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Association between psychotropic and cardiovascular iatrogenic alerts and risk of hospitalizations in elderly people treated for dementia: *A* self-controlled case series study *based on the matching of two French Health Insurance Databases*

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ABSTRACT: 286 words

- **Background:** Elderly people are at risk of repeated hospitalizations, some being drug-related and preventable. In 2011, French experts selected 5 "Iatrogenic Alerts" (IAs), from the existing sets of explicit criteria, to assess the appropriateness of medication in elderly patients.
- **Objectives:** Our objective was to examine the association between hospitalizations and IAs in elderly patients treated for dementia selected for their sensitivity to adverse drug events.
- **Design:** A two-year longitudinal national database study using an approach similar to the "self-controlled case series" between January 1, 2011 and December 31, 2012 was set up to analyze data on drug prescriptions and hospital stays. IAs were defined as: (1) long half-life benzodiazepine; (2) antipsychotic drugs in Alzheimer patients; (3) co-prescription of 3 psychotropic drugs or more, (4) co-prescription of 2 diuretics or more and (5) co-prescription of 4 antihypertensive drugs or more. Data were obtained from the matching of two French National Health Insurance Databases.
- **Setting:** France
- **Participants:** All affiliates, aged 75 or more, in treatment for dementia, still alive on January 1st, 2011 were included.
- **Measurements:** We calculated the relative increase in the number of hospitalizations when IAs were dispensed. The analysis was performed over a period of 6 months.
- **Results:** 10,754 patients were included. During the IA periods, compared to others periods, hospitalization incidence increased by (0.23/year vs. 0.36/year) and the number of hospitalizations doubled (PFC=1.9, CI95%[1.8, 2.1]). We calculated that 22% (CI95% [20%, 23%]) of all hospitalizations were associated with IAs, 80% of which were due to psychotropic IAs.
- **Conclusion:** IAs seem to be a simple and clinically relevant tool that enables the prescribing physicians to assess the appropriateness of the prescription in elderly patients treated for dementia.

Abbreviations in the text: ADE: Adverse Drug Event; PFC: Proportional Fold Change; IA: Iatrogenic Alert

Keywords: Iatrogenic alert; Adverse drug event; Self-controlled analysis

Running Title: Adverse drug hospitalizations and dementia

30 **INTRODUCTION**

31 Demographic ageing is associated with an increase in repeated hospital admissions (1-3).
32 Reducing these hospitalizations is a priority for hospitals and national health plans.
33 Identifying the modifiable factors that are associated with the risk of hospital admission in
34 elderly people is of a major interest with the aim of conceiving risk minimization strategies.
35 Five to 20% of all hospital admissions are known to be related to Adverse Drug Events
36 (ADE) in people aged 65 (4-7) and over 40 to 70% of these ADE-related admissions would be
37 preventable (6,8,9). This has prompted the development of criterion-based tools (explicit
38 measures) to assess and correct inappropriate prescription in elderly people (10-15). However,
39 the evidence that inappropriate prescription, as defined by explicit measures, is associated
40 with adverse patient outcomes and notably hospitalizations, is mixed and contradictory
41 (11,16,17). This could be explained by a too extensive approach of the appropriateness of the
42 prescription inasmuch as these tools are concerned (the risk for serious ADE varying widely
43 from a criterion to another in the context of the same tool) and/or a study population running a
44 too heterogeneous risk for hospitalization.
45 In 2011, with a view to managing national health plan in order to improve medication in
46 elderly people, the French National Authority for Health requested a panel of French health
47 professionals to determine the most prominent criteria regarding cardiovascular and
48 psychotropic drugs known to be involved in ADE-related admissions (4-7,9-12,14,15,18).
49 According to literature data and its clinical practice, five "Iatrogenic Alerts" (IAs) were
50 finally found to be easy to assess and clinically relevant to prevent serious ADE in the elderly
51 (19). There were 3 psychotropic IAs corresponding to (1) the prescription of a long half-life
52 benzodiazepine; (2) the prescription of antipsychotic drugs in Alzheimer patients; and (3) the
53 co-prescription of 3 or more psychotropic drugs; and 2 cardiovascular IAs with (4) the co-

54 prescription of 2 or more diuretics and (5) the co-prescription of 4 or more antihypertensive
55 drugs.
56 The aim of our study is to validate this new screening tool of inappropriate prescriptions in
57 elderly people, by measuring the association between these IAs and the risk of
58 hospitalizations. We focused on patients treated for dementia because they have a high risk
59 for hospitalizations and because one of the IA is specific to this population (19-22).
60 Our main objective was to examine the association between hospitalizations, whatever their
61 leading cause, and IAs in elderly people treated for dementia, using a self-controlled case
62 series design. Second, we examined the association between the potentially ADE-related
63 hospitalizations and the IAs.
64
65 **METHODS**
66 A two-year longitudinal national database study using an approach similar to the "self-
67 controlled case series" (23,24) between January 1, 2011 and December 31, 2012 was set up.
68 The study is reported according to the RECORD recommendation (25). It was divided into 4
69 consecutive six-month periods allowing the sequential analysis in the case of each patient
70 based on a moderate amount of data. Indeed, a monthly analysis would have produced 24
71 one-month periods for each patient making the analysis more complex with little benefit.
72 Conversely, an annual analysis, with only 2 one-year periods for each patient would not have
73 made possible a detailed analysis. The 6-month analysis seemed a good compromise to us.
74 **Databases**
75 Data were obtained from 2 French National Health Insurance Databases. The RSI' database
76 ("Régime Social des Indépendants" – social scheme for the self-employed) included data
77 from 6 million self-employed people, such as age, sex, social security numbers, all
78 ambulatory prescriptions and the prescriber and all hospitalizations in private hospitals (with

79 Major Diagnosis Category (MDC), corresponding to the leading cause of hospital admission
80 (26), **Appendix 1**). The SNIIRAM' database ("Système National d'Information Inter-
81 Régimes de l'Assurance Maladie" – The French National Health Insurance Information
82 System) which collects all individualized and anonymous healthcare claims reimbursed by the
83 French National Health Insurance covering the entire French population (27). In addition, this
84 database contains patient data such as sex, vital status and eligibility for a 100% health
85 insurance coverage for serious and costly long-term diseases (LTDs), encoded in the
86 International Classification of Diseases, 10th revision (ICD 10) (28) and all hospitalizations in
87 public hospital with their MDC (26).

88 **Population selection (figure 1)**

89 All affiliates of the RSI aged 75 years or more on January 1st, 2011 with a diagnosis of
90 dementia and undergoing a specific treatment, were included. "Dementia with a specific
91 treatment" was defined by the WHOs ICD-10 code "Alzheimer's disease" (F00-F03*) (26)
92 and by the prescription of a drug for Alzheimer disease (ATC "Anatomical Therapeutic
93 Chemical » code NO6D (29). All patients undergoing a specific treatment had an ICD-10
94 code. The Charlson comorbidity index (CCI) was calculated for each patient (missing
95 information was replaced by the default – least severe – value, see **Appendix 2**) (28,30,31).

96 **Databases matching (figure 1)**

97 SNIIRAM' and RSI databases have restricted access according to privacy laws (27). We
98 obtained the authorization to match the 2 databases anonymously. In the absence of a unique
99 patient identifier, the matching of the 2 databases was performed based on such criteria as
100 sex, the year of birth, the social security number, the prescriber and the specific Alzheimer's
101 drugs refunded during the first 6-month period (inclusion criteria). Authorizations were
102 obtained in respect of the French regulations (CNIL authorization n° 1537081).
103

104 **Exposure**

105 For each drug delivery, the ATC class of the prescribed drug was available with a precision
106 ranging from 3 to 5 digits (29).

107 We determined, for each patient and for each six-month period:

108 - the presence of an IA: the algorithm for identifying IAs is described in **Appendix 3** (19).
109 It was developed from the ATC codes proposed by French National Authority for Health.
110 The co prescription IAs was defined by the delivery of 2 or more different drugs over the
111 course of the same six-month period.
112 - the delivery of a drug known to increase the risk of ADE-related hospitalization and not
113 included in IAs (4,6): we included antiplatelet agents or anticoagulants (ATC: B01);
114 Nonsteroidal anti-inflammatory drug (NSAID) (ATC: M01); oral antidiabetic drugs
115 (OADs) and insulin (ATC: A10); Digoxin (ATC: C01AA05).
116 - the occurrence of polypharmacy. This was the case when at least five drugs with different
117 ATC codes were delivered during the same six-month period (4,6,32).

118 **Outcomes: Hospitalizations and Major Diagnosis Categories (MDC)**

119 The number of hospitalizations over a six-month period was calculated for each patient.
120 Patients who had more than 10 hospitalizations during the same six-month period (N = 34 –
121 corresponding to chemotherapy, dialysis, reeducation sessions; **Figure 1**) were excluded
122 because these repeated hospitalizations were planned and not related to IAs.

123 The main outcome was the rate of all hospitalizations, whatever their leading cause.

124 For a more detailed second analysis, according to our clinical experience and the literature
125 (4,6,8,9,14,15,18,33,34), we analyzed the association between IAs and the risk of
126 hospitalization, according to 3 pre-specified relevant MDC groups defined as “context”,
127 “potentially ADE-related” and “other” (**Table 1**).

128 - "Context" hospitalizations: hospitalizations the leading cause of which (MDC) was linked
129 to a decompensated disease that could have led to the initial delivery of an IA. More
130 precisely, this included “Diseases and Disorders of the nervous system” (MDC1) and
131 “Mental Diseases and Disorders” (MDC19) for the 3 psychotropic IAs and “Diseases of
132 the respiratory / circulatory system” (MDC 4/5) for the cardiovascular IAs.
133 - “Potentially ADE-related” hospitalizations were those compatible with ADE occurring
134 with cardiovascular or psychotropic drugs. We included in this category hospitalizations
135 related to “Trauma, allergies, poisoning” (MDC 8, 20, 21).
136 - All other MDCs were classified in the “Other” category, with hospitalizations that were *a*
137 *priori* unrelated to the cardiovascular and psychotropic drugs (initial delivery or leading
138 cause of hospital admission): eye/ear/throat diseases (MDC2 and 3), tumors (MDC16-17),
139 infectious diseases (MDC18)), digestive, hepatobiliary and pancreas system (MD6 and
140 MD7); skin, subcutaneous tissue and breast (MD9); endocrine, nutritional and metabolic
141 system (MD10); kidney and urinary tract (MDC11).
142 However, some hospitalizations classified in “context” and “others” categories may be
143 “potentially ADE-related” hospitalizations. Since the codes did not allow us to define it
144 with certainty, we had chosen to classify only traumatic and poisoning hospitalizations in
145 potentially ADE-related hospitalizations (“minimalist” approach).
146
147 **STATISTICAL ANALYSES**
148 The association of each IA with hospitalizations (self-adjusted proportional fold change
149 (PFC)) was investigated separately for all hospitalizations (whatever the leading cause) and
150 then for the 3 pre-specified categories (context, potentially ADE-related, other). Analyses
151 were also done for the occurrence of polypharmacy and other drugs of interest.
152 We used an approach similar to the “self-controlled case series” (23,24) (epidemiological
153 study design for which individuals act as their own controls) to jointly analyze the number of

154 hospitalizations throughout the six-month periods spanning each patient's follow-up,
155 comparing each patient to themselves in a different period. Periods without an IA served as a
156 control for periods with an IA for the same patient: the ratio of hospitalizations was
157 determined by considering the 6-month periods where an IA was present ("at risk" periods)
158 and the others ("non-risk" periods). Patients who had never been hospitalized over a period of
159 2 years did not provide any information to this analysis. Patients who either had a permanent
160 IA or none throughout the four 6-month periods contributed to the estimation of the specific
161 effect of the period. Patients who died during the study period were analyzed except for the
162 final 6-month period of their life, as changes in prescription could occur in terminally ill
163 people. For all statistical analysis, we used the statistical software R (version 3.1.0) with
164 package multinomRob (http://CRAN.R-project.org/package=multinomRob). The details of
165 the statistical analysis are described in **appendix 4.**
166
167 **RESULTS**
168 **Population**
169 The average age of the population was 85 (± 5.0), the majority of them being women (61%).
170 The average CCI was 5.5 (± 1.0), with a large prevalence of cardiovascular diseases in 29%
171 (hypertension, diabetes, heart failure, coronary failure, atrial fibrillation), neuropsychiatric
172 diseases in 10% (Parkinson's disease, stroke, depression) and cancer in 12%. Over the span of
173 2 years, 2196 individuals died (death rate 10% per year). Patients who were hospitalized at
174 least once had more comorbidities (1.0 ± 0.9 vs. 0.8 ± 0.8, $p < 0.001$) and more medications
175 (polypharmacy: 90.3% vs. 88.4%, $p < 0.0001$) than patients never hospitalized, with no
176 difference with age. The description of the population is summarized in **table 2**.
177 **Exposure to Iatrogenic Alerts**
178 At least one IA was present in 35% of all six-month periods, psychotropic IAs were more
179 common (30% of periods) than cardiovascular IAs (9% of periods). The prevalence of IAs per

180 6-month periods in the population was: 16.5% for IA antipsychotic drugs, 15.5% for IA ≥ 3
181 psychotropic drugs, 9.7% for IA long half-life benzodiazepine, 5.9% for IA ≥ 2 diuretics,
182 5.4% for IA ≥ 4 antihypertensive drugs (**table 2).** Patients could present several IAs in the
183 same period, but there was no correlation between the presence of psychotropic and
184 cardiovascular IAs (P=0.52).

185 **Hospitalizations**

186 The average number of hospitalizations for a six-month period was 0.27, with a slight
187 decreasing trend over time from 0.31 in early 2011 to 0.24 in late 2012. The average number
188 of hospitalizations for a six-month period decreased with age, from 0.29 in the 75-80 years
189 old to 0.26 in the >90 years old and increased with the CCI index, from 0.27 (CCI ≤ 7) to 0.38
190 (CCI > 7). Patients who were hospitalized at least once had more IAs (Long half-life
191 benzodiazepine: 10.3% vs. 8.8%, p < 0.0001; Antipsychotic: 17.5% vs. 15.3%, p < 0.0001; ≥
192 3 psychotropic drugs: 17.6% vs. 13%, p < 0.0001; ≥ 2 diuretics: 6.5% vs. 5.1%, p < 0.0001; ≥
193 4 antihypertensive drugs: 6.1% vs. 4.4%, p < 0.0001), more polypharmacy (90.3% vs. 88.4%,
194 p <0.0001), more antiplatelet and anticoagulant drugs (55.8% vs. 44.5%, p <0.0001), more
195 oral antidiabetic agents and / or insulin (12.1% vs. 10.6%, p = 0.002) and more digoxin (4.4%
196 vs. 3.5%, p <0.0001) than patients never hospitalized (**table 2**).

197 **Outcomes**

198 *Association between hospitalization rate and IAs*

199 On average, there were 0.23 hospitalizations over a period of six months without IAs *vs.* 0.36
200 when at least one IA was present. The self-controlled analysis showed that the number of
201 hospitalizations was double for periods with an IA relative to others periods (PFC 1.9, CI95%
202 [1.8, 2.1]), with PFC ranging from 1.7 [1.5, 1.8] to 2.1 [1.8, 2.3] depending on the IA type.
203 We calculated that 22% (CI95% [20%, 23%]) of all hospitalizations were associated to IAs,
204 the 80% of which were due to psychotropic IAs. All results are shown in **table 3.**

205 *Association between potentially ADE-related admissions and IAs*

206 "Context" hospitalizations represented 28% of all hospitalizations and "potentially ADE-
207 related" represented 18% of all hospitalizations. The impact of IAs changed with the type of
208 hospitalization (**Figure 2, Table 3**): the largest increase occurred for the "context"
209 hospitalizations (with PFC between 2.2 [1.8, 2.8] and 3.0 [2.6, 3.4] in the presence of an IA);
210 for "potentially ADE-related" hospitalizations the PFC ranged between 1.3 [0.8, 1.9] and 2.2
211 [1.8, 2.7]; and it ranged between 1.3 [1.1, 1.5] and 1.8 [1.6, 2.1] for "other" hospitalizations.
212 We calculated that 17% of "potentially ADE-related" hospitalizations were associated to
213 psychotropic IAs and 4% to cardiovascular IAs: this amounted, respectively, to 3% (=17% *
214 18%) and 1% (=4%*18%) of all hospitalizations.

215 *Association between hospitalization rate and other drugs*

216 Periods of six months in polypharmacy patients were associated with a large increase of all
217 hospitalization causes (proportional fold change, PFC: 3.6 [3.2, 4.0]), with hospitalizations for
218 "Endocrine, Nutritional & Metabolic System" (MDC10) increasing the most (PFC=10.1 [3.8,
219 26.5]). A similar increase was observed in periods of use of anticoagulant / antiplatelet drugs
220 (overall proportional fold change: 3.2 [2.9, 3.5]), NSAID (proportional fold change: 1.3 [1.2,
221 1.4]), oral anti-diabetic / insulin drugs (proportional fold change: 1.7 [1.4, 2.1]) and digoxin
222 (proportional fold change: 1.7 [1.4, 2.1]). The largest increase of MDCs hospitalization
223 changed according to the drugs was: "Circulatory System" (MDC5 – PFC 5.6 [4.5, 7.0]) for
224 anticoagulants, "Kidney And Urinary Tract" (MDC11 – PFC=1.6[1.1, 2.5]) for NSAID,
225 "Endocrine, Nutritional & Metabolic System" (MDC10 – PFC = 5.8 [2.4, 13.9]) for oral
226 antidiabetic drugs and "Respiratory system" (MDC4 – PFC = 2.6 [1.5, 4.7]) for digoxin.
227

228 **DISCUSSION**

229 The Iatrogenic Alerts (IAs) represent a restricted selection of explicit criteria developed by
230 French health professionals (19) from the existing sets (10-15) to assess the appropriateness
231 of prescription in elderly people.

232 To our knowledge, this is the first study to analyze the potential association between these IAs
233 and hospitalizations in a selected population known to be at risk for repeated admissions (the
234 elderly people treated for dementia). We found that IAs were closely linked to hospitalization,
235 since 22% of all hospitalizations (whatever the leading cause) in this population were
236 associated with cardiovascular and/or psychotropic IAs. In our secondary more accurate
237 analysis, we calculated that 17% of "potentially ADE-related" hospitalizations were
238 associated with psychotropic IAs and 4% with cardiovascular IAs. This estimate is in
239 agreement with previous assessments that 5-20% of hospital admissions could be related to
240 drug side effects (5,6).

241 As expected, IAs were generally common with 40% of the population experiencing at least
242 one six-month period with an IA. But, a surprising finding was that an IA was present for 2
243 years (at all times) for 15% of the patients. This clearly shows the lack of information of
244 practitioners regarding the absence of benefice of some psychotropic and cardiovascular
245 drugs combinations given the potential risks and possibility of alternative treatment.

246 The population under study showed typical characteristics of elderly populations regarding
247 prescriptions and hospitalizations. The incidence of polypharmacy was significant, as was the
248 case with previous reports (4,6,32,35). The risk of hospitalization was typical of old age
249 (4,33), and it increased in the case of morbidity, polypharmacy, prescription of anticoagulant,
250 antidiabetic and digoxin, as previously described (4-7,32,35-37). These associations between
251 hospitalizations and drugs known to be the highest purveyors of ADE (anticoagulant /

antiplatelet drugs, oral anti-diabetic / insulin drugs, NSAID and digoxin) showed the validity of our analysis.

We found an association between inappropriate prescribing as defined by the IAs (19) and hospitalizations in a large sample of older people treated for dementia, unlike the usual sets of explicit criteria focused on misuse and overuse (16,38,39). This could be explained first by the clinical relevance of the IAs. Indeed, the IAs do not encompass large number of drugs known to be inappropriate in elderly but are restricted to drugs of two classes known to be highly implicated in severe ADE in Western countries (4-7,9-15,18). Moreover, the IAs are mainly focused on the duplication of these drug classes, and so detect only prescribing with very high risk for ADE. Second, the choice of a study population both with high risk of inappropriate psychotropic exposure and of ADE could have facilitated the detection of this association. Interestingly, recent study from a longitudinal cohort found also an association between inappropriate drug use and hospitalizations in a population closed to ours (people with dementia according to DSM-III-R criteria) (40). Criteria defining inappropriate drug use in this study cross-referenced psychotropic IAs (use of 3 or more psychotropic drugs, use of long-acting benzodiazepines), suggesting that psychotropic IAs could be pertinent also in people suffered from dementia, with or without treatment. However, further studies are needed to explore the association between the whole of IAs and hospitalizations in patients with dementia whatever their treatment and in older population whatever their diseases. Moreover, the association between IAs and hospitalizations need also to be further studied to better understand if IAs are causes and/or consequences and/or independent markers of the risk of hospitalizations. Interventions studies assessing the impact of reduction of the IAs on hospitalizations rate would be especially desirable.

Strengths of the study

276 We chose to use an approach similar to the "self-controlled case series" (23,24), built on the
277 change in exposure over time in the same patient, to reduce the bias of confusion. Indeed, it is
278 well known that adjusting to differences between patients, besides the exposure of interest, is
279 required in the analysis of observational data. This is why, comparing each patient to
280 themselves is "the ultimate form of adjustment" (41). It automatically takes into account
281 factors associated with hospitalization among the elderly: marital status, education, autonomy,
282 place of living, tobacco or alcohol use (4,6,14,15). This was particularly relevant as such data
283 are not available in databases primary purpose of which is either administrative or
284 compensation (27). An additional feature was the inclusion of patients who either had an IA
285 or not in the four 6-month periods under study, as it allowed further adjustment in
286 hospitalization rates over time (estimation of the period specific effect), for example due to
287 seasonal changes (winter /summer).

288 **Limits of the study**

289 The population under study differed from the general elderly population with dementia in
290 several aspects. First, it included only patients treated for dementia. To match the 2 databases
291 (RSI and SNIIRAM) we had to exclude people without treatment (and 1408 patients with
292 database matching unsuccessful). It is known that these patients are at greater risk of
293 hospitalizations than the others and take more medications (20-22). This could lead to
294 increased hospitalization rates compared to the rest of the elderly population with dementia
295 and increased prevalence of IAs. Second, the sample was selected from retired self-employed
296 persons (RSI' database), limiting the relevance of the population. However, the population of
297 the study benefits from the same general practitioners and hospitals as the rest of the
298 population, so eventually this should not affect the results.

299 For our secondary analysis, defining causes of hospitalizations that are likely due to ADEs
300 was a difficult task without proper coding. For example, epilepsy might be related to

301 psychotropic side effects, acute renal failure to diuretics, and so on. We adopted a
302 "minimalist" approach, considering only poisoning and trauma as "potentially ADE-related"
303 and more likely to be affected by change in prescriptions. The maximum impact of reducing
304 the prevalence of the IAs is therefore likely to be in the range defined by the "avoidable part"
305 (3% of all hospitalizations) and the "attributable part" (22% of all hospitalizations).
306 Finally, the analysis of six-month periods could have led to the categorization of periods with
307 sequential prescription of several drugs as periods when a combination of drugs was present,
308 increasing the occurrence of periods with an IAs. However, this condition should only lead to
309 underestimating the strength of association of IAs with hospitalization; it should not challenge
310 our results. A last aspect of this grouping is that it was not possible to tell whether the
311 iatrogenic alert took place before, during or after the hospitalization within the same semester.
312

313 **CONCLUSION**

314 The present study provides the first evaluation of the association between IAs and
315 hospitalizations. We showed that the risk of hospitalization nearly doubled in elderly patients
316 in treatment for dementia when they were exposed to psychotropic and/or cardiovascular
317 Iatrogenic Alerts. These Iatrogenic Alerts, resulting from a selection of existing explicit
318 criteria by French experts, are a promising simple way of reducing serious ADE in this
319 vulnerable population. Interventional studies are now needed to explore if the reduction of
320 theses IAs can be associated with better clinical outcomes and notably with reduction of
321 hospital admissions.
322

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Data sharing: No additional data available. The scientific protocol and statistical code files for this analysis are available on request.

Transparency: The lead authors affirm that the article is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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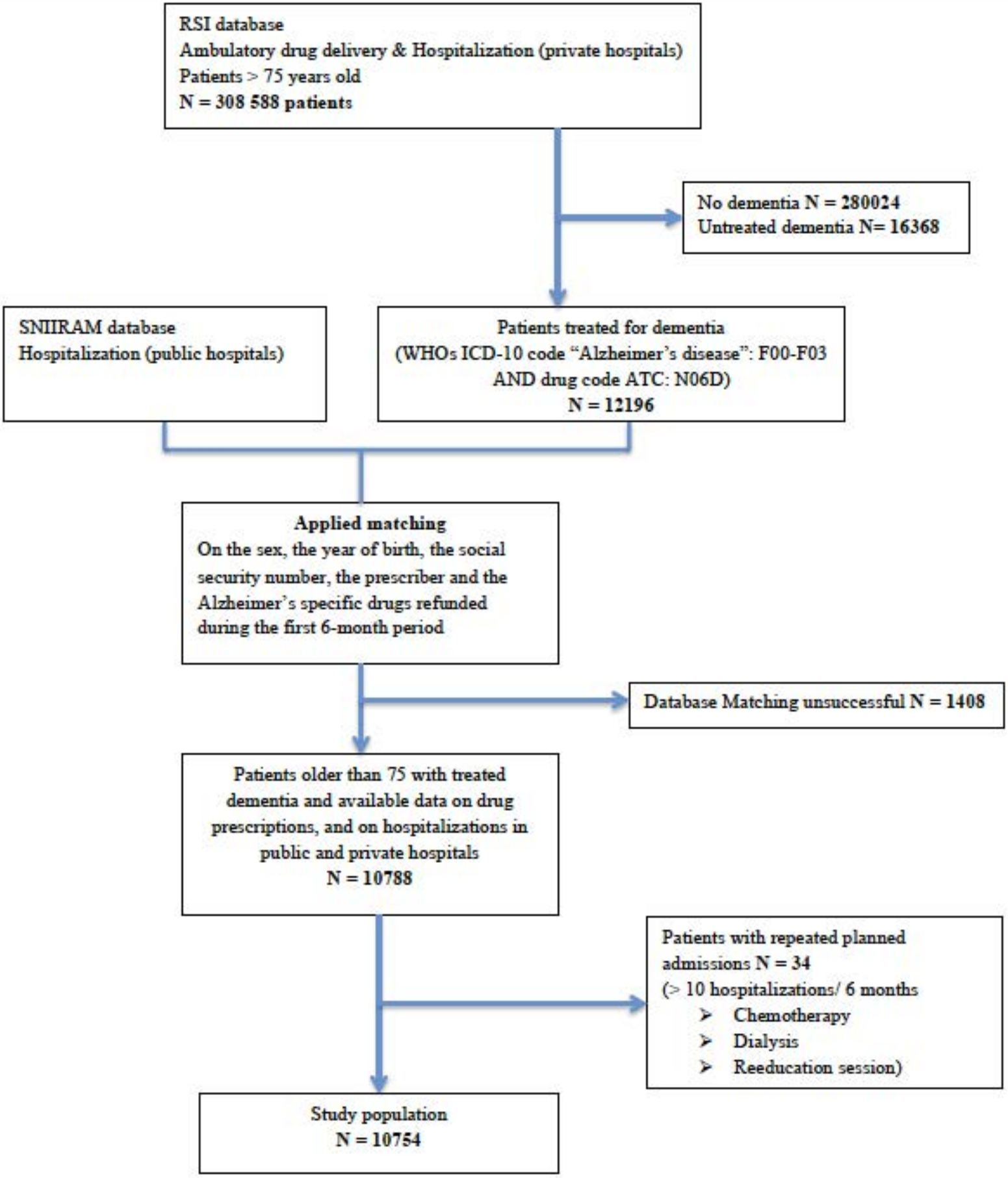
459

460 • **FIGURE 1: Flow Chart of patient selection from Health Insurance databases.**
461
462 • **TABLE 1: Classification of hospitalization with Major Diagnostic Categories (MDC)**
463 **by relevance with Cardiovascular and Psychotropic drug prescriptions**
464
465 • **TABLE 2: Patients characteristics and Iatrogenic Alerts**
466
467 • **TABLE 3: Proportional Fold Change in the number of hospitalizations per six-**
468 **month period by iatrogenic alert and hospitalization type.**
469
470 • **FIGURE 2: Proportional Fold change in the number of hospitalizations (using**
471 **Major Diagnostic Categories) per six-month period with the presence of an IA**
472 **(Iatrogenic Alert)**
473
474



- **RSI** = « Régime social indépendant », a branch of the French National Mandatory Health Insurance System for self-employed individuals
- **SNIIRAM** = The French National Health Insurance Information System, database with information on all beneficiaries of the French National Mandatory Health Insurance System.
- **ATC** = Anatomical Therapeutic Chemical

	Psychotropic IAs**			Cardiovascular IAs**		
Leading primary cause of hospitalization By major diagnosis categories (MDC*)	CTXT	ADE	OTHR	CTXT	ADE	OTHR
Nervous system (1)	◆					◆
Mental Diseases and Disorders (19)	◆					◆
Respiratory System (4)			◆	◆		
Circulatory System (5)			◆	◆		
Musculoskeletal System And Connective Tissue (8)		◆			◆	
Alcohol/Drug Use or Induced Mental Disorders (20)		◆			◆	
Injuries, Poison And Toxic Effect of Drugs (21)		◆			◆	
Eye (2)			◆			◆
Ear, Nose, Mouth And Throat (3)			◆			◆
Digestive System (6)			◆			◆
Hepatobiliary System And Pancreas (7)			◆			◆
Skin, Subcutaneous Tissue And Breast (9)			◆			◆
Endocrine, Nutritional And Metabolic System (10)			◆			◆
Kidney And Urinary Tract (11)			◆			◆
Blood and Blood Forming Organs and Immunological Disorders (16)			◆			◆
Poorly Differentiated Neoplasms (17)			◆			◆
Infectious and Parasitic Diseases & Disorders (18)			◆			◆

* MDC 12-15 (reproduction & newborns), 22-25 (Burns, Multiple Trauma, HIV), MDC 26 (Severe multiple trauma), MDC27 (organ transplants), MDC 28 and 90 (Errors and other unclassifiable stays) were not present in the database

** CTXT: Context; ADE: potentially ADE related; OTHR: Other.

	Overall	Hospitalization		P-value
		Never	Once or more	
	N = 10754	N = 4396	N = 6358	
Age (years, mean ± SD**)**	85.0 ± 5.0	85.1 ± 5.1	85.0 ± 5.0	0.40
Sex (% Female)	61%	66%	58%	**<0.001**
Charlson index (mean ± SD)	5.5 ± 1.0	5.4 ± 0.9	5.5 ±1.0	**<0.001**
Comorbidities (mean ± SD)	0.9 ± 0.9	0.8 ± 0.8	1.0 ± 0.9	**<0.001**
Parkinson disease	5.2%	4.3%	5.8%	**0.001**
Depression	0.4%	0.2 %	0.5%	**0.02**
Arterial hypertension	11.3%	11.0%	11.6%	0.28
Diabetes	11.0%	10.0%	11.8%	**0.003**
Atrial fibrillation	4.4%	3.5%	5.1%	**0.001**
Heart failure	4.3%	3.5%	4.9%	**0.006**
Cancer	11.5 %	9.6%	13.0%	**<0.001**
Death (%)*	4.6%	3.1%	5.7%	**<0.001**
Iatrogenic alerts (%)*				
Long half-life benzodiazepine	9.7%	8.8%	10.3%	**<0.0001**
Antipsychotic	16.5%	15.3%	17.5%	**<0.0001**
≥ 3 psychotropic drugs	15.5%	13.0%	17.6%	**<0.0001**
≥ 2 diuretics	5.9%	5.1%	6.5%	**<0.0001**
≥ 4 antihypertensive drugs	5.4%	4.4%	6.1%	**<0.0001**
Other drugs (%)*				
Anticoagulant / Antiplatelet	51.0%	44.5%	55.8%	**<0.0001**
NSAID	9.6%	9.5%	9.7%	0.15
Oral anti-diabetic / Insulin	11.4%	10.6%	12.1%	**0.002**
Digoxin	4.0 %	3.5%	4.4%	**<0.0001**
Polypharmacy (%)*	89.5 %	88.4%	90.3%	**<0.0001**

* Percentage per 6-month periods
NSAID: Nonsteroidal anti-inflammatory drug

	Hospitalization type							
	All		Context		Potentially ADE-related		Other	
Iatrogenic Alerts	PFC	AR	PFC	AR	PFC	AR	PFC	AR
Any	1.95 [1.8, 2.1]	22%						
Long half-life benzodiazepine	1.65 [1.5, 1.8]	5%	2.3 [1.9, 2.7]	8%	1.7 [1.3, 2.3]	6%	1.3 [1.1, 1.5]	3%
Antipsychotic in Alzheimer patients	1.79 [1.7, 1.9]	9%	2.7 [2.4, 3.1]	23%	2.1 [1.7, 2.5]	19%	1.5 [1.4, 1.7]	12%
≥ 3 psychotropic drugs	2.04 [1.9, 2.2]	12%	3.0 [2.6, 3.4]	16%	2.2 [1.8, 2.7]	13%	1.6 [1.4, 1.8]	9%
≥ 2 diuretics	1.73 [1.5, 2.0]	3%	2.2 [1.8, 2.8]	5%	1.3 [0.8, 1.9]	2%	1.6 [1.3, 1.9]	3%
≥ 4 antihypertensive drugs	2.08 [1.8, 2.3]	5%	2.8 [2.3, 3.4]	6%	1.4 [1.0, 2.0]	3%	1.8 [1.6, 2.1]	4%

PFC: Proportional Fold Change, AR = Attributable ratio

ADE: adverse drug event

APPENDIX 1: Major Diagnostic Categories (MDC)

MDC 1	Nervous system
MDC2	Eye
MDC3	Ear, Nose, Mouth And Throat
MDC4	Respiratory System
MDC5	Circulatory System
MDC6	Digestive System
MDC7	Hepatobiliary System And Pancreas
MDC8	Musculoskeletal System And Connective Tissue
MDC9	Skin, Subcutaneous Tissue And Breast
MDC10	Endocrine, Nutritional And Metabolic System
MDC11	Kidney And Urinary Tract
MDC12	*Male Reproductive System*
MDC13	*Female Reproductive System*
MDC14	*Pregnancy, Childbirth And Puerperium*
MDC15	*New-born And Other Neonates (Perinatal Period*
MDC16	Blood and Blood Forming Organs and Immunological Disorders
MDC17	Myeloproliferative DDs (Poorly Differentiated Neoplasms)
MDC18	Infectious and Parasitic DDs
MDC19	Mental Diseases and Disorders
MDC20	Alcohol/Drug Use or Induced Mental Disorders
MDC21	Injuries, Poison And Toxic Effect of Drugs
MDC22	*Burns*
MDC23	*Factors Influencing Health Status*
MDC24	*Multiple Significant Trauma*
MDC25	*Human Immunodeficiency Virus Infection*
MDC26	*Severe multiple trauma*
MDC27	*Organ transplants*
MDC28	*Sessions*
MDC90	*Errors and other unclassifiable stays*

MDC in italic were not present in our database

APPENDIX 2: ICD-10 Coding Algorithms for Charlson Comorbidities

Comorbidities	ICD-10 codes	Points
Myocardial infarction	I21.x, I22.x, I25.2	1
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0,	1
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9	1
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x-I69.x	1
Dementia	*100% of patients (included on the ATC code N06D)*	1
Chronic pulmonary disease	I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3	1
Rheumatic disease	M05.x, M06.x, M31.5, M32.x-M34.x, M35.1, M35.3, M36.0	1
Peptic ulcer disease	K25.x-K28.x	1
Mild liver disease	B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-K76.4, K76.8, K76.9, Z94.4	1
Diabetes without chronic complication	E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9	1
Diabetes with chronic complication	E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7	2
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9	2
Renal disease	I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2, Z94.0, Z99.2	2
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x, C81.x-C85.x, C88.x, C90.x-C97.x	2
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7	3
Metastatic solid tumor	C77.x-C80.x	6
AIDS	B20.x-B22.x, B24.x	6
Age:	71-80 years 81-90 years More than 90 years	3 4 5

APPENDIX 3: ATC Coding Algorithms for identifying IAs

Iatrogenic Alerts	ATC classes
Any prescription of a long half-life benzodiazepine	N05BA01, N05BA05, N05BA08, N05BA09, N05BA11, N05BA16, N05BA18, N05CD02, N05CD03, N03AE01
Antipsychotic in Alzheimer patients	N05AA01, N05AA02, N05AA06, N05AB02, N05AB03, N05AC01, N05AC02, N05AC04, N05AD01, N05AD05, N05AD08, N05AE04, N05AF05, N05AG03, N05AG02, N05AH05, N05AH1, N05AH2, N05AH3, N05AH4, N05AL01, N05AL02, N05AL03, N05AL05, N05AX08, N05AX12, N05AX13, N07XX06
3 or more psychotropic drugs	N03AE01, N05AA01, N05AA02, N05AA06, N05AB02, N05AB03, N05AC01, N05AC02, N05AC04, N05AD01, N05AD05, N05AD08, N05AE04, N05AF01, N05AF05, N05AG02, N05AG03, N05AH05, N05AH1, N05AH2, N05AH3, N05AH4, N05AL01, N05AL02, N05AL03, N05AL05, N05AX08, N05AX12, N05AX13, N05BA01, N05BA04, N05BA05, N05BA08, N05BA09, N05BA11, N05BA12, N05BA16, N05BA18, N05BA21, N05BA56, N05BB01, N05BB02, N05BC01, N05BE01, N05BX03, N05CD02, N05CD03, N05CD04, N05CD06, N05CD07, N05CD11, N05CF01, N05CF02, N06AA02, N06AA04, N06AA06, N06AA09, N06AA12, N06AA16, N06AA17, N06AA21, N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10, N06AG02, N06AF03, N06AF05, N06AX03, N06AX11, N06AX14, N06AX16, N06AX17, N06AX21, N06X22, N07XX06
Any combination of 2 or more diuretics (some of them are already a combination of 2 diuretics*. For the algorithms, these drugs were considered as a sum of 2 drugs.)	C02LA01, C03AA02, C03AA03, C03AA05, C03AB04, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03CA04, C03DA01, C03DA02, C03DA04, C03DB01, **C03EA01***, **C03EA04*, C03EB01*, C03EB02***, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DX01, C09DX03, C09XA52, C09XA54
4 or more antihypertensive drugs (some of them are already a combination of 2* or 3** antihypertensive drugs. For the algorithms, these drugs were considered as a sum of 2 or 3 drugs *)	**C02LA01*,** C02AB02, C02AC01, C02AC02, C02AC04, C02AC05, C02AC06, C02CA01, C02CA03, C02CA06, C03AA02, C03AA03, C03AA04, C03AA05, C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03CA04, C03CB02, C03DA01, C03DA02, C03DA04, C03DB01, **C03EA01***, **C03EA04***, C03EB01, C07AA02, C07AA03, C07AA06, C07AA07, C07AA12, C07AA15, C07AA16, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB09, C07AB12, C07AG01, C07AG02, **C07BA02*, C07BB02***, **C07BB03*, C07BB07***, **C07BB12*, C07CA03*, C07DA06****, **C07FB02*, C07FB03***, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA06, C08CA07, C08CA08, C08CA11, C08CA12, C08CA13, C08DA01, C08DB01, C08EA02, C08EX02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA11, C09AA13, C09AA15, C09AA16, **C09BA01*, C09BA02*, C09BA03*, C09BA04*, C09BA05*, C09BA06*, C09BA07*, C09BA09*, C09BA15*, C09BB02*, C09BB04*, C09BB10*, C09DA01*, C09DA02*, C09DA03*, C09DA04*, C09DA06*, C09DA07*, C09DA08*, C09DB01*, C09DB02*, C09DB04*, C09DX01**, C09DX03***

APPENDIX 4: Statistical analysis

More precisely, we assumed that the number H_{ij} of hospitalizations in patient i and six-month period j had average $\lambda_i \exp(\beta_{AI}\, a_{ij} + \beta_j)$ where λ_i was a patient specific rate - including the effect of all factors that do not change significantly over 2 years' time (sex, age, …), β_j was a (6-month) period specific effect adjusting for time trends in hospitalization and β_{AI} was the IA specific effect of interest ($a_{ij} = 1$ if an IA occurs in period j for patient i). The coefficient $\mathrm{PFC} = \exp(\beta_{AI})$ quantifies the self-adjusted proportional fold change (PFC) in the number of hospitalizations over a 6-month period depending if an IA is present. Conditionally on the total number of hospitalizations, the joint distribution of (H_{1i}, H_{i2}, H_{i3}, H_{i4}) was multinomial with parameters $\{\exp(\beta_{AI}\, a_{ij} + \beta_j)/\sum_{k=1}^{4} \exp(\beta_{AI}\, a_{ik} + \beta_k)\}$ for $1 \leq j \leq 4$, where the patient-specific rate of hospitalization λ_i had been cancelled out and was not estimated. Finally, we calculated the population-level fraction of hospitalizations attributable to an iatrogenic alert as $AF = \sum_{i,j} h_{ij} \left(1 - exp(-\beta_{AI} a_{ij})\right) / \sum_{i,j} h_{ij}$, i.e. the fraction of hospitalization avoided had no IA occurrence.