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Prevalence of Chronic Pain Among People with Dementia: A Nationwide Study Using French Administrative Data

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ABSTRACT

Objective: *Alzheimer's disease or Related Dementia (ADRD) is known to disturb pain perception and reduce the ability to report it, resulting in underestimation by practitioners and sub-optimal medical management. The aim of this study was to estimate the prevalence of all types of CP among people with ADRD.* ***Design:*** *Nationwide cross-sectional study.Settings: French community-dwelling and nursing home residents.Participants: People with ADRD, >40 years old, treated with cholinesterase inhibitors or memantine, or with a diagnosis/long-term illness of ADRD and matched with a comparison sample.* ***Settings:*** *French community-dwelling and nursing home residents.* ***Participants:*** *People with ADRD, >40 years old, treated with cognitive stimulants (cholinesterase inhibitors and memantine) or with a diagnosis/long-term illness of ADRD and matched with a comparison sample (non-ADRD).* ***Measurements:*** *The capture-recapture method was performed to provide estimates of the prevalence of CP. People treated with analgesic drugs for ≥6 months consecutively or with a medical diagnosis of CP (ICD-10 codes) or referred to a pain center were considered as having CP.* ***Results:*** *A total of 48,288 individuals were included, of which 16,096 had ADRD and 32,192*

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without ADRD. The estimated prevalence of CP in people with ADRD was from 57.7% [52.9;63.3] to 57.9%[53.0;63.9], and slightly higher than the non-ADRD sample (from 49.9%[47.0;53.2] to 50.4%[47.3;53.9], p <0.001). ***Conclusions:*** *The prevalence of CP among people living with ADRD was at least the same as or better than individuals without ADRD. This result should alert practitioners' attention to the need for effective pain assessment and management in this population who has difficulties to express and feel pain.* (Am J Geriatr Psychiatry 2023; ■■:■■−■■)

Highlights

- **What is the primary question addressed by this study?**
  A nationwide cross-sectional study using medical administrative data study to estimate the prevalence of chronic pain among people living with dementia from 2017 to 2019 in French community.
- **What is the main finding of this study?**
  The innovative capture-recapture method used to estimate chronic pain prevalence and avoid the problems of selection bias and generalization to the entire population. The prevalence of chronic pain ranged from 57.7% to 57.9% in patients with dementia. 24.5% of chronic pain patients were no longer treated for their pain after dementia diagnosis.
- **What is the meaning of the finding?**
  These findings argue for policies and medical management that prevent and mitigate chronic pain in patients with dementia.

OBJECTIVES

In Europe, Alzheimer's disease and related dementias (ADRD) affect from 0.6% (60−64 years old) to 40.8% (90+ years old) of the population.[1] Dementias have a strong impact on activities of daily living and are a cause of heavy dependence,[2,3] which may be increased by other comorbidities such as chronic pain (CP).[4]

Chronic pain affects approximately 30% of the general population,[5−8] increases to 50% in community-dwelling older people, and reaches up to 80% in institutionalized individuals.[9] Several recent studies have shown that CP is a risk factor for developing dementia,[10−16] and that the presence of dementia being associated with a higher prevalence and intensity of pain.[17−21] This interrelation can be explained in part by the fact that patients with CP or dementia share common nervous system impairments, including abnormalities of the noradrenergic system,[22] activation of microglia and central neuroinflammation.[23]

Nevertheless, the prevalence of CP is likely underestimated in pauci-communicative populations, such as cognitively impaired older people where cognitive disorders can disturb their perception of pain as well as reduce the ability to report their symptoms.[9] It is therefore likely that the presence of pain may be underestimated in people with dementia. Moreover, no study has precisely assessed the prevalence of CP (all etiology and defined by a duration of at least 3 or 6 months[24]) in people with ADRD. Only a few studies have assessed the presence of pain in this population, but without any notion of the chronicity and etiology. These studies observed a wide prevalence, varying greatly between studies and methodology, from 21.2% to 68.8%.[17−19]

Thus, studies are needed to specifically and reliably estimate the prevalence of CP and provide an opportunity to adapt the management of CP in people with ADRD. In view of the lack of data on the prevalence of CP in patients with ADRD, the objective of this study was to provide new data, using a large number of people and based on a reliable methodology, about the prevalence of CP in patients with

ADRD. To assess CP prevalence among people with ADRD, an innovative statistical method called capture-recapture, and based on log-linear modeling, was used within a representative sample of the French population having ADRD, and using data from the French National Healthcare database. The capture-recapture method is a statistical inference method originally used in biology and zoology to estimate the size of a population,[25] and largely used in clinical epidemiology (e.g., diabetes,[26] multiple sclerosis,[27] juvenile idiopathic arthritis,[28] cancers,[29] and CP[30,31]). The interest of the capture-recapture method is mainly to limit some of the selection biases inherent in retrospective studies and in data available in medical-administrative databases.

METHODS

Data Sources

The data were obtained from the EGB ("*Echantillon Généraliste des Bénéficiaires")* database, created in 2005 and incorporating three databases which contain reimbursements and consumption of care, and hospitalizations and consultations in hospitals and specialized medical units. The EGB database represents a representative sample (1/97th) of the French National Healthcare database (~99% of the French population), i.e., 741,985 subjects in 2017−2019.[32] This research project has been approved by the "*Centre d'épidémiologie sur les causes médicales de décès* (CépiDc) - *Institut national de la santé et de la recherche médicale* (INSERM)," the French data protection authority ("*Commission Nationale de l'Informatique et des Libertés*"- CNIL), and by the local Ethics Committee (IRB00013412, "CHU de Clermont-Ferrand IRB #1," IRB number 2022-CF039) with compliance to the French policy of individual data protection.

Identification of Individuals with Alzheimer's Disease or Related Dementia

All adults older than 40 years and with an ongoing ADRD between January 1, 2017 and December 31, 2019 were included. The cut-off at 40 years old was chosen in order to restrict our sample to the target population and to reduce false inclusions, as ADRD mainly affects older people and the prevalence of ADRD <40 years old is extremely low.[33] An ADRD was identified over the period 2005−2019 by their Anatomical Therapeutic Classification (ATC) code of validated treatment for dementia (cholinesterase inhibitors or memantine) or medical diagnoses according to the International Classification of Disease (ICD-10) or long-term illness (LTI) for ADRD, as previously published by Elyn et al.[34] and Rochoy et al.[35] A comparison non-ADRD sample was generated with matching (2:1; 2 controls for 1 case) on a propensity score with a caliper of 0.1, incorporating age, gender, and the Charlson Comorbidities Index (CCI).[36] The variables chosen for the propensity score correspond to the main factors that can influence CP, including mainly age, gender, and comorbidities. The comorbidities were grouped into a score called the CCI (the higher the score, the more comorbidities), a score widely used in epidemiological studies (for details see Supplementary Methods).

Description of the three Data Sources used to Identify Patients with Chronic Pain

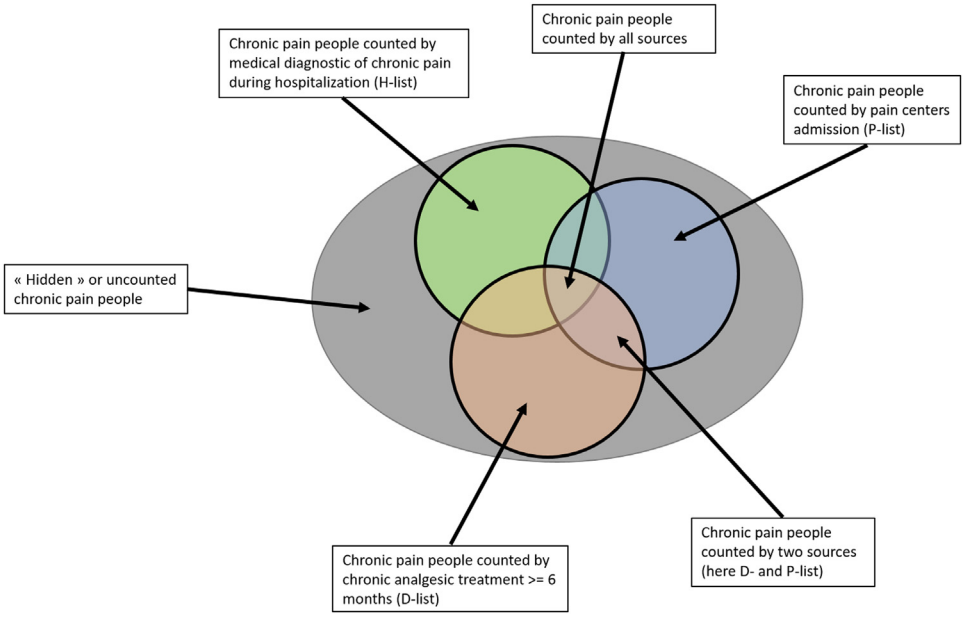
Chronic pain patients were identified from sample of people with or without ADRD between 2017 and 2019 using three sources as previously published by our team[30,31] (Fig. 1 and for details see Supplementary Methods):

(i) The first source (D-list) was the medication reimbursement database. All reimbursed analgesic treatments were identified using their ATC codes. Each patient with at least 6 months duration of continuous analgesic prescription between 2017 and 2019 was identified as a CP patient. To avoid CP misidentification, patients in this source with a history of mental health disorders (ICD-10 codes F00 to F99) or epilepsy (G40 and G41) were excluded from the D-list. Indeed, antidepressants or antiepileptic drugs, used as first and second line analgesics in CP, were also commonly used in other neurological disorders.

(ii) The second source (H-list) was the national hospital discharge database: all patients hospitalized with principal or associated diagnosis of CP (ICD-10) were identified.

(iii) The third source (P-list) corresponded to the pain center database, including consultations and hospitalizations in pain centers.

FIGURE 1. Schematic diagram of the three-source capture–recapture analyses. The grey area corresponds to the unidentified chronic pain individuals in the sources, called population "X". The colored areas correspond to the three data sources (H-, D- and P- lists). The overlapping zones correspond to the "recapture" phases of the capture-recapture method.



Capture-Recapture Method

The capture-recapture method estimates the total number of cases of a specific disease after matching cases reported in at least two sources. In this study, three data sources were used to identify individuals with CP.

The capture-recapture data consisted of overlapping lists of CP patients from three administrative data sources (see above). Each source represented the "capture" step, that is, each source is considered a sample. Overlaps between sources were considered analogous to overlapping "captures" and thus corresponded to the "recapture" step, using the unique identification number (NIR - the French national identification number) as a label or marker. Recapture information (i.e., source overlap or source intersection information) can be used to estimate the size of the unobserved population (called "X") and then the total population under appropriate assumptions (Supplementary Fig. 1A).

In epidemiology, the validity and reliability of the estimates depend on the following assumptions on which the method is based: 1) a closed population, i.e., there is no change during the survey period (no births, no deaths, no immigration or emigration). 2) Patients can be matched without error between sources, i.e., the procedure for matching records between sources must be reliable (no misclassification of records), because accurate determination of the number of overlapping cases is essential to obtain unbiased estimates. 3) Independence between sources: two sources are independent if the probability of a patient being reported in one source does not depend on its probability of being reported in the other source. In the context of three sources, the independence assumption is not crucial because it is possible to adjust for potential dependencies between sources. This adjustment is made by integrating product terms into the log-linear model to take into account potential dependencies between sources, and thus limit this bias (see Hook's review for more details).[37] 4) A homogeneous population, i.e., each patient has the same probability of being observed in the sources or, alternatively, the probability of being observed in a source does not depend on the patient's characteristics (age, gender, severity of illness, etc.). Nevertheless, this bias is actually small when the frequencies

predicted from independent subgroup analyses (here, by gender and age) remain similar to the frequencies observed in the overall population (see Hook's review for more details).[37]

From the 3-source capture-recapture data, there are a number of methods to provide estimates of the number of unobserved patients (population "X"),[38] and in particular the log-linear modeling method have been widely used.[39,40] The log-linear method allows the missing data (total number of cases) to be determined from a 2^s contingency table ("S" being the total number of sources). With 3 sources (S = 3), there are 2^3 or 8 possible combinations of these sources in which cases do or do not appear (Supplementary Fig. 1B). A 3-source analysis was performed by fitting 8 log-linear models to the data arranged in this contingency table 2^s. Using log-linear methods with three lists, estimates are generated by eight models, from the simplest, independence of all sources (the "independent" model), to the most complex, the presence of all two-source interactions (the "saturated" model). In other words, eight types of log-linear models can be identified: the "independent model" which assumes that all sources are independent (Table 1, model n° 8 [P H D]), three models that include a two-source interaction term (Table 1, model n° 5, 6 or 7), 3 models that include two terms of two-source interaction (Table 1, Model No. 2, 3, or 4), and finally, a "saturated model" that incorporates all possible interactions between two sources (Table 1, model n° 1 [P H D PH PD HD]). The dependence between sources is incorporated by introducing interaction terms into the log-linear models.[39]

Theoretically, the saturated model represents the best model that fits the data perfectly, including all possible interactions. However, although the saturated model provides the least biased estimates, it is also associated with a large variance (called "range"), which translates into lower precision of estimates (called "mean precision" or range / 2; the more it tends towards 0, the more precise the estimate is, and vice versa.), compared to more parsimonious models. Statisticians consider this principle as a "trade-off between bias and variance." All model selection methods use some notion of this trade-off (as the number of parameters of a model increases, the bias decreases but the variance increases). Generally, the saturated model is the starting point, i.e., the default model that is used to test the adequacy of the other models, in order to select the most parsimonious model that will achieve an adequate trade-off between bias and variance. This modeling strategy has been validated and described in detail elsewhere[39,40] and has been used previously by our team to identify population of CP patients in general population and in opioid-maintained patients.[30,31]

Briefly, to assess how well different log-linear models fit the data, the log likelihood ratio test, also known as G^2 or deviance, was used (the lower the value of G^2, the better the model fit). Moreover, to select the best-fitting model, two supplemental information criteria were used: the Bayesian information criterion ([BIC = G^2x(log Nobs/2π)(D.F.)]; where "D.F." is the number of degrees of freedom [also called parsimony]) and the Akaike information criterion [AIC = G^2x2(D.F.)]. The best-fitting model was defined as the one that offered the best balance between the lowest G^2, the lowest BIC and/or the lowest AIC, the mean precision and the most parsimonious model (the greatest simplicity, i.e., the least saturated model that includes fewer interaction terms).[39,41] Parsimonious models achieve an adequate trade-off between bias and variance and all model selection methods are based on this principle.[42] Our analyses of the data were therefore based on a parsimonious model that provides an accurate approximation of the structural information of the data in question.

TABLE 1. Characteristics of ADRD, non-ADRD and chronic pain samples. Results are presented as numbers (percentages), mean ± standard deviation or median [25th; 75th percentiles]

No.	Model Description	Source Interactions
1	P H D PH PD HD	"saturated model" = all possible two-source interactions
2	P H D PD HD	2 interactions = PD and HD
3	P H D PH PD	2 interactions = PD and PH interactions
4	P H D PH HD	2 interactions = PH and HD interactions
5	P H D PD	1 interaction = PD
6	P H D HD	1 interaction = PH
7	P H D PH	1 interaction = HD
8	P[a] H[b] D[c]	no interaction

ADRD: Alzheimer's Disease and Related Dementia; CP: Chronic Pain

[a] P = source P-list (people with chronic pain counted by pain centers admission.

[b] H = source H-list (people with chronic pain counted by chronic pain diagnosis during hospitalization.

[c] D = source D-list (people with chronic pain counted by chronic analgesic treatment ≥6 months.

Statistics

The prevalence of CP was determined by dividing the number of CP individuals (addition of the number of identified individuals from the three sources called "estimate," plus the number of unidentified individuals by sources called "X estimate") by the number of total ADRD population. Confidence intervals (CI95%) of goodness of fit were estimated using the likelihood ratio. The Pearson's χ^2 test was used for comparative analysis, and an effect size was performed with Hedges' g test[43,44] to illustrate the importance of the differences observed (an effect size of 0.2 is considered low, 0.5 is medium and 0.8 is high). All p-values were two-sided and $p < 0.05$ was considered statistically significant.

According to the data available in databases, several covariates were analyzed such as gender, age, type of comorbidities, types of dementia and CP (when known), and type of analgesics. All these covariates were expressed as frequency and associated percentage for categorical data and as mean ± standard deviation or median and interquartile range for quantitative data. Sensitivity analysis was also conducted by examining the impact of precision of the estimates of CP with increasing model size. These analyses were performed using the "proc genmod" procedure[38] on the SAS Enterprise Guide statistical software (SAS Institute, version 9.4, NC).

RESULTS

Characteristics of Study Samples

In 2017−2019, 17,325 individuals with ADRD were identified. After matching with individuals without ADRD (comparison sample called "non-ADRD"), 16,096 ADRD and 32,192 non-ADRD were included and analyzed (Fig. 2). Consistent with propensity score matching, incorporating age, gender, and comorbidities, characteristics were similar between ADRD and non-ADRD (Supplementary Table 1), with a median age of 80 [71;86] years, 70% female; and the most common comorbidities were cerebrovascular disease (25%), heart disease (19%−23%), cancer (18%−25%), and diabetes (15%−18%). In the ADRD group, when the type of dementia was informed by ICD-10 codes (n = 7,574; 47.1%), Alzheimer's disease was the most common type of dementia (61.4%).

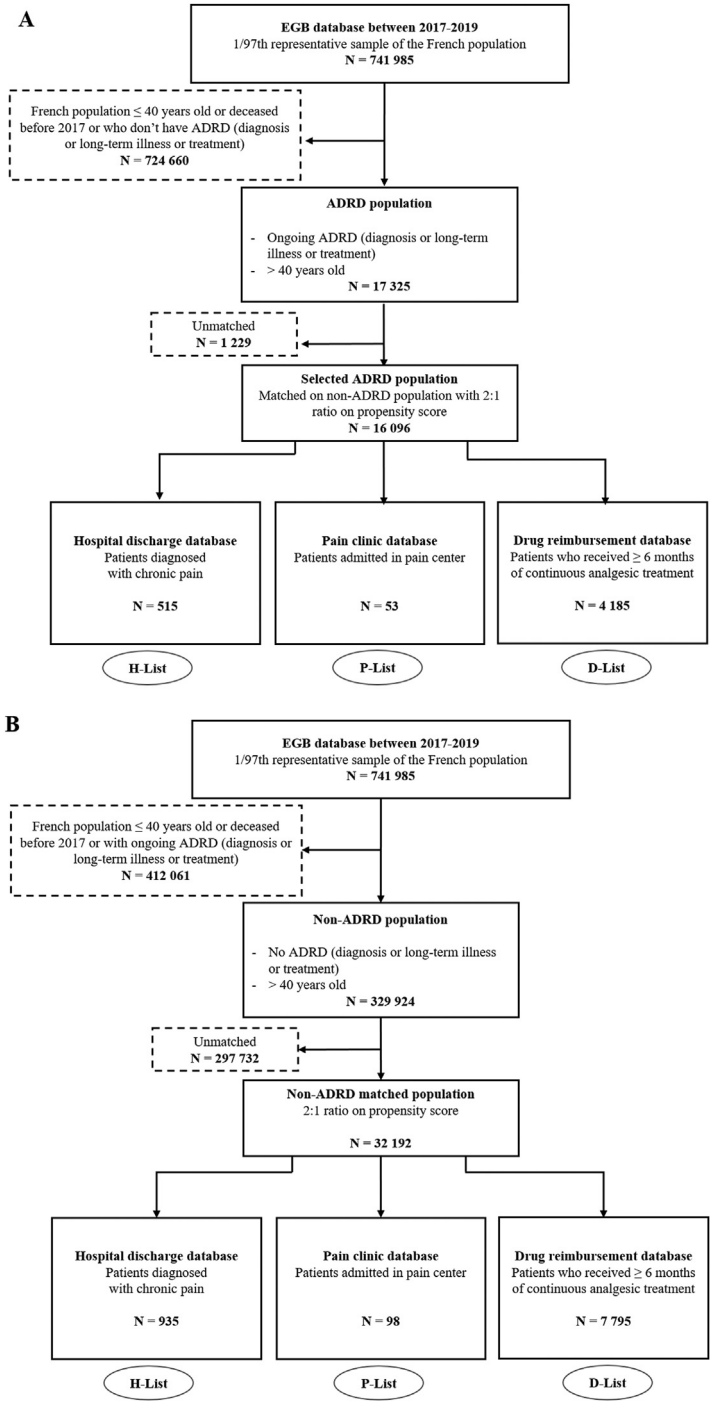
The characteristics of people with CP, with or without ADRD, were similar (Supplementary Table 1). Compared to people without CP, they were older, more often female, and with a higher CCI (more comorbidities). The types of pain, when known, were also similar, but only about 30% of the individuals had a precise diagnosis of their pain. Therapeutic pain treatments were also quite similar between ADRD and non-ADRD, but people with ADRD appeared to receive fewer opioids and more SNRI antidepressants. Overall, individuals with CP were mostly exposed to non-opioids analgesics (∼90%), followed by opioids (40%−45%) and anti-inflammatories (topical and oral, 40%−45% and ∼30% respectively). Among opioids, tramadol was that prescribed most, accounting for approximately 30% of prescriptions. Interestingly, it appears that the diagnosis of ADRD could modify the therapeutic management of pain. Indeed, 24.5% of patients treated for CP (at least a 6-month continuity of analgesic treatment) in the year prior to the diagnosis of their ADRD are no longer treated for their pain after ADRD diagnosis.

Chronic Pain Prevalence Among People with or Without ADRD

Across the eight estimation models generated by the capture-recapture method, the prevalence of CP ranged from 29.5% [28.6;31.4] (model 2) to 73.0% [42.8;100.0] (model 1 "saturated") for people with ADRD and from 27.4% [26.7;28.6] (model 2) to 52.6% [37.8;85.8] (model 1 "saturated") for people without ADRD. To get a more accurate estimate of the prevalence of CP, the best models were chosen according to the conditions described in the materials and methods.

Two models (models 3 and 7) achieved the best balance of lowest G^2, AIC, BIC and the best parsimony. Among the 16,096 individuals with ADRD, 9,283 (model 7; 4,481 were identified by sources + 4,802 by "X estimate") and 9,327 (model 3; 4,481 were identified by sources + 4,846 by "X estimate") individuals were identified with CP (Fig. 3A, Table 2 and Supplementary Table 2). This represents an estimate of prevalence of CP from 57.7% [52.9−63.3] to 57.9% [53.0−63.9]. Similarly, among the 32,192 people without ADRD (non-ADRD) and according to the two models that achieved the best balance (models 3

FIGURE 2. Flowchart of people with ADRD, non-ADRD and chronic pain. (A) People with ADRD and (B) without ADRD (non-ADRD) were included from the administrative EGB database according to the presence or absence of ongoing ADRD (diagnosis or long-term illness or treatment) and >40 years. Chronic pain patients were captured from the 3 different databases merged in the EGB: H-list - the hospital discharge database; P-list - the pain center database; and D-list - the drug reimbursement database. EGB, "*Echantillon Généraliste des Bénéficiaires*"; ADRD, Alzheimer's Disease and Related Dementia.



and 7), the estimate of prevalence of CP was from 50.4% [47.3−53.9] to 49.9% [47.0−53.2] (Fig. 3B, Table 2 and Supplementary Table 3).

A significant difference between the prevalence of CP estimates between ADRD and non-ADRD was observed, with a prevalence of CP higher among people with ADRD whatever the models (models 3 ADRD versus model 3 non-ADRD: Chi test = 246.207, degree of freedom = 1, p-value < 0.001; models 7 ADRD versus model 7 non-ADRD: Chi test = 260.130, degree of freedom = 1, p-value < 0.001), but this difference remains low (Hedge's g effect size = 0.17) (Supplementary Table 4).

Prevalence of Chronic Pain: Stratification by Age and Gender

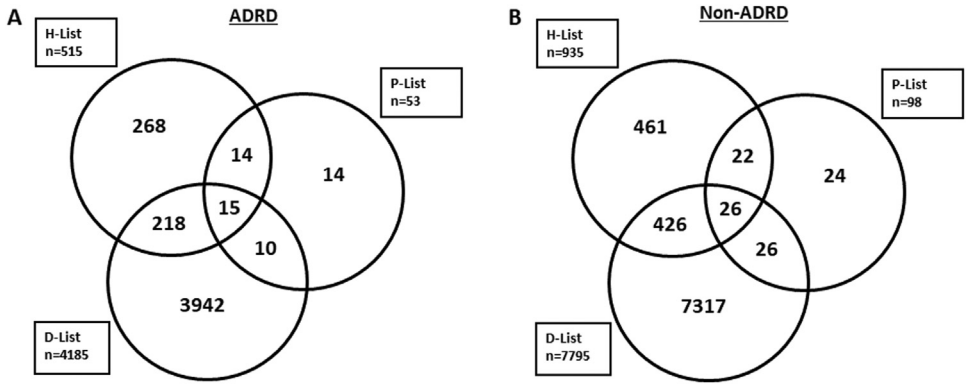
Across the eight estimation models generated by the capture-recapture method, the prevalence of CP ranged from 30.7% [30.0; 32.3] (model 2) to 59.2% [53.7; 65.9] (model 7) for females with ADRD (n = 11,272), and from 31.0% [24.9; 85.7] (model 2) to 100.0% [52.9; 100.0] (model 4) for males with ADRD (n = 4,824). As previously, models 3 and 7 were the best models. The results highlighted that the prevalence of CP was higher in females, from 59.0% [53.3;61.6] to 59.2% [53.7;65.9], than in males, from 54.3% [45.7;66.2] to 55.6% [46.4;68.7] (models three Female versus model three Male: Chi test = 15.796, degree of freedom = 1, p-value < 0.001; models 7 Female versus model 7 Male: Chi test = 33.638, degree of freedom = 1, p-value < 0.001), but this difference remains small (effect size = 0.08−0.11 according to the model).

Concerning stratification by age, the prevalence of CP ranged from 25.1% [24.4; 26.9] (model 2) to 65.7% [36.5; 100.0] (model 4) for people < 80 years old with ADRD (n = 7,514) and from 34.0% [32.1; 41.2] (model 2) to 63.6% [56.9; 72.1] (model 3) for people ≥80 years old with ADRD (n = 8,582).

As previously, models 3 and 7 were the best models, and the same observation was made for individuals over 80 years old with a prevalence of CP from 63.3% [56.8;71.4] to 63.6% [56.9;72.1] compared to those under 80 years old with a prevalence of CP from 51.2% [44.8;59.6] to 51.6% [44.6;60.9] (models 3 ≥80 years versus model 3 <80 years: Chi test = 238.277, degree of freedom = 1, p-value <0.001; models 7 ≥80 years versus model 7 <80 years: Chi test = 240.618, degree of freedom = 1, p-value <0.001), but this difference remains small (effect size = 0.27) (Supplementary Figs. 2−3 and Supplementary Tables 2−6).

Finally, the addition of the number of women and men identified with CP (model 3: 6,652 + 2,684 = 9,336; and model 7: 6,673 + 2,618 = 9,291) was similar to the number of all ADRD individuals with CP in the main analysis (Table 2; model 3 = 9,327; model 7 = 9,283). The same is true for the analysis by age (total subgroups model 3: 9,338 [3,877 + 5,461]; and model 7:

FIGURE 3. Distribution of chronic pain in people with or without ADRD according to data source. The figure represents the distribution of the number of individuals with chronic pain in people with (A) or without (B) ADRD, matched from the 3 different databases merged in the EGB between 2017 and 2019: H-list - the hospital discharge database; P-list - the pain center database; and D-list - the drug reimbursement database. ADRD, Alzheimer's Disease and Related Dementia.



9,280 [3,847 + 5,433]). Thus, these two subgroup analyses (age and gender) showed that there was no heterogeneity between our data sources.

CONCLUSIONS

This study provides an estimate of the prevalence of CP among French people with ADRD using an innovative method called capture-recapture and data from the French National Healthcare database. The prevalence was estimated from 57.7% to 57.9%, and was slightly higher than people without ADRD. Comparison with the literature remains difficult because of the lack of data on the prevalence of CP among people with ADRD. Nevertheless, a few studies have assessed the prevalence of pain (without specifying or identifying chronicity and/or etiology) in this population, and have been grouped in the review by van Kooten et al.[17] Our estimated prevalence is in the high end of the estimates of this review (ranging from 21.2% to 68.8%). However, in our study, the prevalence of CP may be underestimated due to the underestimation of pain in people with dementia despite the existence of many tools to screen and assess pain in non-communicative people.[45] Indeed, people with CP are mainly identified by their pain medication, but people with dementia have a hard time expressing their pain. Therefore, they would also have a hard time getting pain medications. Nevertheless, in our study the capture-recapture method corrects the potential underestimation whatever the sample considered (by including, in the final estimate, unidentified population by sources, called population "X").

Interestingly, about 25% of patients treated for CP, at least a 6-month continuity of analgesic treatment (assuming the presence of CP) in the year prior to the diagnosis of their ADRD are no longer treated for their pain after ADRD diagnosis. This could imply that the onset of ADRD reduced the therapeutic management of CP by the discontinuation or deprescribing of analgesics, as recently observed by Wei et al. for opioid therapy.[46] This deprescribing could be explained by: 1) the decrease of both the capacity of people to express their complaint and the perception of pain due to cognitive disorders (thus, the less "apparent pain" for the clinician induces potential deprescribing); 2) an iatrogenic event (e.g., confusional syndrome) which could have encouraged the deprescribing of analgesics, but which was in fact a prodromal of the ADRD; and 3) the strict application of recommendations on the prescription of analgesics (contraindication of NSAIDs, psychotropics, etc.) for frail older people following their hospitalization in a geriatric ward, also leading to possible deprescribing. Nevertheless, a specific study on this topic is needed to confirm this.

The methodology for selecting people with ADRD, using ICD-10 and ATC coding, was based on recently published studies.[33,34] The people with ADRD analyzed were on average 80 years old, predominantly female, and suffering mainly from cardiac and cerebrovascular comorbidities. These characteristics are consistent with the demographic profile of this population.[47–50] The most common type of dementia, when indicated, was Alzheimer's disease, as previously published in France from health databases.[35] Then, in terms of external validity, our sample is representative of French people with ADRD. In addition, the number of people identified with ADRD was 17,325, or about 2.3% of the total EGB database population (741,985) during our study period. This prevalence of ADRD in people of about 80 years (2.3%) is in line with the results of the French PAQUID cohort,[51] further supporting the reliability of our algorithm to identify people with ADRD.

The algorithm for identifying CP showed, in a previous study,[52] a prevalence of CP in French general population similar to that found in a large French national cohort study,[53] indirectly validating the algorithm. The people with CP had an average age of 82 years old and were mostly female, with mainly nociceptive pain (arthritis, osteoarthritis, joint, and rheumatic pain), characteristics that remain similar to those of other investigations on this population.[17,54–56] Nevertheless, it is important to note that our results concerning the type of pain are to be taken with caution because only about 30% of the patients had a well-defined medical diagnosis of their CP. This being explained by the lack of completeness of ICD-10 codes for CP, as well as a potential lack of coding of pain by clinicians. Concerning their therapeutic management, the class of analgesic drugs prescribed were similar to those of older people in nursing-homes (mainly analgesics, anti-inflammatory drugs and opioids).[55] Our sample differed from the population classically seen in pain centers, which is younger (~50 years old), mainly affected by neuropathic pain and fibromyalgia, and

TABLE 2. Log-linear models and estimates of the number of individuals with chronic pain in people with or without ADRD

			N (Total Individuals With CP)							Prevalence				
ADRD (n = 16,096)				CI 95%							CI 95%			
No.	Model Description	X estimate[a]	Estimate[b]	Low	High	df	G^2	AIC	BIC	Estimate	Low	High	Range	Mean Precision[c]
1	P H D PH PD HD	7,269	11,750	6,888	26,438	0	0	0	0	73.0%	42.8%	100.0%	100.000	60.729
2	P H D PD HD	268	4,749	4,608	5,049	1	55.005	53.005	53.059	29.5%	28.6%	31.4%	2.740	1.370
3	**P H D PH PD**	**4,846**	**9,327**	**8,523**	**10,291**	**1**	**0.534**	**−1.466**	**−1.411**	**57.9%**	**53.0%**	**63.9%**	**10.987**	**5.493**
4	P H D PH HD	5,519	10,000	6,931	16,913	1	0.518	−1.481	−1.427	62.1%	43.1%	100.0%	62.015	31.010
5	P H D PD	4,303	8,784	8,091	9,611	2	97.975	93.975	94.083	54.6%	50.3%	59.7%	9.440	4.720
6	P H D HD	1,590	6,071	5,344	7,410	2	85.211	81.211	81.320	37.7%	33.2%	46.0%	12.841	6.420
7	**P H D PH**	**4,802**	**9,283**	**8,522**	**10,187**	**2**	**0.637**	**−3.362**	**−3.254**	**57.7%**	**52.9%**	**63.3%**	**10.344**	**5.172**
8	P H D	4,311	8,792	8,127	9,578	3	97.979	91.979	92.142	54.6%	50.5%	59.5%	9.016	4.508

			N (total individuals with CP)							Prevalence				
Non-ADRD (n = 32,192)				CI 95%							CI 95%			
No.	Model description	X estimate[a]	Estimate[b]	Low	High	df	G2	AIC	BIC	Estimate	Low	High	Range	Mean Precision[c]
1	P H D PH PD HD	8,638	16,940	12,164	27,623	0	0	0	0	52.6%	37.8%	85.8%	48.021	24.010
2	P H D PD HD	503	8,805	8,582	9,205	1	80.361	78.361	78.415	27.4%	26.7%	28.6%	1.936	0.968
3	**P H D PH PD**	**7,918**	**16,220**	**15,229**	**17,353**	**1**	**0.046**	**−1.954**	**−1.900**	**50.4%**	**47.3%**	**53.9%**	**6.597**	**3.298**
4	P H D PH HD	6,754	15,056	12,178	20,071	1	0.687	−1.313	−1.259	46.8%	37.8%	62.3%	24.516	12.258
5	P H D PD	7,165	15,467	14,592	16,463	2	143.977	139.977	140.085	48.0%	45.3%	51.1%	5.813	2.907
6	P H D HD	2,661	10,963	9,980	12,521	2	122.268	118.268	118.376	34.1%	31.0%	38.9%	7.892	3.946
7	**P H D PH**	**7,761**	**16,063**	**15,137**	**17,114**	**2**	**0.941**	**−3.059**	**−2.951**	**49.9%**	**47.0%**	**53.2%**	**6.142**	**3.071**
8	P H D	7,092	15,394	14,567	16,332	3	144.232	138.232	138.395	47.8%	45.2%	50.7%	5.482	2.741

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; CI: confidence interval; df: degrees of freedom; G^2: goodness-of-fit test; P, H, and D refer to the P-list (pain center patients), H-list (hospital patients), and D-list (chronic use of analgesic drugs ≥ 6 consecutive months), respectively. PD, PH, and DH represent the interactions between the different lists

[a] X estimate correspond to the number of individuals unidentified by the sources (« invisible » individuals).

[b] Estimate correspond to the addition of "X estimate" and individuals identified by sources.

[c] Mean precision = range / 2.

mainly receiving opioids, antidepressants and antiepileptics.[54]

Our results showed a slightly higher prevalence of CP in people with ADRD compared with comparison sample (non-ADRD), despite similar characteristics (age, gender ratio, comorbidities, types of CP, and analgesic treatments). Several recent studies have shown an association between ADRD and CP, with CP as a risk factor for developing dementia,[10–16] and that the presence of ADRD is associated with a higher prevalence of pain.[17–19] The causes of this link are multiple and difficult to determine with precision, with contradictory data such as the recent study by Rouch et al.[57] which did not find a link between the presence of CP and an increased risk of developing Alzheimer's disease. Some studies have also shown an association with opioid use as a risk factor for developing ADRD[58] while others have established a link with the presence of depressive disorders, another risk factor for developing ADRD and CP.[59] Several studies showed that ADRD is itself a source of pain, due to neuronal changes/reorganizations (see for review Moriarty et al.[60] and Dagnino et al.[61]). Overall, these data may therefore explain the high prevalence of CP in people with ADRD, although further studies are needed to clarify the mechanisms involved in this relationship. Finally, CP can also worsen dementia pathology, affecting brain function and thinking, worsening the symptoms of dementia and accelerating deterioration.[10] Add to that the fact that CP can lead to decreased mobility, interfere with daily activities, and increase the risk of falls and additional injuries, our study further supports the importance of CP diagnosis and management in people with ADRD and more broadly with dementia.

Our results also showed that the prevalence of CP is slightly higher in females and increases with age. The result regarding the gender difference is found in several studies in the literature[62–64] and explained in particular by an impairment of descending pain modulatory systems in female.[65–68] Finally, because aging is accompanied by increasing multi-morbidity that can trigger pain,[69] it is logical that the prevalence of CP increases with age (for review see Domenichiello et al.[4]).

Limitations

The generalizability of survey data is an important issue, and representativeness and response rates must be properly considered because selection and non-response bias can seriously affect the validity of a survey. The advantage of the capture-recapture method is that it avoids the problems of selection bias and generalization to the entire population.[38–40] Estimation of the prevalence of CP by capture−recapture methods is also particularly appropriate, since the care of patients with CP is frequently split between hospitals, pain centers, and primary care facilities. Nevertheless, our results should be interpreted with caution because the validity of capture-recapture estimates also depends on potential violations of certain conditions: 1) Common cases between sources must be identifiable. The failure of this assumption could introduce a bias, resulting in either overestimation or underestimation of the estimates. In our study, this assumption can be assumed to hold, because a unique identifier per patient (NIR) was used. Overall, this unique identifier permitted perfect record-linkage, assuming no misclassifications of records.

2) The closed population assumption for our 2-year duration of sampling is difficult to fully achieve because additions (immigration) or deletions (deaths or immigration) cannot be totally ruled out. Due to the advanced age and comorbidities of our target population, it is possible that individuals included may die after their inclusion. Nevertheless, to relax this assumption, the sources had the same geographic coverage and the same time frame, such that the birth, death, and migration rates were assumed negligible. Moreover, as in most epidemiological studies and the fact that our follow-up was short (2 years), we considered that the size of the population of ADRD adults was constant within the period of study.[70] Finally, prevalence estimates have been shown to be robust to violations of the closure assumption, although precision decreases.[71]

3) The data sources must be independent. In our methodology, the independence of sources cannot be certified. Indeed, people seen in pain centers are more likely to have a medical diagnosis for their CP and receive analgesic treatment. The violation of independence was addressed by log-linear models to take into account dependence between the sources.[37] In our study, both of the final models chosen encompassed interaction between the P- and H-lists (model 7, Table 2). The introduction of a second interaction term in the final models (model 3, Table 2) did not change the population size estimates much, reflecting the absence of any significant dependency.[37]

4) Data sources should be homogeneous, but homogeneity between sources is likely to be violated since the probability of belonging to a single source may depend on several covariates such as age and gender.[37] Stratification based on these covariates and capture-recapture analysis for each of the distinct strata, then summation of the results for the total estimate, verifies the heterogeneity observed between sources. For this purpose, additional stratified analyses on age and gender were performed and did not demonstrated heterogeneity.

Overall, the use of three samples is a major strength since when three samples are cross-referenced, as in our study, data show that the usual biases associated with the capture−recapture method can be limited.[72] Indeed, log-linear modeling allows for controlling and reducing (at least partially) dependence and heterogeneity, making these three-source capture −recapture models more powerful.[37]

Finally, another limitation is the coding of information in medical-administrative databases. It is important to mention that lack of data is inherent to all databases, just as it is not possible to go back to the source data and certify the quality of the coding and the information entered in the databases. Coding is the responsibility of the clinician and can sometimes be approximate. This is also the case for CP. Indeed, a study by Lacasse et al.[73] shows that the algorithms for identifying CP in health databases are only 60% sensitive and specific and 80% for fibromyalgia studies. It should also be noted that the ICD-10 coding remains very uninformative (no notion of the precise type of pain, location and intensity). As a result, it was not possible to stratify our analyses according to the type (only 30% of individuals had details about type of pain), location and intensity of CP, which would have provided crucial information on the etiology and severity/impact of pain. To address this, new studies are needed, incorporating the new ICD-11 codes to provide information on the precise type of pain, and/or a cohort study to recover more precisely the etiology and intensity of pain.

As a result of these limitations, although every effort has been made to limit their impact, it is important to note that our prevalence results are only an estimate and not an exact prevalence. Nevertheless, we can assume that our prevalence results are still fairly close to reality. Indeed, as previously informed, the algorithm used to identify people suffering from CP in health databases allows us to find a prevalence of CP in the French general population, about 30%,[52] identical to that found by a large national cohort study conducted by Bouhassira et al. in 2008,[53] indirectly validating the algorithm.

In conclusion, this study assessing the prevalence of CP in people with ADRD showed a high prevalence that was at least equal to or greater than that of people without ADRD. This highlights the need to identify CP in order to manage it and limit its functional impact, improve quality of life and potentially limit the incidence of psychological and behavioral symptoms of dementia (which sometimes originate from a painful symptom). Our results also highlight the need to better understand the clinical aspects and the most efficient management of CP. Probably on nonmedicinal approaches in priority because of the potential iatrogenic effect of analgesic drugs (especially opioids). Finally, it seems necessary to develop diagnostic tools specific to types of pain, such as neuropathic pain, with a diagnosis that currently seems difficult in the context of cognitive disorders, whereas this type of pain requires specific management.

Nevertheless, the assessment and treatment of pain in dementia remain both complex and challenging. Therefore, better understanding of the prevalence, etiology and impact of CP in people with ADRD will assist healthcare professionals in making decisions regarding its assessment and treatment. These results can be used as a reference for healthcare professionals in assessing pain in ADRD people, but future studies are needed: 1) on the differences in diagnosis and treatment related to CP in people with and without dementia, 2) on the evolution of the therapeutic management of CP after the appearance of dementia, and 3) on the relationship between the pathophysiology of ADRD and CP.

AUTHOR CONTRIBUTIONS

NK, NB, and AM contributed substantially to the design of the work, acquisition, analysis, and interpretation of data for this work. NK, NB, AM, AE, CB, and ST wrote the work and critically reviewed it. NK, NA, CB and CC were responsible for all aspects of the work, ensuring that questions about the accuracy or integrity of any part of the work were appropriately addressed and resolved. All authors read and approved the final manuscript.

DATA AVAILABILITY

The data set analyzed during the present study is not publicly available, please contact the INSERM (National Institute of Health and Medical Research) or the CNAM (Caisse Nationale d'Assurance Maladie) for more information.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings

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The authors have no conflicts of interest to disclose related to the manuscript.

SUPPLEMENTARY MATERIALS

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