Non-Cancer Chronic Pain Conditions and Risk for Incident Alzheimer’s Disease and Related Dementias in Community-Dwelling Older Adults: A Population-Based Retrospective Cohort Study of United States Medicare Beneficiaries, 2001–2013

Sumaira Khalid 1,*, Usha Sambamoorthi 2 and Kim E. Innes 1

1 Department of Epidemiology, West Virginia University School of Public Health, Morgantown, WV 26506, USA; karen.innes@hsc.wvu.edu
2 Department of Pharmaceutical Systems and Policy, West Virginia University School of Pharmacy, Morgantown, WV 26506, USA; usambamoorthi@hsc.wvu.edu
* Correspondence: sk0055@mix.wvu.edu

Received: 24 June 2020; Accepted: 23 July 2020; Published: 29 July 2020

Abstract: Accumulating evidence suggests that certain chronic pain conditions may increase risk for incident Alzheimer’s disease and related dementias (ADRD). Rigorous longitudinal research remains relatively sparse, and the relation of overall chronic pain condition burden to ADRD risk remains little studied, as has the potential mediating role of sleep and mood disorders. In this retrospective cohort study, we investigated the association of common non-cancer chronic pain conditions (NCPC) at baseline to subsequent risk for incident ADRD, and assessed the potential mediating effects of mood and sleep disorders, using baseline and 2-year follow-up data using 11 pooled cohorts (2001–2013) drawn from the U.S. Medicare Current Beneficiaries Survey (MCBS). The study sample comprised 16,934 community-dwelling adults aged ≥65 and ADRD-free at baseline. NCPC included: headache, osteoarthritis, joint pain, back or neck pain, and neuropathic pain, ascertained using claims data; incident ADRD (N = 1149) was identified using claims and survey data. NCPC at baseline remained associated with incident ADRD after adjustment for sociodemographics, lifestyle characteristics, medical history, medications, and other factors (adjusted odds ratio (AOR) for any vs. no NCPC = 1.21, 95% confidence interval (CI) = 1.04–1.40; p = 0.003); the strength and magnitude of this association rose significantly with increasing number of diagnosed NCPCs (AOR for 4+ vs. 0 conditions = 1.91, CI = 1.31–2.80, p-trend < 0.00001). Inclusion of sleep disorders and/or depression/anxiety modestly reduced these risk estimates. Sensitivity analyses yielded similar findings. NCPC was significantly and positively associated with incident ADRD; this association may be partially mediated by mood and sleep disorders. Additional prospective studies with longer-term follow-up are warranted to confirm and extend our findings.

Keywords: Alzheimer’s disease; dementia; ADRD; modifiable risk factors; Chronic pain; elderly population; longitudinal study; arthritis; headache

1. Introduction

Alzheimer’s disease and related dementia (ADRD) is a group of serious neurodegenerative disorders characterized by progressive decline in cognitive and psychomotor function [1,2]. Prevalence of ADRD continues to increase worldwide, exacting enormous social, economic and healthcare costs. For example, in the United States, at least 5.8 million adults are living with Alzheimer’s disease (AD), the most common form of dementia, with attributable Medicare costs alone exceeding $146 billion...
annually; these figures are expected to rise steeply in coming years [3]. ADRD is also a significant contributor to mortality and number of life years lived with disability [3,4]. With no cure for ADRD, and no effective disease-modifying treatments yet available despite decades of clinical research [5], efforts are increasingly shifting to prevention and early intervention, including intensive approaches to identify and target modifiable risk factors for ADRD [6].

To date, several factors have been linked to elevated ADRD risk. These include non-modifiable factors such as advancing age, female sex, rurality, and specific genetic profiles, as well as modifiable risk factors [7]. The latter include: poor education and poverty [7,8]; physical inactivity, midlife obesity, and other lifestyle factors [7,9]; history of head injury or stroke [10,11]; and certain chronic physical health disorders (e.g., diabetes, cardiovascular disease, midlife hypertension, respiratory illness [7,9,12]). Specific mental health conditions (e.g., depression, anxiety) and chronic sleep impairment have also been shown to predict subsequent cognitive decline and conversion to ADRD [13–16]. In addition, there is growing evidence from observational and experimental research that chronic pain, an increasingly common and highly burdensome condition, may also contribute to elevated risk for neurocognitive impairment and development of ADRD [17–23].

Although limited at present, there is evidence from longitudinal studies that chronic pain and common non-cancer chronic pain conditions (NCPC) may increase risk for incident cognitive impairment and ADRD [24–34]. For example, recent retrospective cohort investigations of Taiwanese nationals [26,28,29,34] and prospective cohort studies of Japanese and Norwegian elders [25,27,33] have reported significantly increased risk of incident dementia in adults previously diagnosed with fibromyalgia [28], osteoarthritis or knee pain [26,33], and headache [25,27,29,34]. Likewise, findings from a handful of longitudinal studies in US [24,30,32] and British adults [31] suggest that non-specific chronic pain may predict subsequent deterioration in memory [30,32], accelerated cognitive decline [32], new onset cognitive impairment [32], and incident dementia [24,32], although studies varied widely in design, study population, length of follow-up, and measures. However, to our knowledge, no study has investigated the collective and incremental association of common chronic pain conditions to ADRD risk, nor the potential mediating role of depression, anxiety and sleep disorders, conditions strongly and bidirectionally associated with chronic pain and linked to ADRD risk.

In this study, we investigate the association of common NCPC to ADRD risk using multiple retrospective cohorts from a linked database of nationally representative sample of older US Medicare beneficiaries. We hypothesized that the presence of NCPC at baseline will be associated with significantly increased risk of incident ADRD, and that the magnitude of this association will increase with rising number of NCPC at baseline. We further hypothesized that depression, anxiety and/or sleep impairment, will partially mediate the association between NCPC and incident ADRD.

2. Methods

2.1. Study Design

Our study used a retrospective cohort design to assess the association of baseline common non-cancer chronic pain conditions (NCPC) to incident ADRD using data from the Medicare Current Beneficiary Survey (MCBS) [35] linked with Medicare fee-for-service claims. MCBS is a nationally representative survey of adults participating in Medicare health insurance program. As detailed below, multiple three-year MCBS cohorts (2001–2013) were pooled to construct the analytic sample for this study.

2.2. Data Source

First initiated in 1991, MCBS has been recruiting survey participants each year using a complex stratified, three-stage probability sampling design described in detail elsewhere [36,37]. MCBS participants undertake structured in-person interviews at baseline and follow-up rounds each year for up to three years. MCBS generates comprehensive cross-sectional and longitudinal data on
participants’ health status, health services utilization, prescription medications, and payment sources using a combination of survey and administrative records. Our study used data from MCBS Cost and Use files linked with Medicare fee-for-service claims to ascertain demographics, access to care, lifestyle factors, medical history and medication. Based on the recommendations by MCBS investigators [36–38] and sampling strategies documented in prior published studies using MCBS [36,38,39], we combined 11 MCBS cohorts in order to maximize reliability and precision of our study estimates; these included the following cohorts: 2001–2003; 2002–2004; 2003–2005; 2004–2006; 2005–2007; 2006–2008; 2007–2009; 2008–2010; 2009–2011; 2010–2012 and 2011–2013.

2.3. Study Sample

The study sample comprised continuously fee-for-service enrolled community-dwelling Medicare beneficiaries, aged 65 years or over, who had complete information on NCPC status and were still alive at the end of follow-up. Institutionalized participants were excluded, as were participants with diagnosed ADRD at baseline. As depicted in the sample selection flow chart (see supplementary Figure S1), application of all a priori exclusion criteria yielded a final sample size of 16,934 adults (N’s by year = 1874 (2001–2003); 1768 (2002–2004); 1884 (2003–2005); 1766 (2004–2006); 1735 (2005–2007); 1650 (2006–2008); 1495 (2007–2009); 1278 (2008–2010); 1034 (2009–2011); 1159 (2010–2012); and 1291 (2011–2013)).

IRB/ethics approval: The present study was approved as exempt protocol by the WVU Institutional Review Board (IRB), due to the deidentified nature of the data used in the study.

2.4. Dependent Variable: Incident Alzheimer’s Disease and Related Dementia (ADRD) at Follow-Up– Yes/No

The Medicare fee-for-service (FFS) claims for inpatient (IP), skilled nursing facility (SNF), outpatient (OT), home health agency (HHA), and physician office (PO) visits for years 2001–2013 as well as MCBS self-reported Health Status and Functioning files were used to ascertain the presence of ADRD at baseline and follow-up. The presence of ADRD at both baseline (year 1) and follow-up (years 2 and 3) was ascertained using a validated CMS algorithm (Centers for Medicare and Medicaid Services (CMS) Chronic Condition Algorithms) [40] of at least one fee-for-service claim with any of these International Classification of Diseases, ninth Edition, clinical modification (ICD-9-CM) diagnostic codes: 331.0, 331.11, 331.19, 331.2, 331.7, 290.0, 290.10, 290.11, 290.12, 290.13, 290.20, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 294.0, 294.10, 294.11, 294.20, 294.21, 294.8, and 797, or an affirmative response to the self-reported Health Status question “Has a doctor ever told you that you had Alzheimer’s?” [41]. Using a combination of claims and survey data to ascertain ADRD has been recommended by MCBS investigators to increase capture of ADRD and has been shown to yield results similar to those of expert in-person-assessment [42].

2.5. Key Independent Variable: Non-Cancer Chronic Pain Condition (NCPC) and Number of NCPCs

Baseline NCPC were identified using Medicare fee-for-service claims. NCPC included five common NCPC (back or neck pain, headache, joint pain, neuropathic pain, and osteoarthritis). The presence of any NCPC was identified using either two outpatient claims (90 days apart) or one inpatient claim using ICD9-CM codes as recommended by the Centers for Medicare and Medicaid Services [40] and consistent with prior studies of NCPC [43,44]. Any NCPC was assessed as a binary variable (yes/no) during baseline. Relative NCPC burden was ascertained with a count variable (0–5 NCPCs).

2.6. Covariates

To account for the influence of potential confounding, specific baseline characteristics known or suspected to be associated with ADRD risk and/or chronic pain based on prior research were selected a priori for inclusion as covariates in our multivariable models. These included age group (65–69, 70–74, 75–79, and ≥80 years), based on prior research indicating the risk in adults doubles approximately
every 4 years after age 65 [3,45]. Other biological factors i.e., sex (female/male), and race/ethnicity (Non-Hispanic White, African American, Hispanic, and other); other demographic characteristics, i.e., marital status (married, widowed, divorce/separated, other), educational level (less than high school, high school, some college, college), family income, measured as percentage of federal poverty line (FPL) (poor/low-income (<200%), middle to high-income (≥200%)); health insurance status (insured by Medicaid (yes/no) or private insurance (yes/no)); rurality (metropolitan areas, yes/no); and lifestyle factors, i.e., smoking status (current smoker, past smoker, never smoked) and body mass index (BMI, kg/m²) (underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), and obese ≥30).

Also included as covariates were other chronic physical health conditions reported at baseline (yes/no). These included hypertension, diabetes, heart disease, respiratory illness, and history of stroke, traumatic brain injury (TBI), and cancer (with the exception of non-melanotic skin cancer), as well as specific auto-immune conditions associated with chronic pain, including rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE). In addition, certain commonly used medications that have been linked to ADRD risk and/or used in chronic pain management were also evaluated as covariates. These included non-steroidal anti-inflammatory drugs (NSAIDS) [46], opioid analgesics [47], benzodiazepines [48] and certain other psychotropic drugs (e.g., selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), monoamino oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), and atypical antidepressants) [49]. Benzodiazepine use was evaluated as a separate medication category given that: (1) a significant number of study participants (10%) were prescribed these medications; and (2) prior research has suggested that benzodiazepines not only has multidimensional neurological effects [50,51], but is also associated with elevated risk for ADRD [48].

Mediators: To examine the potential mediating influence of mood and sleep disorders on the relation of NCPC to incident ADRD, we evaluated the effects of diagnosed depression, anxiety and insomnia-related sleep disorders both separately and in combination (see supplementary Table S1 for ICD-9-CM diagnostic codes).

2.7. Statistical Analysis

Potential differences in baseline characteristics by NCPC and ADRD status were determined using Rao-Scott chi-square tests (categorical variables). Logistic regressions were used to assess the unadjusted and independent association of NCPC and NCPC burden to incident ADRD. In these multivariable logistic regressions, we carried out block-wise adjustment for demographic and socioeconomic factors; lifestyle factors and chronic physical health conditions; and analgesics and psychotropic medications to assess the adjusted associations of NCPC to ADRD risk. Similar nested multivariable logistic regression models were used to evaluate potential mediating effects of baseline diagnoses of depression, anxiety, and sleep disorders both individually and in combination. To assess the linear relationship of NCPC to risk of ADRD, regression models with polynomial contrast were used. For our sensitivity analyses, we used multinomial logistic regression to build competing risk of death models with the following four outcomes: ADRD-free and alive at the end of follow-up (N = 15,785) (referent category); ADRD-free and not alive at the end of follow-up (N = 1220); ADRD positive and Alive at the end of follow-up (N = 1149); ADRD positive and not alive at the end of follow-up (N = 259).

All bivariate and multivariable analyses were carried out using MCBS complex survey design sampling weights. MCBS data-cycles are released with cross-sectional as well as longitudinal weights. We used 3-year backward longitudinal weights for analysis of our pooled cohorts to yield up to two years of continuous follow-up. All analyses were performed using SAS survey procedure (SAS version 9.4, SAS Institute, Inc.).

3. Results

Our analytical sample comprised 16,934 eligible participants with a mean age at baseline of 74 ± 0.07 years. The majority of the cohort were female (57%), white (83%), married (56.5%) and
reported a family income at or above 200% of the FPL. Study participants were predominantly from metropolitan areas (71%) and most had private insurance (79%).

Overall baseline prevalence of any NCPC in this study was 36% (weighted), with significant differences by cohort (range 31% to 39%, \( p < 0.0001 \)). Pain burden in this population was high, with 37.5% reporting at least two co-existing NCPCs and 15% indicating three or more NCPCs. A significantly higher percentage of participants with baseline NCPC reported a history of chronic physical health conditions associated with ADRD, including hypertension (82% vs. 68.7%), heart disease (31.5% vs. 19.9%), stroke (14% vs. 10%), diabetes (23.5% vs. 19%) (\( p's < 0.0001 \)). Participants with baseline NCPC were also significantly more likely to report mood disorders, including depression (11% vs. 4.5%) and anxiety (7.9% vs. 3.5%), as well as sleep disorders (25.5% vs. 10.2%) when compared to participants without baseline NCPC (Table 1).

Table 1. Baseline characteristics by non-cancer chronic pain conditions in older Medicare beneficiaries *, analyzed using linked data from the Medicare Current Beneficiary Survey and Medicare claims, 2001–2013.

| Variables                        | Total            | Any NCPC        | \( p\)-Value $^\S$ |
|----------------------------------|------------------|-----------------|--------------------|
|                                  | N ¥ | Wt.% | N | Wt.% | N | Wt. % |
| ALL ¥                           | 16,934 | 100 | 6369 | 100.0 | 10,565 | 100.0 |
| Sociodemographics                |      |      |      |       |      |      |
| Sex                              |      |      |      |       |      |      |
| Female                           | 9669 | 56.9 | 4215 | 66.4 | 5454 | 51.5 |
| Male                             | 7265 | 43.1 | 2154 | 33.6 | 5111 | 48.5 |
| Age in Years                     |      |      |      |       |      |      |
| 65–69                            | 4188 | 31.8 | 1335 | 26.4 | 2853 | 34.9 |
| 70–74                            | 3484 | 22.5 | 1230 | 22.1 | 2254 | 22.8 |
| 75–79                            | 3674 | 21.4 | 1411 | 22.8 | 2263 | 20.6 |
| 80+                              | 5588 | 24.3 | 2393 | 28.8 | 3195 | 21.7 |
| Race/Ethnicity                   |      |      |      |       |      |      |
| White                            | 14,085 | 83.2 | 5293 | 83.4 | 8792 | 83.0 |
| Black                            | 1159 | 6.7 | 438 | 6.7 | 721 | 6.7 |
| Hispanic                         | 956 | 5.6 | 359 | 5.7 | 597 | 5.6 |
| Other                            | 709 | 4.5 | 268 | 4.3 | 441 | 4.6 |
| Education                        |      |      |      |       |      |      |
| <High School                     | 4605 | 25.0 | 1744 | 25.4 | 2861 | 24.7 |
| High School                      | 6174 | 36.4 | 2349 | 37.0 | 3825 | 36.1 |
| Some College                     | 2431 | 15.0 | 950 | 15.7 | 1481 | 14.6 |
| College                          | 3675 | 23.6 | 1306 | 21.9 | 2369 | 24.6 |
| Marital Status                   |      |      |      |       |      |      |
| Married                          | 9139 | 56.5 | 3208 | 52.8 | 5931 | 58.7 |
| Widowed                          | 5803 | 30.6 | 2491 | 35.7 | 3312 | 32.6 |
| Divorce/sep                        | 1455 | 9.5 | 490 | 8.3 | 965 | 10.2 |
| Other                            | 532 | 3.3 | 179 | 3.1 | 353 | 3.5 |
| Household Income                 |      |      |      |       |      |      |
| <200% Federal Poverty Level      | 8260 | 45.9 | 3221 | 48.4 | 5039 | 44.6 |
| ≥200% Federal Poverty Level      | 8674 | 54.1 | 3148 | 51.6 | 5526 | 55.4 |
| Insurance                         |      |      |      |       |      |      |
| Medicaid                         |      |      |      |       |      |      |
| Yes                              | 2147 | 11.9 | 1005 | 15.4 | 1142 | 9.9 |
| No                               | 14,787 | 88.1 | 5364 | 84.6 | 9423 | 90.1 |
| Private Insurance                |      |      |      |       |      |      |
| Yes                              | 13,418 | 79.4 | 5147 | 80.8 | 8271 | 78.5 |
| No                               | 3514 | 20.6 | 1221 | 19.2 | 2293 | 21.5 |
| Residence                        |      |      |      |       |      |      |
| Metropolitan Status              |      |      |      |       |      |      |
| Metro                            | 11,375 | 70.6 | 4415 | 72.5 | 6960 | 69.5 |
| Rural                            | 5558 | 29.4 | 1954 | 27.5 | 3604 | 30.5 |

Lifestyle Characteristics
Table 1. Cont.

| Variables                              | Total | Any NCPC | p-Value $^\dagger$ |
|----------------------------------------|-------|----------|--------------------|
|                                        | N     | Wt.%     | N                  | Wt. % |
| **Body Mass Index**                    |       |          |                    |       |
| Underweight                            | 312   | 1.7      | 100                | 1.4   |
| Normal                                 | 5867  | 34.0     | 1984               | 30.4  |
| Overweight                             | 6709  | 40.0     | 2491               | 39.2  |
| Obese                                  | 3881  | 24.3     | 1734               | 29.0  |
| **Mean BMI 27.2 (±0.052)**             |       |          |                    |       |
| **Smoking Status**                     |       |          |                    |       |
| Current                                | 1594  | 10.2     | 457                | 7.8   |
| Past                                   | 7976  | 47.5     | 2965               | 47.2  |
| Never                                  | 7326  | 42.4     | 2936               | 45.1  |
| **Baseline Health History**            |       |          |                    |       |
| **Physical Health Conditions**         |       |          |                    |       |
| Hypertension                           |       |          |                    |       |
| Yes                                    | 12,713| 73.5     | 5263               | 82.0  |
| No                                     | 4221  | 26.5     | 1106               | 18.0  |
| Heart disease                          |       |          |                    |       |
| Yes                                    | 4357  | 24.1     | 2097               | 31.5  |
| No                                     | 12,577| 75.9     | 4272               | 68.5  |
| Stroke                                 |       |          |                    |       |
| Yes                                    | 2139  | 11.5     | 979                | 14.3  |
| No                                     | 14,795| 88.5     | 5390               | 85.7  |
| Diabetes                               |       |          |                    |       |
| Yes                                    | 3495  | 20.7     | 1468               | 23.5  |
| No                                     | 13,439| 79.3     | 4901               | 76.5  |
| Respiratory disease                    |       |          |                    |       |
| Yes                                    | 2423  | 14.2     | 1045               | 16.7  |
| No                                     | 14,511| 85.8     | 5324               | 83.3  |
| Cancer                                 |       |          |                    |       |
| Yes                                    | 7101  | 40.3     | 2911               | 44.4  |
| No                                     | 9833  | 59.7     | 3458               | 55.6  |
| Traumatic Brain Injury                 |       |          |                    |       |
| Yes                                    | 221   | 1.2      | 146                | 2.2   |
| No                                     | 16,713| 98.8     | 6223               | 97.8  |
| Rheumatoid Arthritis                   |       |          |                    |       |
| Yes                                    | 508   | 2.9      | 349                | 5.5   |
| No                                     | 16,426| 97.1     | 6020               | 94.5  |
| Lupus                                  |       |          |                    |       |
| Yes                                    | 136   | 0.8      | 94                 | 1.4   |
| No                                     | 16,798| 99.2     | 6275               | 98.6  |
| **Number of NCPCs**                    |       |          |                    |       |
| 0                                      | 6385  | 39.1     | -                  | -     |
| 1                                      | 4194  | 24.4     | -                  | -     |
| 2                                      | 3818  | 22.0     | -                  | -     |
| 3                                      | 1908  | 10.9     | -                  | -     |
| ≥4                                     | 629   | 3.7      | -                  | -     |
| **Sleep and Mood Disorders**           |       |          |                    |       |
| **Sleep Disorder**                     |       |          |                    |       |
| Yes                                    | 2728  | 15.8     | 1630               | 25.5  |
| No                                     | 14,206| 84.2     | 4739               | 74.5  |
| Depression                             |       |          |                    |       |
| Yes                                    | 1158  | 6.9      | 686                | 11.1  |
| No                                     | 15,776| 93.1     | 5683               | 88.9  |
| Anxiety                                |       |          |                    |       |
| Yes                                    | 862   | 5.1      | 492                | 7.9   |
| No                                     | 16,072| 94.9     | 5877               | 92.1  |

+$^\dagger$ Indicates statistically significant differences.
Table 1. Cont.

| Variables                     | Total   |  | Any NCPC |  |
|-------------------------------|---------|---|----------|---|
|                               | N \(^\dagger\) Wt. % |  | N Wt. % | N Wt. % |  |
| Medication Use                |         |  |          |       |  |
| NSAIDs                        |         |  |          |       |  |
| Yes                           | 3241    | 18.6 | 1936     | 30.2  | 1305 | 12.0 |
| No                            | 13,693  | 81.4 | 4433     | 69.8  | 9260 | 88.0 |
| Opioid Analgesics             |         |  |          |       |  |
| Yes                           | 3353    | 19.4 | 2059     | 32.2  | 1294 | 12.0 |
| No                            | 13,581  | 80.6 | 4310     | 67.8  | 9271 | 88.0 |
| Benzodiazepines               |         |  |          |       |  |
| Yes                           | 1734    | 9.7  | 935      | 14.5  | 799  | 7.1  |
| No                            | 15,200  | 90.3 | 5434     | 85.5  | 9766 | 92.9 |
| Psychotropic medications      |         |  |          |       |  |
| Yes                           | 2871    | 17.0 | 1448     | 23.3  | 1423 | 13.5 |
| No                            | 14,063  | 83.0 | 4921     | 76.7  | 9142 | 86.5 |

* Based on 11 pooled cohorts of 16,934 older community-dwelling adults (age > 65 years), enrolled in fee-for service Medicare, alive at the end of follow-up. \(^\dagger\) Numbers for some variables may not add up to \(N = 16,934\), due to missing values. § Statistically significant group differences in presence of NCPC were examined with Rao-Scott chi-square test. Abbreviation: NCPC, non-cancer chronic pain conditions; BMI, body mass index; NSAIDs, nonsteroidal anti-inflammatory drugs.

Table 2 summarizes the baseline characteristics of the study sample by incident ADRD status. A total of 1149 participants were diagnosed with incident ADRD during the 2-year follow-up period (overall incidence rate = 6.8 per 100 participants). Incident ADRD rates did not differ by study cohorts (range 4.9 to 6.2 per 100, \(p = 0.9\)), and were significantly higher in women (6.2% vs. 5.0% in men), and in participants who were black (7.4% vs. 5.5% in Non-Hispanic whites), widowed (8.2% vs. 4.5% in married), and more poorly educated (\(p’s < 0.0001\)). The proportion of participants diagnosed with incident ADRD was also significantly higher in those who were <200% of the federal poverty level (7.4% vs. 4.3%), were on Medicaid (9.1% vs. 5.2%) and who lacked private insurance (7.2% vs. 5.3%) (\(p’s < 0.0001\)). In addition, the percentage diagnosed with ADRD was significantly greater in those who indicated a history of specific physical health conditions at baseline, including hypertension, heart disease, stroke, and TBI, as well as in those who reported use of opioid analgesics (6.9% vs. 5.4%), benzodiazepines (8.5% vs. 5.4%), or other psychotropics (9.8% vs. 4.8%) (\(p’s < 0.0001\)). The proportion of participants with incident ADRD increased significantly with rising number of comorbid physical health conditions (range 4.6% to 10.6%, \(p < 0.0001\)). Participants who reported sleep, depression or anxiety disorders at baseline also included a significantly higher proportion of ADRD cases (\(p’s < 0.0001\)). Notably, as detailed in Table 2, incident ADRD rates were significantly higher in those who reported any NCPC at baseline (6.6 vs. 4.3 per 100), and rose with increasing number of NCPC conditions, from 6.2 in those with 1 NCPC condition to 17.3 per 100 participants in those with 4 or more NCPC conditions (\(p’s < 0.0001\)).

Table 2. Baseline characteristics by incident Alzheimer’s disease and related dementias (ADRD) in older Medicare beneficiaries *, analyzed using linked data from the Medicare Current Beneficiary Survey and Medicare claims, 2001-2013.

| Variables                     | Incident ADRD |  |
|-------------------------------|---------------|---|
|                               | Yes | Wt. % | No | Wt. % |  |
| ALL \(^\dagger\)              | 1149 | 6.8  | 15,785 | 93.2 |
| Any NCPC                      |         |    |      |       |  |
| Yes                           | 798   | 6.6 | 9677  | 93.4 |
| No                            | 351   | 4.3 | 6108  | 95.7 |

\(p’s < 0.0001\)
Table 2. Cont.

| Variables                      | Incident ADRD |      |      | p-Value § |
|-------------------------------|---------------|------|------|-----------|
|                               | Yes           | N    | Wt. %| No        | N    | Wt. %|
| Number of NCPC’s              |               |      |      |           |      |      |
| 0                             | 351           | 4.3  | 6108 | 95.7      |      |      |
| 1                             | 304           | 6.2  | 3948 | 93.8      |      |      |
| 2                             | 273           | 6.0  | 3605 | 94.0      |      |      |
| 3                             | 155           | 7.3  | 1742 | 92.7      |      |      |
| ≥4                            | 66            | 17.3 | 382  | 82.7      |      |      |
| Sociodemographic              |               |      |      |           |      |      |
| Sex                           |               |      |      | <0.0001  |      |      |
| Female                        | 725           | 6.2  | 8944 | 93.8      |      |      |
| Male                          | 424           | 5    | 6841 | 95        |      |      |
| Age in Years                  |               |      |      | <0.0001  |      |      |
| 65–69                         | 101           | 1.9  | 4087 | 98.1      |      |      |
| 70–74                         | 139           | 4    | 3345 | 96        |      |      |
| 75–79                         | 220           | 5.9  | 3454 | 94.1      |      |      |
| 80+                           | 689           | 12   | 4899 | 88        |      |      |
| Race/Ethnicity                |               |      |      | 0.066     |      |      |
| White                         | 922           | 5.5  | 13,163 | 94.5      |      |      |
| Black                         | 106           | 7.4  | 1053 | 92.6      |      |      |
| Hispanic                      | 70            | 5.9  | 886  | 94.1      |      |      |
| Other                         | 51            | 6.5  | 638  | 93.5      |      |      |
| Education                     |               |      |      | <0.0001  |      |      |
| <High School                  | 417           | 7.8  | 4188 | 92.2      |      |      |
| High School                   | 398           | 5.5  | 5776 | 94.5      |      |      |
| Some College                  | 141           | 4.8  | 2290 | 95.2      |      |      |
| College                       | 186           | 4.1  | 3489 | 95.9      |      |      |
| Marital Status                |               |      |      | <0.0001  |      |      |
| Married                       | 494           | 4.5  | 8645 | 95.5      |      |      |
| Widowed                       | 541           | 8.2  | 5262 | 91.8      |      |      |
| Divorce/separated             | 76            | 4.4  | 1379 | 95.6      |      |      |
| Other                         | 38            | 6    | 494  | 94        |      |      |
| Household Income              |               |      |      | <0.0001  |      |      |
| <200% Federal Poverty Level   | 699           | 7.4  | 7561 | 92.6      |      |      |
| ≥200% Federal Poverty Level   | 450           | 4.3  | 8224 | 95.7      |      |      |
| Insurance                     |               |      |      |           |      |      |
| Medicaid                      |               |      |      | <0.0001  |      |      |
| Yes                           | 223           | 9.1  | 1924 | 90.9      |      |      |
| No                            | 926           | 5.2  | 13,861 | 94.8      |      |      |
| Private Insurance             |               |      |      | <0.0001  |      |      |
| Yes                           | 847           | 5.3  | 12,571| 94.7      |      |      |
| No                            | 300           | 7.2  | 3214 | 92.8      |      |      |
| Residence                     |               |      |      | 0.649     |      |      |
| Metropolitan Status           |               |      |      |           |      |      |
| Metro                         | 787           | 5.7  | 10,588| 94.3      |      |      |
| Rural                         | 362           | 5.5  | 5196 | 94.5      |      |      |
| Lifestyle Characteristics     |               |      |      |           |      |      |
| Body Mass Index               |               |      |      | <0.0001  |      |      |
| Underweight                   | 43            | 12.2 | 269  | 87.8      |      |      |
| Normal                        | 484           | 6.9  | 5383 | 93.1      |      |      |
| Overweight                    | 417           | 5.2  | 6292 | 94.8      |      |      |
| Obese                         | 195           | 4.3  | 3686 | 95.7      |      |      |
| Smoking Status                |               |      |      | <0.0001  |      |      |
| Current                       | 96            | 4.8  | 1498 | 95.2      |      |      |
| Past                          | 472           | 5    | 7504 | 95        |      |      |
| Never                         | 580           | 6.6  | 6746 | 93.4      |      |      |
| Variables                      | Incident ADRD |    |    |    |    |
|-------------------------------|---------------|----|----|----|----|
|                               | Yes           | N  | Wt. % | N  | Wt. % | p-Value $ |
| **Baseline Health History**   |               |    |    |    |    |    |
| **Physical Health Conditions**|               |    |    |    |    |    |
| Hypertension                  |               |    |    |    |    |    |
| Yes                           | 935           | 6.3 | 11,778 | 93.7 |    | <0.0001 |
| No                            | 214           | 4.1 | 4007   | 95.9 |    |    |
| Heart disease                 |               |    |    |    |    |    |
| Yes                           | 368           | 7.6 | 3989   | 92.4 |    | <0.0001 |
| No                            | 781           | 5.1 | 11,796 | 94.9 |    |    |
| Stroke                        |               |    |    |    |    |    |
| Yes                           | 281           | 11.9 | 1858 | 88.1 |    | <0.0001 |
| No                            | 868           | 4.9 | 13,927 | 95.1 |    |    |
| Diabetes                      |               |    |    |    |    |    |
| Yes                           | 264           | 6.4 | 3231   | 93.6 |    | 0.032 |
| No                            | 885           | 5.5 | 12,554 | 94.5 |    |    |
| Respiratory disease           |               |    |    |    |    |    |
| Yes                           | 170           | 5.9 | 2253   | 94.1 |    | 0.576 |
| No                            | 979           | 5.6 | 13,532 | 94.4 |    |    |
| Cancer                        |               |    |    |    |    |    |
| Yes                           | 505           | 6.2 | 6596   | 93.8 |    | 0.043 |
| No                            | 644           | 5.3 | 9189   | 94.7 |    |    |
| Traumatic Brain Injury        |               |    |    |    |    |    |
| Yes                           | 30            | 12.8 | 191  | 87.2 |    | <0.0001 |
| No                            | 1119          | 5.6 | 15,594 | 94.4 |    |    |
| Rheumatoid Arthritis          |               |    |    |    |    |    |
| Yes                           | 39            | 6.8 | 469    | 93.2 |    | 0.247 |
| No                            | 1110          | 5.6 | 15,316 | 94.4 |    |    |
| Lupus                         |               |    |    |    |    |    |
| Yes                           | 13            | 8.9 | 123    | 91.1 |    | 0.119 |
| No                            | 1136          | 5.7 | 15,662 | 94.3 |    |    |
| **Sleep and Mood Disorders**  |               |    |    |    |    |    |
| Sleep Disorder                |               |    |    |    |    |    |
| Yes                           | 267           | 8.5 | 2461   | 91.5 |    | <0.0001 |
| No                            | 882           | 5.2 | 13,324 | 94.8 |    |    |
| Depression                    |               |    |    |    |    |    |
| Yes                           | 170           | 12.9 | 988  | 87.1 |    | <0.0001 |
| No                            | 979           | 5.1 | 14,797 | 94.9 |    |    |
| Anxiety                       |               |    |    |    |    |    |
| Yes                           | 109           | 10.9 | 753   | 89.1 |    | <0.0001 |
| No                            | 1040          | 5.4 | 15,032 | 94.6 |    |    |
| **Medication Use**            |               |    |    |    |    |    |
| NSAIDs                        |               |    |    |    |    |    |
| Yes                           | 226           | 6   | 3015   | 94   |    | 0.496 |
| No                            | 923           | 5.6 | 12,770 | 94.4 |    |    |
| Opioid Analgesics             |               |    |    |    |    |    |
| Yes                           | 266           | 6.9 | 3087   | 93.1 |    | <0.0001 |
| No                            | 883           | 5.4 | 12,698 | 94.6 |    |    |
| Benzodiazepines               |               |    |    |    |    |    |
| Yes                           | 167           | 8.5 | 1567   | 91.5 |    | <0.0001 |
| No                            | 982           | 5.4 | 14,218 | 94.6 |    |    |

* Based on 11 pooled cohorts of 16,934 older community-dwelling adults (age ≥ 65 years), enrolled in fee-for-service Medicare, alive at the end of follow-up. ¥ Numbers for some variables may not add up to N = 1149, due to missing values. § Statistically significant group differences in presence of NCPC were examined with Rao-Scott chi-square test. Abbreviations: NCPC, non-cancer chronic pain conditions; ADRD, Alzheimer’s disease and related dementias; NSAIDs, nonsteroidal anti-inflammatory drugs.
3.1. Association of NCPC to Incident ADRD

In our unadjusted logistic regression model, those with baseline NCPC were 54% more likely to have incident ADRD (odds ratio (OR) = 1.54, 95% confidence interval (CI) = 1.34–1.78, \( p < 0.0001 \)) (Table 3). Adjustment for demographic and socioeconomic characteristics (sex, race, age, education, poverty, Medicaid insurance, private insurance, and marital status) attenuated but did not eliminate this association (adjusted OR (AOR) = 1.33, 95% confidence interval (CI) = 1.14–1.53, \( p < 0.0001 \)).

The magnitude of this association was modestly reduced after additional adjustment for lifestyle factors and comorbid physical health conditions (AOR = 1.28, CI 1.10–1.48, \( p = 0.001 \)), and further attenuated by inclusion of medications in the model (AOR adjusted for NSAIDs and opioid analgesics (AOR = 1.25, CI 1.08–1.45, \( p = 0.003 \)) (Table 3). Further adjustment for benzodiazepines and other psychotropics only slightly reduced the magnitude of this estimate (AOR = 1.21 (1.04–1.40, \( p = 0.01 \)).

As detailed in Table 3, the association of NCPC to incident ADRD rose significantly in both strength and magnitude with increasing number of pain conditions. Relative to beneficiaries with no NCPC at baseline, those with \( \geq 4 \) NCPCs were twice as likely to be subsequently diagnosed with ADRD after adjustment for demographics, socioeconomic status, lifestyle factors, and medical conditions (AOR = 1.98, CI = 1.36–2.89, \( p \)-trend <0.00001). Further adjustment for analgesic medications only slightly attenuated these associations (AOR for \( \geq 4 \) vs. no NCPC = 1.91, CI 1.31–2.80, \( p \)-trend = 0.0008). When number of NCPCs at baseline were assessed as a continuous variable, risk for incident ADRD increased 12% for each additional NCPC in the fully adjusted model (AOR = 1.12, CI = 1.06–1.20, \( p = 0.0007 \)).

3.2. Sensitivity Analyses

Analyses using competing risk of death models yielded findings consistent with those from our primary analyses (Table 4). Relative to participants without NCPC at baseline, those with any NCPC and still alive at follow-up were significantly more likely to be diagnosed with incident ADRD after adjustment for demographics, lifestyle characteristics, physical health conditions, analgesics, and other factors (AOR for any NCPC = 1.26, 95% CI = 1.08–1.46, \( p < 0.003 \)). In contrast, baseline NCPC status was unrelated to death during the follow-up period, either with or without a diagnosis of incident ADRD (AORs, respectively = 0.99 and 0.97, \( p \)'s \( \geq 0.6 \)). Further adjustment for psychotropics did not appreciably change these estimates. These findings suggest survival bias is unlikely to explain the positive association observed between baseline NCPC and incident ADRD.

3.3. Potential Mediating Effects of Sleep and Mood Disorders

As illustrated in Table 5, inclusion of mood disorders in fully adjusted model modestly attenuated the relation of NCPC to incident ADRD (AORs for any NCPC and \( 4+ \) NCPCs vs. no NCPC, respectively = 1.17 (1.01–1.37) and 1.57 (1.06–2.34), \( p \)'s \( \leq 0.04 \)). Likewise, the addition of sleep disorders to the model attenuated the association of NCPC to ADRD risk (AORs for any NCPC and \( 4+ \) NCPCs vs. no NCPC, respectively = 1.20 (1.04–1.39) and 1.66 (1.12–2.45) \( p \)'s \( < 0.02 \)) as did that of both sleep and mood disorders (AORs for any NCPC and \( 4+ \) NCPCs, respectively = 1.18 (1.01–1.38) and 1.41 (0.94–2.12)). Adding mood and sleep disorders to models adjusted only for sociodemographics yielded similar risk estimates (AORs for any NCPC = 1.19, CI 1.02–1.47, \( p < 0.05 \)), again suggesting that mood and sleep disorders may in part mediate the relation of NCPC to incident ADRD. Additional adjustment for benzodiazepines and psychotropics did not appreciably alter these associations (AOR = 1.17, CI = 1.01–1.37, \( p = 0.04 \)). A number of demographic, lifestyle, and health-related factors remained significantly associated with incident ADRD in our fully adjusted models. These include: black (vs. non-Hispanic white) race (AOR = 1.48, CI 1.09–2.00); age (80+ vs. 65–69, AOR 6.12, CI = 4.7–7.9); poverty (<200% vs. \( >200\% \), AOR 1.17, CI = 1.02–1.34); Medicaid insurance (AOR 1.27, 95% CI = 1.01–1.6); BMI (underweight vs. normal, AOR = 1.48, CI = 1.04–2.12); history of stroke (AOR 1.87, CI = 1.6–2.2) or TBI (AOR = 1.52, CI = 1.04–2.23); and psychotropic medications (AOR = 2.04, CI = 1.74–2.39) (\( p \)'s < 0.05). Use of neither NSAIDs nor opioids was significantly associated with ADRD risk in the adjusted analyses (AORs respectively = 0.96 (0.80–1.16) and 1.03 (0.87–1.22)), nor was use of benzodiazepines (AOR = 1.17, CI = 0.97–1.40) (\( p \)'s > 0.05).
Table 3. Association of baseline non-cancer chronic pain conditions (NCPC) and burden to incident Alzheimer’s disease and related dementias (ADRD) in older Medicare beneficiaries*: analysis using linked Medicare Current Beneficiary Survey and Medicare claims data, 2001–2013 (odds ratios (OR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI) calculated using separate logistic regression models).

| NCPC Presence/Number | Unadjusted Model | Model 1 ¥ | Model 2 ¥¥ | Model 3 ¥¥ |
|----------------------|------------------|-----------|-----------|-----------|
|                      | OR (95% CI)      | p         | AOR (95% CI) | p         | AOR (95% CI) | p         | AOR (95% CI) | p         |
| Any NCPC ** vs. None |                  |           |            |            |            |           |            |            |
| None (referent)      | 1.00             | 0.0001    | 1.00       | 0.0001     | 1.00       | 0.0001    | 1.00       | 0.0001     |
| One                  | 1.47 (1.26,1.71) | <0.0001   | 1.27 (1.08,1.50) | 0.0039 | 1.24 (1.05,1.46) | 0.0125 | 1.23 (1.04,1.45) | 0.0179 |
| Three                | 1.75 (1.42,2.16) | <0.0001   | 1.45 (1.17,1.80) | 0.0007 | 1.38 (1.11,1.71) | 0.0041 | 1.34 (1.07,1.68) | 0.0122 |
| Four or more         | 3.03 (2.14,4.29) | <0.0001   | 2.32 (1.62,3.31) | <0.0001 | 1.98 (1.36,2.89) | 0.0004 | 1.91 (1.31,2.80) | 0.0008 |
| Number of NCPCs      |                  |           |            |            |            |           |            |            |
| (per additional NCPC)| 1.00             | 0.0001    | 1.10 (0.87,1.40) | 0.42  | 1.21 (1.07,1.36) | 0.0024 |

*p Based on 11 pooled cohorts of 16,934 older community-dwelling adults (age > 65 years), enrolled in fee-for-service Medicare. ** Including back and neck pain, headache and migraine, joint pain, neuropathic pain and osteoarthritis. ¥ Socio-demographics: sex, age, race/ethnicity, education, income, Medicaid insurance, private insurance, marital status, region. ¥¥ Lifestyle and chronic physical health conditions: smoking, body mass index, hypertension, diabetes, heart disease, cancer, respiratory disorder, history of stroke, traumatic brain injury. ¥¥ Analgesics: nonsteroidal anti-inflammatory drugs and opioid analgesics. ++ Regression results from polynomial contrast for linear relation indicate a strong linear effect of NCPC on risk of ADRD.

Table 4. Association of baseline non-cancer chronic pain conditions to incident Alzheimer’s disease and related dementias in older Medicare beneficiaries*: competing risk analysis using linked Medicare Current Beneficiary Survey (MCBS) and Medicare claims data, 2001–2013 (odds ratios (OR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI) calculated from multinomial logistic regression).

| Any Non-Cancer Chronic Pain Condition (NCPC) ** | Alive at Follow-Up, No ADRD (Referent) | Alive at Follow-Up, Incident ADRD | Died before Follow-Up, Incident ADRD | Died before Follow-Up, No ADRD |
|-----------------------------------------------|----------------------------------------|----------------------------------|------------------------------------|-------------------------------|
| Model 1. Unadjusted model                     | 1.00 (-)                               | 1.55 (1.34,1.78)                | <0.0001                            | 1.29 (1.03,1.42)              | 0.029 | 1.25 (1.12,1.40) | <0.0001 |
| Model 2. Adjusted for sociodemographics ¥     | 1.00 (-)                               | 1.34 (1.16,1.55)                | <0.0001                            | 1.10 (0.87,1.40)              | 0.42  | 1.21 (1.07,1.36) | 0.0024 |
| Model 3. Also adjusted for lifestyle and chronic physical health conditions ¥¥ | 1.00 (-)                               | 1.28 (1.11,1.49)                | 0.0009                            | 1.03 (0.79,1.34)              | 0.8287 | 1.05 (0.93,1.18) | 0.4461 |
| Model 4. Also adjusted for NSAID and opioid analgesic use | 1.00 (-)                               | 1.26 (1.08,1.46)                | 0.0026                            | 0.99 (0.75,1.31)              | 0.96  | 0.97 (0.85,1.10) | 0.60   |

* Based on 11 pooled cohorts of older community-dwelling adults (age > 65 years), enrolled in fee-for-service Medicare. ** Referent for Any NCPC ‘No NCPC’. ¥ Sex, age, race/ethnicity, education, income, Medicaid insurance, private insurance, marital status, region. ¥¥ Smoking status, body mass index, hypertension, diabetes, heart disease, cancer, respiratory illnesses, history of stroke and traumatic brain injury.
Table 5. Association of baseline non-cancer chronic pain conditions (NCPC’s) and burden to incident Alzheimer’s disease and related dementias in older Medicare beneficiaries*: analysis using linked Medicare Current Beneficiary Survey and Medicare claims data, 2001–2013: Potential mediating influence of diagnosed mood and sleep disorders (odds ratios (OR) and adjusted odds ratios (AOR) with 95% confidence intervals (CI)).

| NCPC Presence/Number | Fully Adjusted Model ¥ | Model ¥ + Mood Disorders § | Model ¥ + Sleep Disorders §§ | Model ¥ + Mood and Sleep Disorders |
|----------------------|------------------------|-----------------------------|-----------------------------|----------------------------------|
|                      | OR (95% CI) p          | OR (95% CI) p               | OR (95% CI) p               | OR (95% CI) p                    |
| Any NCPC vs. None ** | 1.25 (1.08,1.45) 0.0032 | 1.17 (1.01,1.37) 0.0388     | 1.20 (1.04,1.39) 0.0155     | 1.18 (1.01,1.38) 0.0336          |
| Number of NCPCs      |                        |                             |                             |                                  |
| None (referent)      | 1.00 (referent)        | 1.00 (referent)             | 1.00 (referent)             | 1.00 (referent)                  |
| One                  | 1.23 (1.04,1.45) 0.0179 | 1.19 (1.01,1.41) 0.0408     | 1.20 (1.02,1.43) 0.0311     | 1.17 (0.99,1.39) 0.0594          |
| Two                  | 1.20 (1.01,1.43) 0.0435 | 1.13 (0.95,1.36) 0.1722     | 1.16 (0.97,1.38) 0.1008     | 1.11 (0.92,1.32) 0.2713          |
| Three                | 1.34 (1.07,1.68) 0.0122 | 1.22 (0.96,1.55) 0.0962     | 1.25 (0.99,1.58) 0.0589     | 1.17 (0.92,1.48) 0.2112          |
| Four or more         | 1.91 (1.31,2.80) 0.0008 | 1.57 (1.06,2.34) 0.0255     | 1.66 (1.12,2.45) 0.0113     | 1.41 (0.94,2.12) 0.0941          |
| p for linear trend **| <0.0001                | <0.0001                     | <0.0001                     | <0.0001                          |
| Number of NCPCs (per additional NCPC) | 1.12 (1.05,1.20) 0.0007 | 1.08 (1.01,1.16) 0.027      | 1.09 (1.02,1.16) 0.0101     | 1.06 (0.99,1.13) 0.1001          |

* Based on 11 pooled cohorts of older community-dwelling adults (age > 65 years), enrolled in fee-for-service Medicare. ** Including back or neck pain, headache and migraine, joint pain, neuropathic pain, and osteoarthritis. ¥ sex, age, race/ethnicity, education, income, Medicaid insurance, private insurance, marital status, region, smoking status, body mass index, chronic physical health conditions (hypertension, diabetes, heart disease, cancer, respiratory disorder, history of stroke, traumatic brain injury), NSAID and opioid analgesics. § Depression and anxiety; §§ insomnia-related sleep disorders. ++ Regression results from polynomial contrast for linear relation indicate a strong linear effect of NCPC on risk of ADRD.
4. Discussion

In this retrospective cohort study of older community-dwelling Medicare fee-for-service enrollees, diagnosed NCPC at baseline remained significantly and positively associated with risk for incident ADRD after adjustment for demographics, socioeconomic factors, medical history, medications, and other factors. The strength and magnitude of this association rose with increasing number of NCPCs, indicating increasing risk for incident ADRD with rising chronic pain condition burden. The relation between NCPC and risk of ADRD appeared to be mediated in part by the presence of sleep and mood disorders. To our knowledge, this investigation is the first large retrospective cohort study to assess the collective and incremental association of NCPC to incident ADRD, and to explore the potential mediating role of mood and sleep disorders in this association.

The significant positive associations NCPC to ADRD risk observed in this study are consistent with those of prior longitudinal studies regarding the relation of specific chronic pain conditions to risk for dementia. Recent large retrospective matched cohort studies in Taiwanese nationals [26,28,29,34,52], prospective cohort investigations in Norwegian adults [25,27] and a small retrospective cohort study of Canadian elders [53] all indicated significantly increased risk for incident all-cause dementia in those diagnosed with headache [25,27,29,34,52,53], OA/knee pain [26,33], and fibromyalgia [28] after adjusting for demographics, comorbid conditions, and other potential confounders. Although the few longitudinal studies investigating the association of non-specific chronic pain to subsequent cognitive deterioration or incident ADRD, all in British [31] and U.S. adults [24,30,32], have varied widely in study population, design, and methodology, results have likewise indicated that severe chronic pain [30,31], persistent pain [32], and/or reported pain interference [24] may predict subsequent worsening in memory [30,31], accelerated cognitive decline [32], and dementia [24,32].

While some longitudinal studies investigating the association between pain and dementia risk have included depression and/or anxiety as covariates in their adjusted models [24,28–30,32,34], no studies to our knowledge have explored the potential mediating role of mood disorders or evaluated the influence of sleep impairment on the association of chronic pain to incident ADRD. Sleep and mood disorders are common in older adults, have been strongly and reciprocally associated with chronic pain [54,55], and have been shown to be independent risk factors for ADRD [13–15,56,57], suggesting that sleep and mood impairment may mediate the observed associations between pain and ADRD risk. The role of sleep and mood neuromodulators, such as serotonin [58,59], dopamine and histamine [60,61] has been well documented in pain expression, likely contributing to the documented bidirectional relationships of sleep [54] and mood disorders [55,62] to pain conditions. In the current study, inclusion of depression, anxiety, and insomnia-related sleep disorders in the model weakened but did not eliminate the observed associations between NCPC and incident ADRD risk, suggesting a partial mediating role. In agreement with prior research, sleep [15,54] and mood disorders [13,14,57] remained strongly and positively associated with both baseline NCPC and with risk for incident ADRD in this cohort after adjustment for other factors.

NCPC and increased ADRD risk; possible pathways: although the mechanisms underlying the observed association of NCPC to incident ADRD remain speculative, chronic pain may operate via several pathways to increase risk for dementia [21,23,63–65]. Adults experiencing chronic pain have demonstrated diminished attention, impaired learning and memory, altered processing speed, reduced psychomotor efficiency, and compromised executive function [17–19,22,23], hallmarks of cognitive decline that may ultimately presage the development of cognitive impairment and dementia. Contributing to the documented decline in cognitive function that accompanies chronic pain, NCPC may promote specific adverse neurostructural and neurofunctional changes. For example, experimental and neuroimaging studies have demonstrated neurodegenerative changes in subjects with chronic pain that parallel those observed in ADRD [21,65,66], including reduction in grey matter volume in the amygdala, hippocampus and frontal cortices, the brain regions integrally involved in cognitive and behavioral functioning [66,67]. The increases in both peripheral and systemic inflammation that have been linked to chronic pain [68,69] may contribute to these neurodegenerative changes by contributing
to neuroinflammation [63]. For example, chronic pain-induced microglial neuroinflammation has been directly implicated in Alzheimer’s disease pathogenesis via production of amyloid beta plaques and neurofibrillary tangles [21]; persistent inflammation negatively affects neuroplasticity and synaptic performance via reduction in brain-derived neurotrophic factors [66,68,69]. Neuronal receptors in the brain are neither infinite nor mutually exclusive and serve a range of neurologic functions under limited resources. During persistent pain, nerve endings fire rapid pain impulses to the brain for remedial actions, which in turn, exhausts the neuronal resources that are also involved in cognitive functions [69–71]. In addition, the presence of chronic pain conditions has been correlated with dysregulation of noradrenergic-modulated endogenous pain autoinhibition [69], which has, in turn, been linked to negative cognitive outcomes, including decline in working and long-term memory [70,71].

In agreement with previously published research [3,7,45], risk for ADRD increased strongly with age in this study, and was elevated among African Americans and in adults who had less education or lower family income, were on Medicaid, or had a history of diabetes, stroke, or TBI. Similarly, the significant positive relationships between baseline sleep and mood disorders and likelihood of incident ADRD observed in this sample of US Medicare beneficiaries are consistent with the findings of numerous prior investigations [14,15]. Both psychotropics and analgesics are frequently employed to manage chronic mood disorders, insomnia, and pain conditions in the older population. NSAIDs have been reported to reduce risk of ADRD in most but not all studies [46], whereas prior research has demonstrated modest or no association of opioid analgesics to ADRD risk [47]. In this study, use of neither NSAIDs nor opioid analgesics was significantly related to risk for ADRD. In agreement with some [49] but not all previous studies [48,72], use of psychotropics, but not benzodiazepines, remained significantly associated with incident ADRD after adjustment for multiple confounders. However, as noted above, adjustment for these medications only slightly attenuated the observed relationships of NCPCs to incident ADRD.

Strengths and Limitations

This study has several strengths, including the population-based design, the use of longitudinal data from multiple cohorts, and the large, nationally representative sample of U.S. community-dwelling elders enrolled in FFS Medicare plans. Comprehensive information was available on a broad range of demographic and lifestyle characteristics, as well as on medical history, medication use, and other factors, allowing us to assess the potential confounding influence of these factors. Furthermore, NCPC’s, medication use, and history of other health conditions were ascertained using claims data and established algorithms. ADRD was identified using a combination of Medicare claims and survey data, likely leading to greater capture of this often under-reported and underdiagnosed outcome [41,73,74]. Notably, previous studies have indicated high specificity (89-95%) and acceptable sensitivity (64-85%) for the ascertainment of ADRD using multiple years of Medicare claims data [41,73,74]. We used a 3-year backward cohort design, with a two-year continuous follow-up and incident ADRD measured at two time points.

Our study also has a number of limitations, including the relatively short follow-up period and lack of information on NCPC duration or on chronic pain symptoms, precluding a more comprehensive assessment of the potential role of chronic pain and chronic pain conditions in the development of ADRD. Given that ADRD is often underdiagnosed and progression is generally slow and insidious, and that the study follow-up period was short, under-ascertainment of ADRD is likely in this study, potentially biasing our risk estimates toward the null. In addition, given that we used a conservative method [75] for ascertaining chronic pain (i.e., ≥1 inpatient visit or two outpatient visits for any chronic pain conditions 90 days apart), and that NCPC is typically under-reported in medical claims data [76–78], NCPC may have been under-ascertained in this study, again potentially biasing risk estimates towards the null. Moreover, as sleep and mood disorders often accompany the development of ADRD, these disorders may have reflected prodromal ADRD in some who were diagnosed with
incident ADRD. While we were able to adjust for a wide range of potential confounders, including smoking and BMI, we lacked information on certain lifestyle-related and other factors strongly linked to ADRD risk, including alcohol consumption, physical activity, genetic and familial predisposition, and social isolation [7,9]. Due to small cell sizes, we were also unable to adjust for Parkinson’s disease and related movement disorders, conditions which have been linked to chronic pain, as well as to mood and sleep disorders and cognitive impairment [79,80]. However, small cell sizes would also suggest that any residual confounding from these movement disorders is unlikely to explain our findings. Both ADRD and chronic pain have been associated with increased mortality [81–83], introducing potential survival bias. However, competing risk of death analyses yielded findings similar to those of our primary analyses, arguing against a substantive effect of survival bias on our study results. Finally, definitive conclusions regarding causality are not possible due to the short follow-up period in this study and the insidious nature of ADRD development and progression. However, while reverse causality cannot be ruled out, a growing literature suggests chronic pain can disrupt neurocognitive function and may increase risk for cognitive decline and incident dementia [18,65,84], whereas evidence for an inverse relationship remains sparse [22].

5. Conclusions

In this large, population-based study in a nationally representative sample of US community-dwelling elders enrolled in FFS Medicare, NCPC at baseline remained significantly and positively associated with risk for incident ADRD after adjustment for demographics, lifestyle factors, medical history, medications, and other factors. This association increased in magnitude with increasing NCPC burden and appeared to be partially mediated by the presence of mood and sleep disorders. Additional large, prospective studies with longer term follow-up are warranted to confirm our findings; to further elucidate the potentially important contribution of chronic pain to accelerated cognitive decline, new onset cognitive impairment and the development of ADRD; to clarify the potential mediating role of sleep and mood disorders; and to explore possible underlying mechanisms.

Supplementary Materials: The following are available online at http://www.mdpi.com/1660-4601/17/15/5454/s1, Figure S1: ADRD-NCPC Study Cohort: Medicare Current Beneficiary Survey (MCBS), 2001–2013, Table S1: ICD-9_Clinial Modification (ICD-9-CM) Diagnostic Codes.

Author Contributions: Conceptualization, design, and methodology, and to the interpretation and presentation of results, S.K., U.S. and K.E.I.; statistical analyses, S.K. and U.S.; manuscript draft, S.K.; subsequent iterations, S.K., U.S. and K.E.I.; critical review of the final draft, U.S. and K.E.I. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Institute of General Medical Sciences of the National Institutes of Health (Award Number 2U54GM104942-02), the WVCTSI and the Alzheimer’s Research and Prevention Foundation (ARPF).

Acknowledgments: Research reported in this publication was supported in part by the National Institute of General Medical Sciences of the National Institutes of Health (Award Number 2U54GM104942-02), the WVCTSI and the Alzheimer’s Research and Prevention Foundation (ARPF). S.K. received a Fulbright fellowship for doctoral research. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the ARPF or the Fulbright fellowship program.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Wilson, R.S.; Segawa, E.; Boyle, P.A.; Anagnos, S.E.; Hizel, L.P.; Bennett, D.A. The natural history of cognitive decline in Alzheimer’s disease. *Psychol. Aging* **2012**, *27*, 1008. [CrossRef] [PubMed]
2. McNeill, A.S. *Neurodegeneration: Theory, Disorders and Treatments*; Nova Science Publishers: Suffolk County, NY, USA, 2011.
3. Alzheimer’s Association. 2019 Alzheimer’s disease facts and figures. *Alzheimer’s Dement.* **2019**, *15*, 321–387. [CrossRef]
4. Nichols, E.; Szoeke, C.E.; Vollset, S.E.; Abbasi, N.; Abd-Allah, F.; Abdela, J.; Aichour, M.T.E.; Akinyemi, R.O.; Alahdab, F.; Asgedom, S.W. Global, regional, and national burden of Alzheimer’s disease and other dementias, 1990–2016: A systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 2019, 18, 88–106. [CrossRef]

5. Mehta, D.; Jackson, R.; Paul, G.; Shi, J.; Sabbagh, M. Why do trials for Alzheimer’s disease drugs keep failing? A discontinued drug perspective for 2010–2015. *Expert Opin. Investig. Drugs* 2017, 26, 735–739. [CrossRef]

6. Barnes, D.E.; Yaffe, K. The projected effect of risk factor reduction on Alzheimer’s disease prevalence. *Lancet Neurol.* 2011, 10, 819–828. [CrossRef]

7. Baumgart, M.; Snyder, H.M.; Carrillo, M.C.; Fazio, S.; Kim, H.; Johns, H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. *Alzheimer’s Dement.* 2015, 11, 718–726. [CrossRef]

8. Musicco, M.; Palmer, K.; Salamone, G.; Lupo, F.; Perri, R.; Mosti, S.; Spalletta, G.; Di Iulio, F.; Pettenati, C.; Cravello, L.; et al. Predictors of progression of cognitive decline in Alzheimer’s disease: The role of vascular and sociodemographic factors. *J. Neurol.* 2009, 256, 1288. [CrossRef]

9. Cooper, C.; Sommerlad, A.; Lyketsos, C.G.; Livingston, G. Modifiable predictors of dementia in mild cognitive impairment: A systematic review and meta-analysis. *Am. J. Psychiatry* 2015, 172, 323–334. [CrossRef]

10. Lye, T.C.; Shores, E.A. Traumatic brain injury as a risk factor for Alzheimer’s disease: A review. *Neuropsychol. Rev.* 2000, 10, 115–129. [CrossRef]

11. Zhou, J.; Yu, J.-T.; Wang, H.-F.; Meng, X.-F.; Tan, C.-C.; Wang, J.; Wang, C.; Tan, L. Association between stroke and Alzheimer’s disease: Systematic review and meta-analysis. *J. Alzheimer’s Dis.* 2015, 43, 479–489. [CrossRef]

12. Qu, C.; Xu, W.; Fratiglioni, L. Vascular and psychosocial factors in Alzheimer’s disease: Epidemiological evidence toward intervention. *J. Alzheimer’s Dis.* 2010, 20, 689–697. [CrossRef]

13. Gulpers, B.; Ramakers, I.; Hamel, R.; Köhler, S.; Voshaar, R.O.; Verhey, F. Anxiety as a predictor for cognitive decline and dementia: A systematic review and meta-analysis. *Am. J. Geriatr. Psychiatry* 2016, 24, 823–842. [CrossRef]

14. Ownby, R.L.; Crocco, E.; Acevedo, A.; John, V.; Loewenstein, D. Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. *Arch. Gen. Psychiatry* 2006, 63, 530–538. [CrossRef]

15. Bubu, O.M.; Brannick, M.; Mortimer, J.; Umasabor-Bubu, O.; Sebastiao, Y.V.; Wen, Y.; Schwartz, S.; Borenstein, A.R.; Wu, Y.; Morgan, D. Sleep, cognitive impairment, and Alzheimer’s disease: A systematic review and meta-analysis. *Sleep* 2016, 40, 32. [CrossRef]

16. Palma, J.-A.; Urrestarazu, E.; Iiarote, J. Sleep loss as risk factor for neurologic disorders: A review. *Sleep Med.* 2013, 14, 229–236. [CrossRef]

17. Ikram, M.; Innes, K.; Sambamoorthi, U. Association of Osteoarthritis and Pain with Alzheimer’s Diseases and Related Dementias among Older Adults in the United States. *Osteoarthr. Cartil.* 2019, 27, 1470–1480. [CrossRef]

18. Innes, K.E.; Sambamoorthi, U. The association of perceived memory loss with osteoarthritis and related joint pain in a large Appalachian population. *Pain Med.* 2017, 19, 1340–1356. [CrossRef]

19. Van Der Leeuw, G.; Eggermont, L.H.; Shi, L.; Milberg, W.P.; Gross, A.L.; Hausdorff, J.M.; Bean, J.F.; Leveille, S.G. Pain and cognitive function among older adults living in the community. *J. Gerontol. Ser. A Biomed. Sci. Med. Sci.* 2015, 70, 398–405. [CrossRef]

20. Scherder, E.J.; Plooij, B.; Achterberg, W.P.; Pieper, M.; Wiegersma, M.; Lobbezoo, F.; Oosterman, J.M. Chronic pain in “probable” vascular dementia: Preliminary findings. *Pain Med. (Malden Mass.)* 2015, 16, 442–450. [CrossRef]

21. Cao, S.; Fisher, D.W.; Yu, T.; Dong, H. The link between chronic pain and Alzheimer’s disease. *J. Neuroinflamm.* 2019, 16, 204. [CrossRef]

22. Cravello, L.; Di Santo, S.; Varrassi, G.; Benincasa, D.; Marchettini, P.; de Tommaso, M.; Shofany, J.; Assogna, F.; Perotta, D.; Palmer, K. Chronic Pain in the Elderly with Cognitive Decline: A Narrative Review. *Pain Ther.* 2019, 8, 53–65. [CrossRef] [PubMed]

23. Berryman, C.; Stanton, T.R.; Bowering, K.J.; Tabor, A.; McFarlane, A.; Moseley, G.L. Evidence for working memory deficits in chronic pain: A systematic review and meta-analysis. *Pain* 2013, 154, 1181–1196. [CrossRef] [PubMed]
24. Ezzati, A.; Wang, C.; Katz, M.J.; Derby, C.A.; Zammit, A.R.; Zimmerman, M.E.; Pavlovic, J.M.; Sliwinski, M.J.; Lipton, R.B. The Temporal Relationship between Pain Intensity and Pain Interference and Incident Dementia. *Curr. Alzheimer Res.* 2019, 16, 109–115. [CrossRef]

25. Hagen, K.; Stordal, E.; Linde, M.; Steiner, T.J.; Zwart, J.-A.; Stovner, L.J. Headache as a risk factor for dementia: A prospective population-based study. *Cephalalgia Int. J. Headache* 2014, 34, 327–335. [CrossRef] [PubMed]

26. Huang, S.-W.; Wang, W.-T.; Chou, L.-C.; Liao, C.-D.; Liou, T.-H.; Lin, H.-W. Osteoarthritis increases the risk of dementia: A nationwide cohort study in Taiwan. *Sci. Rep.* 2015, 5, 10145. [CrossRef] [PubMed]

27. Røttereng, A.K.S.; Bosnes, O.; Stordal, E.; Zwart, J.-A.; Linde, M.; Stovner, L.J.; Hagen, K. Headache as a predictor for dementia: The HUNT Study. *J. Headache Pain* 2015, 16, 89. [CrossRef]

28. Tzeng, N.S.; Chung, C.H.; Liu, F.C.; Chiu, Y.H.; Chang, H.A.; Yeh, C.B.; Huang, S.Y.; Lu, R.B.; Yeh, H.W.; Kao, Y.C.; et al. Fibromyalgia and Risk of Dementia—A Nationwide, Population-Based, Cohort Study. *Am. J. Med. Sci.* 2018, 355, 153–161. [CrossRef]

29. Tzeng, N.-S.; Chung, C.-H.; Lin, F.-H.; Yeh, C.-B.; Huang, S.-Y.; Lu, R.-B.; Chang, H.-A.; Kao, Y.-C.; Chiang, W.-S.; Chou, Y.-C.; et al. Headaches and Risk of Dementia. *Am. J. Med. Sci.* 2017, 353, 197–206. [CrossRef]

30. van der Leeuw, G.; Ayers, E.; Leiveille, S.G.; Blankenstein, A.H.; van der Horst, H.E.; Verghese, J. The effect of pain on major cognitive impairment in older adults. *J. Pain* 2018, 19, 1435–1444. [CrossRef]

31. Veronese, N.; Koyanagi, A.; Solmi, M.; Thompson, T.; Maggi, S.; Schofield, P.; Mueller, C.; Gale, C.R.; Cooper, C.; Stubbs, B. Pain is not associated with cognitive decline in older adults: A four-year longitudinal study. *Maturitas* 2018, 115, 92–96. [CrossRef]

32. Whiltlock, E.L.; Díaz-Ramírez, L.G.; Glymour, M.M.; Boscardin, W.J.; Covinsky, K.E.; Smith, A.K. Association Between Persistent Pain and Memory Decline and Dementia in a Longitudinal Cohort of Elders. *JAMA Intern. Med.* 2017, 177, 1146–1153. [CrossRef]

33. Yamada, K.; Kubota, Y.; Tabuchi, T.; Shirai, K.; Iso, H.; Kondo, N.; Kondo, K. A prospective study of knee pain, low back pain, and risk of dementia: The JAGES project. *Sci. Rep.* 2019, 9, 10690. [CrossRef] [PubMed]

34. Yang, F.-C.; Lin, T.-Y.; Chen, H.-J.; Lee, J.-T.; Pan, Q.; Kwong, P.L.; Stineman, M.G. Identifying neuropsychiatric disorders in the Medicare Current Beneficiary Survey: The benefits of combining health survey and claims data. *BMC Health Serv. Res.* 2016, 16, 537.

35. MCBS. Medicare Current Beneficiary Survey (MCBS), Centers for Medicare and Medicaid Services (CMS) Medicare and Medicaid Research Data. Available online: https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS (accessed on 5 July 2020).

36. Adler, G.S. A profile of the Medicare current beneficiary survey. *Health Care Financ. Rev.* 1994, 15, 153.

37. MCBS. Medicare Current Beneficiary Survey (MCBS), Centers for Medicare and Medicaid Services (CMS) Medicare and Medicaid Research Data Briefs. Available online: https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/Data-Briefs.html (accessed on 1 February 2019).

38. Ciol, M.A.; Hoffman, J.M.; Dudgeon, B.J.; Shumway-Cook, A.; Yorkston, K.M.; Chan, L. Understanding the use of weights in the analysis of data from multistage surveys. *Arch. Phys. Med. Rehabil.* 2006, 87, 299–303. [CrossRef] [PubMed]

39. Briesacher, B.A.; Tjàa, J.; Doubeni, C.A.; Chen, Y.; Rao, S.R. Methodological issues in using multiple years of the Medicare current beneficiary survey. *Medicare Medicaid Res. Rev.* 2012, 2, 2. [CrossRef]

40. CMS. Chronic Conditions Data Warehouse: Your Source for National Centers for Medicare and Medicaid Services (CMS) Medicare and Medicaid Research Data. Available online: https://www.ccwdata.org/web/guest/condition-categories (accessed on 26 February 2020).

41. Lin, P.-J.; Kaufer, D.I.; Maciejewski, M.L.; Ganguly, R.; Paul, J.E.; Biddle, A.K. An examination of Alzheimer’s disease case definitions using Medicare claims and survey data. *Alzheimer’s Dement.* 2010, 6, 334–341. [CrossRef]

42. Rose, S.M.S.-F.; Xie, D.; Streim, J.E.; Pan, Q.; Kwong, P.L.; Stineman, M.G. Identifying neuropsychiatric disorders in the Medicare Current Beneficiary Survey: The benefits of combining health survey and claims data. *BMC Health Serv. Res.* 2016, 16, 537.

43. Edlund, M.J.; Martin, B.C.; Devries, A.; Fan, M.-Y.; Braden, J.B.; Sullivan, M.D. Trends in use of opioids for chronic non-cancer pain among individuals with mental health and substance use disorders: The TROUP study. *Clin. J. Pain* 2010, 26, 1–8. [CrossRef]
44. Sullivan, M.D.; Edlund, M.J.; Fan, M.-Y.; DeVries, A.; Braden, J.B.; Martin, B.C. Trends in use of opioids for non-cancer pain conditions 2000–2005 in commercial and Medicaid insurance plans: The TROUP study. Pain 2008, 138, 440–449. [CrossRef] [PubMed]

45. Kot, C.; Gray, S.; Brookmeyer, R.; Fozard, J.; Zonderman, A. Age-specific incidence rates of Alzheimer’s disease: The Baltimore Longitudinal Study of Aging. Neurology 2000, 54, 2072–2077. [CrossRef] [PubMed]

46. Etminan, M.; Gill, S.; Samii, A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer’s disease: Systematic review and meta-analysis of observational studies. BMJ 2003, 327, 128. [CrossRef] [PubMed]

47. Hooten, W.M. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clin. Proc. 2016, 91, 955–970. [CrossRef]

48. Islam, M.M.; Iqbal, U.; Walther, B.; Atique, S.; Dubey, N.K.; Nguyen, P.-A.; Poly, T.N.; Masud, J.H.B.; Li, Y.-C.J.; Shabbir, S.-A. Benzodiazepine use and risk of dementia in the elderly population: A systematic review and meta-analysis. Neuroepidemiology 2016, 47, 181–191. [CrossRef]

49. Menefee, L.A.; Cohen, M.J.; Anderson, W.R.; Doghramji, K.; Frank, E.D.; Lee, H. Sleep disturbance and nonmalignant chronic pain: A comprehensive review of the literature. Pain Med. 2013, 14, 1–7. [CrossRef] [PubMed]

50. Kroenke, K.; Wu, J.; Bair, M.J.; Krebs, E.E.; Damush, T.M.; Tu, W. Reciprocal relationship between pain and depression: A 12-month longitudinal analysis in primary care. J. Pain 2011, 12, 964–973. [CrossRef] [PubMed]

51. Pask, S.; Dell’Olio, M.; Murtagh, F.E.; Boland, J.W. The effects of opioids on cognition in older adults with cancer and chronic non-cancer pain: A systematic review. J. Pain Symptom Manag. 2020, 59, 871–893. [CrossRef]

52. Islam, M.M.; Iqbal, U.; Walther, B.; Atique, S.; Dubey, N.K.; Nguyen, P.-A.; Poly, T.N.; Masud, J.H.B.; Li, Y.-C.J.; Shabbir, S.-A. Benzodiazepine use and risk of dementia in the elderly population: A systematic review and meta-analysis. Neuroepidemiology 2016, 47, 181–191. [CrossRef]

53. Morton, R.E.; John, P.D.; Tyas, S.L. Migraine and the risk of all-cause dementia, Alzheimer’s disease, and vascular dementia: A prospective cohort study in community-dwelling older adults. Int. J. Geriatr. Psychiatry 2019, 34, 1667–1676. [CrossRef]

54. Moraros, J.; Nwankwo, C.; Patten, S.B.; Mousseau, D.D. The association of antidepressant drug usage with cognitive impairment or dementia, including Alzheimer disease: A systematic review and meta-analysis. Depress. Anxiety 2017, 34, 217–226. [CrossRef]

55. Pariente, A.; de Gage, S.B.; Moore, N.; Bégaud, B. The benzodiazepine–dementia disorders link: Current state of knowledge. CNS Drugs 2016, 30, 1–7. [CrossRef]

56. Kroenke, K.; Wu, J.; Bair, M.J.; Krebs, E.E.; Damush, T.M.; Tu, W. Reciprocal relationship between pain and depression: A 12-month longitudinal analysis in primary care. J. Pain 2011, 12, 964–973. [CrossRef] [PubMed]

57. Hooten, W.M. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clin. Proc. 2016, 91, 955–970. [CrossRef]

58. Islam, M.M.; Iqbal, U.; Walther, B.; Atique, S.; Dubey, N.K.; Nguyen, P.-A.; Poly, T.N.; Masud, J.H.B.; Li, Y.-C.J.; Shabbir, S.-A. Benzodiazepine use and risk of dementia in the elderly population: A systematic review and meta-analysis. Neuroepidemiology 2016, 47, 181–191. [CrossRef]

59. Hooten, W.M. Chronic Pain and Mental Health Disorders: Shared Neural Mechanisms, Epidemiology, and Treatment. Mayo Clin. Proc. 2016, 91, 955–970. [CrossRef]

60. Lin, J.-S.; Sergeeva, O.A.; Haas, H.L. Histamine H3 receptors and sleep-wake regulation. J. Pharmacol. Exp. Ther. 2011, 336, 17–23. [CrossRef] [PubMed]
66. Malfliet, A.; Coppieters, I.; Van Wilgen, P.; Kregel, J.; De Pauw, R.; Dolphens, M.; Ickmans, K. Brain changes associated with cognitive and emotional factors in chronic pain: A systematic review. *Eur. J. Pain* **2017**, *21*, 769–786. [CrossRef] [PubMed]

67. Mutso, A.A.; Radzicki, D.; Bališki, M.N.; Huang, L.; Banisadr, G.; Centeno, M.V.; Radulovic, J.; Martina, M.; Miller, R.J.; Aρkarian, A.V. Abnormalities in hippocampal functioning with persistent pain. *Trends Neurosci.* **2015**, *38*, 237–246. [CrossRef] [PubMed]

68. Descalzi, G.; Ikegami, D.; Ushijima, T.; Nestler, E.J.; Zachariou, V.; Narita, M. Epigenetic mechanisms of chronic pain. *Trends Neurosci.* **2015**, *38*, 237–246. [CrossRef] [PubMed]

69. Ossipov, M.H.; Morimura, K.; Porreca, F. Descending pain modulation and chronification of pain. *Curr. Opin. Support. Palliat. Care* **2014**, *8*, 143.

70. Sara, S.J. The locus coeruleus and noradrenergic modulation of cognition. *Nat. Rev. Neurosci.* **2009**, *10*, 211. [CrossRef]

71. Chamberlain, S.R.; Müller, U.; Blackwell, A.D.; Robbins, T.W.; Sahakian, B.J. Noradrenergic modulation of working memory and emotional memory in humans. *Psychopharmacology* **2006**, *188*, 397–407. [CrossRef]

72. Khoury, R.; Grossberg, G.T. Impact of antidepressant use on the trajectory of Alzheimer’s disease: Evidence, mechanisms, and therapeutic implications. *CNS Drugs* **2019**, *33*, 17–29. [CrossRef] [PubMed]

73. Østbye, T.; Taylor, D.H., Jr.; Clipp, E.C.; Scovoy, L.V.; Plassman, B.L. Identification of dementia: Agreement among national survey data, medicare claims, and death certificates. *Health Serv. Res.* **2008**, *43*, 313–326. [CrossRef]

74. Taylor, D.H., Jr.; Fillenbaum, G.G.; Ezell, M.R. The accuracy of medicare claims data in identifying Alzheimer’s disease. *J. Clin. Epidemiol.* **2002**, *55*, 929–937. [CrossRef]

75. Tonelli, M.; Wiebe, N.; Fortin, M.; Guthrie, B.; Hemmelgarn, B.R.; James, M.T.; Klarenbach, S.W.; Lewanczuk, R.; Manns, B.J.; Ronksley, P. Methods for identifying 30 chronic conditions: Application to administrative data. *BMC Med. Inform. Decis. Mak.* **2015**, *15*, 31.

76. Tian, T.Y.; Zlateva, I.; Anderson, D.R. Using electronic health records data to identify patients with chronic pain in a primary care setting. *J. Am. Med Inform. Assoc.* **2013**, *20*, e275–e280. [CrossRef] [PubMed]

77. Treede, R.-D.; Rief, W.; Barke, A.; Aziz, Q.; Bennett, M.I.; Benoliel, R.; Cohen, M.; Evers, S.; Finnerup, N.B.; First, M.B.; et al. A classification of chronic pain for ICD-11. *Pain* **2015**, *156*, 1003–1007. [CrossRef] [PubMed]

78. Ward, M.M. Estimating disease prevalence and incidence using administrative data: Some assembly required. *J. Rheumatol.* **2013**, *40*, 1241–1243. [CrossRef] [PubMed]

79. Fil, A.; Cano-de-la-Cuerda, R.; Muñoz-Hellín, E.; Vela, L.; Ramiro-González, M.; Fernández-de-las-Peñas, C. Pain in Parkinson disease: A review of the literature. *Parkinsonism Relat. Disord.* **2013**, *19*, 285–294. [CrossRef] [PubMed]

80. Aarsland, D.; Zuccalli, J.; Brayne, C. A systematic review of prevalence studies of dementia in Parkinson’s disease. *Mov. Disord. J. Mov. Disord. Soc.* **2005**, *20*, 1255–1263. [CrossRef] [PubMed]

81. Smith, D.; Wilkie, R.; Uthman, O.; Jordan, J.L.; McBeth, J. Chronic pain and mortality: A systematic review. *PLoS ONE* **2014**, *9* (Suppl. 1), e99048. [CrossRef]

82. Taylor, C.A.; Greenlund, S.F.; McGuire, L.C.; Lu, H.; Croft, J.B. Deaths from Alzheimer’s Disease—United States, 1999–2014. *MMWR Morb. Mortal. Wkly. Rep.* **2017**, *1*, 343–344.

83. Zissimopoulos, J.M.; Tysinger, B.C.; Clair, P.A.; Crimmins, E.M. The impact of changes in population health and mortality on future prevalence of Alzheimer’s disease and other dementias in the United States. *J. Gerontol. Ser. B* **2018**, *73*, S38–S47. [CrossRef]

84. Higgins, D.M.; Martin, A.M.; Baker, D.G.; Vasterling, J.J.; Risbrough, V. The relationship between chronic pain and neurocognitive function: A systematic review. *Clin. J. Pain* **2018**, *34*, 262. [CrossRef]