years (AHR: 1.19; 95% CI: 1.12-1.26). Compared with longer follow-up period, the increased risk of dementia was more prominent in the shorter follow-up period. The Kaplan-Meier method with log-rank tests showed that patients with CP had a higher cumulative incidence rate of dementia, including subtypes with Alzheimer's disease and vascular dementia, than those without CP during the follow-up period (Fig. 2).

Discussion

This large nationwide population-based cohort study showed that 13.4% of the patients aged ≥ 50 years had CP. Among patients, CP was more common in women than in men. Also, those with CP had a higher risk of dementia during the entire follow-up period, even after 5 years, compared with patients without CP. The increased risk was more prominent in the shorter follow-up period than in the longer follow-up period. In the analysis of age subgroups, the increased risk of dementia was more prominent in the 50-64 years, followed by the 65-74 and 75-84 years. The difference in dementia risk in the ≥ 85 years age subgroup was not significant.

The possible mechanisms for the association between CP and dementia are disruptions of attention and memory traces (24-26), decision-making task impairment, processing speed and psychomotor speed (27,28), affective stress that might provoke endogenous cortisol associated with hippocampal degeneration and memory dysfunction (4,29-32), and underlying comorbidities (33-36). CP may contribute to chronic attention and memory interruption, decision-making ability impairment, and subsequent widespread pain and movement avoidance and social contact withdrawal (24,27). The undertreatment of CP results in the consequence of disability and more pain, and therefore more disability and increased risk for impaired cognitive function (24,27). CP may increase the production of endogenous cortisol via the hypothalamic-pituitary-adrenal axis, which contributes to neuronal loss in the hippocampus and prefrontal cortex (32). The association among underlying comorbidities, CP, and dementia is complex and probably multidirectional. For example, diabetes may contribute to diabetic neuropathy, a common cause of CP (11). Our study showed that CP increased the risk of dementia. However, diabetes itself may also increase the risk of dementia via vascular disease and alterations in glucose, insulin, and amyloid metabolism (11). The complex relationship needs further studies for clarification.

Altered brain function, brain chemistry, and

Table 2. *Comparison of the risk for dementia between patients with and without CP using competing risk survival analysis.*

Variable	With CP		Without CP		Crude HR (95% CI)	AHR (95% CI)*	*P* value†
	Mortality (n, %)	Dementia (n, %)	Mortality (n, %)	Dementia (n, %)			
Overall analysis	9,521 (34.3)	4,616 (16.6)	7,090 (25.5)	3,740 (13.5)	1.27 (1.21-1.32)	1.21 (1.15-1.26)	< 0.001
Subtypes of dementia							
Alzheimer's disease	11,820 (42.5)	231 (0.8)	8846 (31.8)	201 (0.7)	1.15 (0.95-1.39)	1.16 (0.96-1.41)	0.128
Vascular dementia	11,622 (41.8)	527 (1.9)	8708 (31.3)	427 (1.5)	1.24 (1.09-1.41)	1.09 (0.96-1.24)	0.208
Stratified analysis							
Age (years)							
50-64	2,823 (23.8)	896 (7.5)	1,352 (11.4)	592 (5.0)	1.54 (1.39-1.71)	1.28 (1.14-1.43)	< 0.001
65-74	3,412 (35.2)	1,970 (20.3)	2,706 (27.9)	1,589 (16.4)	1.28 (1.20-1.37)	1.20 (1.12-1.28)	< 0.001
75-84	2,873 (51.2)	1,598 (28.5)	2,649 (47.2)	1,412 (5.1)	1.17 (1.09-1.26)	1.17 (1.08-1.26)	< 0.001
≥ 85	413 (68.8)	152 (25.3)	383 (63.8)	147 (24.5)	1.06 (0.85-1.33)	1.05 (0.83-1.34)	0.688
Gender							
Male	5,004 (41.4)	1,930 (16.0)	3,862 (32.0)	1,545 (12.8)	1.28 (1.19-1.37)	1.22 (1.14-1.31)	< 0.001
Female	4,517 (28.8)	2,686 (17.1)	3,228 (20.6)	2,195 (14.0)	1.26 (1.19-1.33)	1.19 (1.13-1.27)	< 0.001
Comorbidity							
Hypertension	4,945 (36.4)	2,618 (19.3)	2,681 (32.5)	1,463 (17.7)	1.09 (1.03-1.17)	1.16 (1.08-1.23)	< 0.001
Diabetes	2,582 (44.0)	1,075 (18.3)	1,426 (40.2)	604 (17.0)	1.08 (0.98-1.19)	1.14 (1.03-1.26)	0.011
Hyperlipidemia	1,042 (28.2)	673 (18.2)	553 (25.7)	339 (15.8)	1.16 (1.01-1.32)	1.22 (1.07-1.40)	0.003
Depression	195 (29.3)	166 (24.9)	73 (27.9)	64 (27.8)	1.01 (0.76-1.35)	1.23 (0.91-1.67)	0.184
Coronary artery disease	1,777 (40.2)	935 (21.1)	1,008 (39.0)	507 (19.6)	1.10 (0.98–1.22)	1.19 (1.06-1.33)	0.002
Malignancy	1,113 (64.5)	197 (11.4)	382 (47.5)	100 (33.7)	0.92 (0.72-1.17)	1.02 (0.80-1.31)	0.848
Stroke	1,422 (43.8)	765 (23.6)	598 (48.9)	320 (26.2)	0.87 (0.77-1.00)	1.07 (0.93-1.22)	0.353
Congestive heart failure	1,592 (55.7)	574 (20.1)	928 (56.0)	305 (18.4)	1.10 (0.96-1.27)	1.17 (1.02-1.35)	0.029
Chronic obstructive pulmonary disease	1,929 (45.6)	791 (18.7)	958 (44.2)	370 (17.1)	1.11 (0.98-1.25)	1.15 (1.01-1.30)	0.033
Liver disease	1,196 (40.5)	462 (15.7)	618 (36.3)	205 (12.0)	1.34 (1.13-1.57)	1.39 (1.17-1.64)	< 0.001
Renal disease	1,110 (51.5)	333 (15.5)	558 (47.9)	174 (14.9)	1.04 (0.86-1.25)	1.12 (0.93-1.35)	0.218
Alcoholism	247 (55.1)	52 (11.8)	101 (52.6)	32 (16.7)	0.68 (0.44-1.06)	0.79 (0.48-1.28)	0.331
Head injury	20 (37.0)	10 (18.5)	5 (17.9)	9 (32.1)	0.55 (0.22-1.34)	0.66 (0.11-4.02)	0.656
Follow-up period (year)							
≤ 1	1,240 (4.5)	394 (1.4)	579 (2.1)	218 (0.8)	1.81 (1.54-2.14)	1.57 (1.32-1.87)	< 0.001
≤ 2	2,109 (7.6)	747 (2.7)	1,162 (4.2)	453 (1.6)	1.66 (1.48-1.86)	1.46 (1.29-1.65)	< 0.001
≤ 3	2,925 (10.5)	1,140 (4.1)	1,784 (6.4)	719 (2.6)	1.60 (1.46-1.76)	1.42 (1.29-1.56)	< 0.001
≤ 4	3,747 (13.5)	1,493 (5.4)	2,402 (8.6)	1,016 (3.7)	1.49 (1.37-1.61)	1.33 (1.23-1.45)	< 0.001
≤ 5	4,532 (16.3)	1,861 (6.7)	2,975 (39.6)	1,303 (4.7)	1.45 (1.35-1.55)	1.32 (1.22-1.42)	< 0.001
> 5	4,989 (23.3)	2,755 (12.9)	4,115 (17.5)	2,437 (10.4)	1.27 (1.20-1.34)	1.19 (1.12-1.26)	< 0.001

*Adjusted for all comorbidities, including hypertension, diabetes, hyperlipidemia, depression, coronary artery disease, malignancy, stroke, congestive heart failure, chronic obstructive pulmonary disease, liver diseases, renal diseases, alcoholism, and head injury. †AHR.
HR, hazard ratio; AHR, adjusted hazard ratio; CI, confidence interval; CP, chronic pain.

neocortical gray matter loss by CP may also explain the increased risk of dementia (37-39). CP alters the functional connectivity of cortical regions, the default mode network (DMN), which is known to be active at rest (37). The DMN is balanced by positive and negative correlations between activity in component brain regions (37). A study using functional magnetic resonance imaging showed that CP contributed to reduced

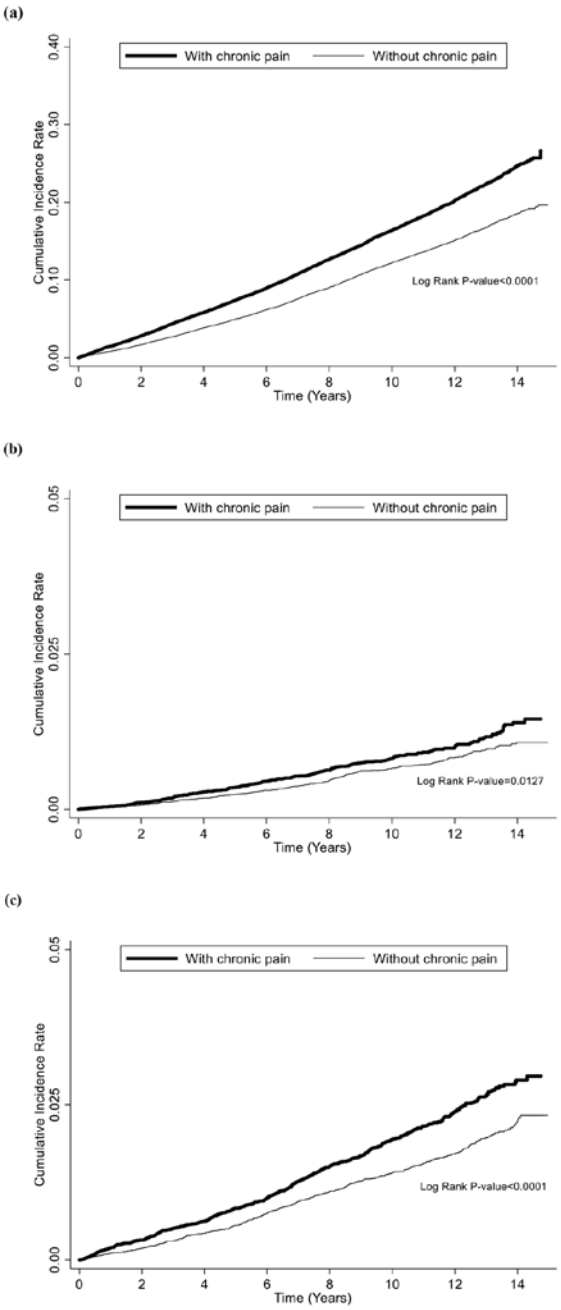

Fig. 2. *Kaplan-Meier curve and log-rank test for comparing the risk for (a) all dementia, (b) Alzheimer's disease, and (c) vascular dementia between patients with and without chronic pain.*

deactivation in several key DMN regions (37). The result suggests that CP had a widespread impact on overall brain function and that disruptions of the DMN may be the underlying mechanism for the cognitive and behavioral impairments accompanying CP (37). An in vivo proton magnetic resonance spectroscopy study revealed that CP alters human brain chemistry (38). N-acetyl aspartate and glucose in the dorsolateral prefrontal cortex were reduced, and the interrelationship between chemicals within and across brain regions was abnormal (38). A study using magnetic resonance imaging showed that patients with CP had 5%-11% less neocortical gray matter volume than the controls without CP (39). The longer pain duration, the more decreased gray matter volume (39).

Our study showed that the impact of CP on the risk of dementia was more prominent in the younger age subgroups and shorter follow-up period. The possible explanation for the age difference is that the older age subgroup has more comorbidities responsible for increased risk of dementia than the younger population. Therefore, the impact of CP on cognition may not be significant as the individual becomes older. The possible reason for the difference in follow-up periods is that the impact of CP on cognition may be more severe in the early years. As the follow-up period extends and the patient ages, the risk of dementia may be affected by more and more risk factors, including older age, increased comorbidity, and decreased physical activity (40). The competing risk survival analyses showed that the increased risk of dementia subtypes (i.e., Alzheimer's disease and vascular dementia) were not significant and different from the results by the Kaplan-Meier curve and log-rank test. The few case numbers of dementia subtypes may be the reason, and therefore, recruiting more patients may be helpful to clarify this issue in the future.

This study has several strengths. First, this was a nationwide population-based cohort study with a large sample size. Second, we investigated not only the risk of dementia but also the subtypes of dementia, including Alzheimer's disease and vascular dementia. There are some limitations as follows. First, we used "analgesics use at least 3 months" as the surrogate criteria of CP because there is no specific diagnostic code for CP in the NHIRD. Therefore, the diagnosis of CP may be underestimated. Patients with untreated pain who are not on any analgesics may carry a much higher risk for cognitive problems. The criteria for diagnosing patients with CP could have been more precise and stringent (rather than based on an analgesic prescription for 3 months or more) such as the presence of spinal disorders, cancer-related pain, and diabetic neuropathy, etc.

Second, the severity of CP and degree of dementia are not available in the NHIRD; therefore, we could not evaluate their association in this study. Third, the duration of pain, different analgesic use and dose (nonopioid vs. opioid analgesics), time to develop dementia after diagnosis of CP, patients using predominantly opioids, and for a prolonged duration of time were not evaluated because the main aim of this study is to investigate the association between CP and dementia. Fourth, despite matching age and gender and adjusting all the common comorbidities in this study, some confounding factors, including physical activities and social engagement, were not available. Further studies about these limitations are warranted.

Conclusions

This nationwide population-based cohort study showed that the risk of dementia increased in the patients with CP even following up for more than 5 years. The possible mechanisms are disruptions of attention and memory traces, decision-making task impairment, processing speed and psychomotor speed, affective stress that might provoke endogenous cortisol associated with hippocampal degeneration and memory dysfunction, underlying medical diseases, and altered brain function, brain chemistry, and neocortical gray matter loss. The impact of CP on dementia is more prominent in the middle-aged population (50-64 years) and not significant in the older elderly (≥ 85 years). We suggest an early assessment and intervention for CP to prevent the subsequent impact on cognition.

Declarations

Acknowledgment

We thank Enago for the English revision.

Availability of Data and Materials

Data are available from the National Health Insurance Research Database (NHIRD) published by the Taiwan National Health Insurance (NHI) Bureau. Because of legal restrictions imposed by the government of Taiwan in relation to the "Personal Information Protection Act," data cannot be made publicly available. Requests for data can be sent as a formal proposal to the NHIRD (http://nhird.nhri.org.tw).

Author Contributions

PHK and CCHuang designed and conceived this study and wrote the manuscript. CHH and YCC performed the statistical analysis and wrote the manuscript. FLJ, CCHsu, CCC, HJL, and JJW provided professional suggestions and wrote the manuscript. All authors read and approved the final manuscript.

References

1. British Medical Association. Chronic pain: supporting safer prescribing of analgesics [Internet]. 2017. Available from www.bma.org.uk/what-we-do/population-health/prescription-and-illicit-drugs/chronic-pain-supporting-safer-prescribing-of-analgesics
2. Steingrímsdóttir ÓA, Landmark T, Macfarlane GJ, Nielsen CS. Defining chronic pain in epidemiological studies: A systematic review and meta-analysis. *Pain* 2017; 158:2092-2107.
3. Breivik H, Eisenberg E, O'Brien T, OPENMinds. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health* 2013; 13:1229.
4. Whitlock EL, Diaz-Ramirez LG, Glymour MM, Boscardin WJ, Covinsky KE, Smith AK. Association between persistent pain and memory decline and dementia in a longitudinal cohort of elders. *JAMA Intern Med* 2017; 177:1146-1153.
5. Henderson JV, Harrison CM, Britt HC, Bayram CF, Miller GC. Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients. *Pain Med* 2013; 14:1346-1361.
6. Jakobsson U. The epidemiology of chronic pain in a general population: results of a survey in southern Sweden. *Scand J Rheumatol* 2010; 39:421-429.
7. Bauer H, Emeny RT, Baumert J, Ladwig KH. Resilience moderates the association between chronic pain and depressive symptoms in the elderly. *Eur J Pain* 2016; 20:1253-1265.
8. Zanocchi M, Maero B, Nicola E, et al. Chronic pain in a sample of nursing home residents: Prevalence, characteristics, influence on quality of life (QoL). *Arch Gerontol Geriatr* 2008; 47:121-128.
9. Reid MC, Eccleston C, Pillemer K. Management of chronic pain in older adults. *BMJ* 2015; 350:h532.
10. Gosselin RD, Suter MR, Ji RR, Decosterd I. Glial cells and chronic pain. *Neuroscientist* 2010; 16:519-531.
11. Fine PG. Long-term consequences of chronic pain: mounting evidence for pain as a neurological disease and parallels with other chronic disease states. *Pain Med* 2011; 12:996-1004.
12. Sheng J, Liu S, Wang Y, Cui R, Zhang X. The link between depression and chronic pain: Neural mechanisms in the brain. *Neural Plast* 2017; 2017: 9724371.
13. Delgado PL. Common pathways of depression and pain. *J Clin Psychiatry* 2004; 65 Suppl 12:16-19.
14. IsHak WW, Wen RY, Naghdechi L, et al. Pain and depression: A systematic review. *Harv Rev Psychiatry* 2018; 26:352-363.
15. Rayner L, Hotopf M, Petkova H, Matcham F, Simpson A, McCracken LM. Depression in patients with chronic pain attending a specialised pain treatment centre: prevalence and

impact on health care costs. *Pain* 2016; 157:1472-1479.

16. Zis P, Daskalaki A, Bountouni I, Sykioti P, Varrassi G, Paladini A. Depression and chronic pain in the elderly: Links and management challenges. *Clin Interv Aging* 2017; 12:709-720.
17. van der Leeuw G, Eggermont LH, Shi L, et al. Pain and cognitive function among older adults living in the community. *J Gerontol A Biol Sci Med Sci* 2016; 71:398-405.
18. Rossor MN, Fox NC, Mummery CJ, Schott JM, Warren JD. The diagnosis of young-onset dementia. *Lancet Neurol* 2010; 9:793-806.
19. Chen Y, Yeh H, Wu J, et al. Taiwan's National Health Insurance Research Database: Administrative health care database as study object in bibliometrics. *Scientometrics* 2011; 86:365-380.
20. Chung KM, Ho CH, Chen YC, et al. Chronic pain increases the risk for major adverse cardiac and cerebrovascular events: A nationwide population-based study in Asia. *Pain Med* 2020; 21:1985-1990.
21. Huang YL, Tsay WI, Her SH, et al. Chronic pain and use of analgesics in the elderly: A nationwide population-based study. *Arch Med Sci* 2020; 16:627-634.
22. Tsai MH, Tsay WI, Her SH, et al. Long-term mortality in older adults with chronic pain: A nationwide population-based study in Taiwan. *European Geriatric Medicine* 2019; 10:777-784.
23. Hung YN, Kadziola Z, Brnabic AJ, et al. The epidemiology and burden of Alzheimer's disease in Taiwan utilizing data from the National Health Insurance Research Database. *Clinicoecon Outcomes Res* 2016; 8:387-395.
24. Eccleston C, Crombez G. Pain demands attention: A cognitive-affective model of the interruptive function of pain. *Psychol Bull* 1999; 125:356-366.
25. Dick BD, Rashiq S. Disruption of attention and working memory traces in individuals with chronic pain. *Anesth Analg* 2007; 104:1223-1229.
26. Oosterman JM, Derksen LC, van Wijck AJ, Veldhuijzen DS, Kessels RP. Memory functions in chronic pain: Examining contributions of attention and age to test performance. *Clin J Pain* 2011; 27:70-75.
27. Apkarian AV, Sosa Y, Krauss BR, et al. Chronic pain patients are impaired on an emotional decision-making task. *Pain* 2004; 108:129-136.
28. Hart RP, Martelli MF, Zasler ND. Chronic pain and neuropsychological functioning. *Neuropsychol Rev* 2000; 10:131-149.
29. Peavy GM, Salmon DP, Jacobson MW, et al. Effects of chronic stress on memory decline in cognitively normal and mildly impaired older adults. *Am J Psychiatry* 2009; 166:1384-1391.
30. Munoz E, Sliwinski MJ, Scott SB, Hofer S. Global perceived stress predicts cognitive change among older adults. *Psychol Aging* 2015; 30:487-499.
31. Segerstrom SC, Geiger PJ, Boggero IA, Schmitt FA, Sephton SE. Endogenous cortisol exposure and declarative verbal memory: A longitudinal study of healthy older adults. *Psychosom Med* 2016; 78:182-191.
32. McEwen BS, Sapolsky RM. Stress and cognitive function. *Curr Opin Neurobiol* 1995; 5:205-216.
33. Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: A systematic review. *Lancet Neurol* 2006; 5:64-74.
34. Nagai M, Hoshide S, Kario K. Hypertension and dementia. *Am J Hypertens* 2010; 23:116-124.
35. Luchsinger JA, Mayeux R. Cardiovascular risk factors and Alzheimer's disease. *Curr Atheroscler Rep* 2004; 6:261-266.
36. Liao KM, Ho CH, Ko SC, Li CY. Increased risk of dementia in patients with chronic obstructive pulmonary disease. *Medicine (Baltimore)* 2015; 94: e930.
37. Baliki MN, Geha PY, Apkarian AV, Chialvo DR. Beyond feeling: Chronic pain hurts the brain, disrupting the default-mode network dynamics. *J Neurosci* 2008; 28:1398-1403.
38. Grachev ID, Fredrickson BE, Apkarian AV. Abnormal brain chemistry in chronic back pain: An in vivo proton magnetic resonance spectroscopy study. *Pain* 2000; 89:7-18.
39. Apkarian AV, Sosa Y, Sonty S, et al. Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J Neurosci* 2004; 24:10410-10415.
40. Chen JH, Lin KP, Chen YC. Risk factors for dementia. *J Formos Med Assoc* 2009; 108:754-764.