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Antipsychotic drug utilisation and safety in older persons with dementia: an international pharmacoepidemiologic inquiry

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Dedication

I would like to dedicate this dissertation to the few but important people in my life: to my father for his friendly and constant interest in my work; to my mother for her unquestioning belief in my ability to turn challenges into opportunities; to my sister for so rarely taking me seriously; to Shaun for providing an ironic but ultimately very effective stimulus to start writing; to Michael for providing many warm rays of sunshine.

Foreword

The present thesis is a collection of work carried out during the course of three years' work at the Department of Clinical and Experimental Medicine, at the University of Messina. I have had the privilege to collaborate with several experts in the field of pharmacoepidemiology, pharmacology, geriatrics and statistics, and all of whom have enriched my understanding of the small part of "science" that I have worked on. As I dug deeper into my chosen field of research, I was increasingly humbled by how much there is to learn, including many lessons learned from my own errors. However, I find this somewhat encouraging in the light of the following words by Neils Bohr, the Danish 1922 recipient of the physics Nobel Prize*:* "An expert is a person who has made all the mistakes that can be made in a very narrow field."

Acknowledgement

I am grateful to Prof. E. Spina for the opportunity to take part in the PhD programme in Biomedical, Clinical and Experimental Sciences and for the scientific freedom given to me. I am equally grateful to Dott. G. Trifiro' for involving me in several pharmacoepidemiology studies, some of which form the basis of the present dissertation.

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1. Introduction

The world is increasingly composed of an elderly population, bringing healthcare of older populations to the forefront. A number of older persons are privileged enough to enjoy healthy aging or have conditions that can be managed without significantly impacting their quality of life. However, many others are affected by dementia of various aetiologies, which leads to memory impairment and confusion. Often, this disorientation can give rise to psychological and behavioural symptoms of dementia (BPSD) including aggression, wandering and hallucinations. The only licensed pharmacological management of BPSD, specifically of aggression in dementia, is the short-term use of the antipsychotic risperidone. Nevertheless, several other antipsychotics are also used in dementia patients. The widespread use of antipsychotics in dementia, as well as concern about the serious adverse effects of these drugs and the lack of convincing data on their efficacy in BPSD has led to an awareness of the need to study antipsychotic drug utilisation and safety, in order to improve the appropriateness of drug prescribing.

The investigation of drug prescribing patterns as well as drug safety in the general population has been made possible on a large scale in past decade due the availability of electronic healthcare databases. There are several types of such databases, although these are primarily divided into electronic medical records (EMR) databases and electronic claims databases. Examples of EMR include The Health Improvement Database (THIN), a UK nationwide GP database, Health Search Database (HSD), an Italian nationwide GP database and the Integrated Primary Care Information database (IPCI), a Dutch nationwide database. These databases contain information that general practitioners register routinely during clinical practice. Unlike electronic medical records, claims data is registered when a person makes a claim for a medical service, drug prescription and so on. The claims are administrative data used for billing rather than for clinical purposes. Examples of claims databases include Arianna database (Caserta, in the Campania region of Italy), Medicare/Medicaid (samples of which are available for each state of the U.S.A., for groups of states or from all the U.S.A.) and the German Pharmacoepidemiological Research Database (Gepard), a German nationwide claims database.

The use of population-based data sources can provide a pharmacoepidemiologic perspective on drug utilisation and safety which has the following characteristics: it is a reflection of actual medical practice on a large scale which is often representative of a whole country; this permits researchers to capture information on potentially inappropriate prescribing practices and adverse outcomes without having to create ethical dilemmas. Further real-world aspects of drug utilisation such as low adherence, dose variations and medication switching can also often be captured with electronic healthcare databases, while they often cannot be captured using other study designs and data sources. There are other widely acknowledged advantages to using these data sources, such as the inclusion of data from persons who are not usually included in randomised clinical trials, such as frail elderly persons and persons with multi-morbidity and/or polypharmacy as well as the relatively long observation periods available for patients in population-based databases, compared to the much shorter observation periods available in prospective clinical studies. Other data sources and the associated study designs, which for the greater part consist of clinical trials, or other similar prospective studies, tend to reflect a somewhat artificial scenario as data is not collected during routine medical practice but on the basis of a protocol. As a result, these approaches are not suited for drug utilisation research. With regards to the evaluation of drug safety, clinical trials and other prospective study designs tend to have a short duration can therefore not be used to assess the long-term safety of drug use. This is a significant limitation in that several drugs are used chronically and associated adverse effects may take years to develop.

They may be able to capture short-term safety events, but clinical trials tend to be aimed at measuring effectiveness rather than safety as an outcome. As a result, such trials are not usually rich in short-term safety data. On the other hand, safety studies carried out using electronic healthcare databases are able to capture outcomes related to short-term and long-term drug exposure. In summary, observational studies carried out using electronic healthcare databases are currently the best tool in the public health inventory to investigate drug utilisation and safety.

The aim of this thesis is to present a population-based pharmacoepidemiologic perspective on antipsychotic drug use and safety in dementia, through three approaches: a literature review on antipsychotic-associated safety outcomes in dementia, the implementation of drug utilisation studies using large general practice databases (THIN, HSD and IPCI) and a discussion of some specific topics of interest in the area, namely drug interactions in dementia patients, the role of frailty as a predictor of mortality and the influence of public health interventions on changing prescribing patterns and underlying risk of adverse events.

All the material presented in this thesis has been published in peer-reviewed

2. Reviews of safety concerns with antipsychotic use in dementia

The two papers presented in this chapter address the need for an updated review of observational studies investigating antipsychotic safety. The first paper in section 2.1. provides a comprehensive overview of several safety outcomes while the second paper in section 2.2. focuses on pneumonia as an outcome of antipsychotic use in the elderly.

2.1. Are the safety profiles of antipsychotic drugs used in dementia the same? An updated review of observational studies. Trifiró G[1], Sultana J[1], Spina E[1]. Drug Saf. 2014 Jul;37(7):501-20.

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Abstract

With an increase in the global prevalence of dementia there is also an increase in behavioural and psychological symptoms of dementia (BPSD) for which antipsychotic drugs are often used. Despite several safety warnings on antipsychotic use in dementia as a class, there is little evidence to support the efficacy of antipsychotics in individual BPSD symptoms or to evaluate the drug safety profile by individual antipsychotic drug. There is emerging but scarce evidence that suggests an inter-drug variability between antipsychotic safety outcomes in BPSD. The objective of this review was to examine the existing literature on antipsychotic drug use in dementia patients, in particular to see whether inter-drug differences regarding antipsychotic safety were reported. A literature search was conducted for observational studies published in English from 2004-2014 that reported the risk of all-cause mortality, cerebrovascular events, pneumonia and other outcomes such as hip/femur fracture, deep vein thrombosis and hyperglycaemia. Six out of 16 mortality studies (38%), 7 out of 28 stroke studies (25%), 1 out of 6 pneumonia (17%) studies and 2 out of 6 fracture studies (33%) investigated inter-drug safety outcomes in elderly patients/dementia patients, while to our knowledge there are no studies investigating the inter-drug variation of deep-vein thrombosis and hyperglycaemia risk. The results of the observational studies provide mixed results on the safety of antipsychotics in BPSD but it is clear that there are differences between the safety profiles of antipsychotic drugs. Robust evidence of such inter-drug variability could significantly improve patient safety as antipsychotics become more targeted to the clinical risk factors.

Key points

- Despite increasing awareness of the safety issues surrounding antipsychotic drug use in BPSD, there is currently very limited in information on the inter-drug variation in risk as the vast majority of studies focus on all antipsychotics as a group or on atypical/conventional antipsychotics as a class.
- It is becoming apparent that there is indeed a difference between the risks associated with individual antipsychotic drugs in BPSD. Robust evidence of the risks associated with individual antipsychotic drugs could significantly improve the standards of clinical care by tailoring the specific therapeutic/safety properties to the clinical needs of individual patients.

1. Introduction

Globally, the estimated number of patients with dementia was 25 million in 2000 and is projected to rise to 63 million by 2030 [1].The clinical manifestations of dementia consist of cognitive and/or memory deterioration with progressive impairment of activities of daily living, as well as a variety of behavioural and psychological symptoms (BPSD)[2],[3]. These neuropsychiatric symptoms occur in more than 90% of patients with dementia and present a significant challenge for clinicians as well as care-givers[3]. BPSD is not a single behavior but comprises several symptoms such as agitation, psychosis and mood disorders, which usually co-occur and often recur. Patients with BPSD are more likely to need physical restraint, have a higher risk of early institutionalization and a higher risk of mortality [4],[5],[6]. In addition, BPSD negatively affects the quality of life of caregivers and other residents, if in a nursing home [7],[8]. The etiology of these symptoms still is not fully known.

Antipsychotics are often the first-line treatment for BPSD. They are generally distinguished as conventional (first-generation) or atypical (second-generation) antipsychotics. Conventional agents include butyrophenones (e.g. haloperidol), phenothiazines (e.g. chlorpromazine and thioridazine) and several others (e.g. indoles, thioxanthenes). Conventional antipsychotics were approved in the 1950's mainly for the treatment of schizophrenia. Since then, these agents have also been used for the treatment of a broad spectrum of psychiatric disorders including BPSD despite a lack of scientific evidence supporting their use in dementia [9]. Currently, atypical antipsychotics include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine and amisulpride. The receptor binding profile among atypical antipsychotics differs substantially across different compounds such that these drugs cannot be truly considered a unique homogeneous therapeutic class [9-13]. Atypical antipsychotics were initially licensed in the 1990s and approved by the US Food and Drug Administration (FDA) exclusively for the treatment of schizophrenia. Nowadays, they are also approved for the treatment of bipolar mania, while their use in dementia has remained off-label. Only risperidone has been approved for the treatment of aggression in patients with Alzheimer's disease in most European countries. Despite their off-label status in dementia, atypical antipsychotics have become the new standard of care for BPSD owing to their reported advantages over conventional agents, particularly a lower incidence of extrapyramidal symptoms (EPS) and tardive dyskinesia [9].In the late 1990s, atypical agents accounted for more than 80% of antipsychotic prescriptions in dementia in US nursing homes as well as in Canada[14]. In Europe, the use of atypical antipsychotics was lower even though it increased dramatically early after their introduction on the market[15].

1.1. Efficacy of antipsychotics in dementia

To date, more than 20 placebo controlled randomized clinical trials (RCTs) have investigated the efficacy of atypical antipsychotics for the treatment of BPSD, of which some were not published in full [21]. In their systematic review of 16 RCTs on atypical antipsychotics (olanzapine, quetiapine, risperidone, aripiprazole) for treatment of aggression, agitation and psychosis in dementia, Ballard and Waite concluded that risperidone and olanzapine have a modest efficacy in reducing aggression and psychosis, but both drugs were associated with serious adverse cerebrovascular events and extrapyramidal symptoms[21].Another meta-analysis of 7 RCTs of atypical antipsychotics (risperidone, olanzapine and quetiapine) reported neither a statistically nor a clinically significant difference in effectiveness as compared to placebo[22]. The findings from the meta-analyses were confirmed by a recent report of the CATIE-AD (Clinical Antipsychotic Trials of Intervention Effectiveness in Alzheimer's Disease) study which concluded that adverse effects

(olanzapine, risperidone, quetiapine versus placebo) offset the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease[23].More recently, a systematic review on the efficacy of atypical antipsychotics for off-label use in the treatment of elderly dementia patients with BPSD identified 14 placebo-controlled trials and assessed the efficacy of atypical antipsychotics using a total global outcome score including symptoms such as psychosis, mood alterations, and aggression. This systematic review reported small but statistically significant effect sizes ranging from 0.12 and 0.20 for aripiprazole, olanzapine, and risperidone, but indicated an absence of benefit with quetiapine[24].

In general, these randomized clinical trials (RCTs) had a short duration which may not reflect the use of antipsychotic drugs in clinical scenarios. In addition, placebo-controlled trial of 4 or more week's duration may present significant potential for patient selection bias. This is because subjects with more severe psychosis or agitation may not choose to be enrolled into a placebo controlled trial as their symptoms are too severe to take the chance of getting a placebo treatment. This leaves more mildly psychotic or agitated subjected being enrolled into placebo-controlled trials resulting in an underestimation of the positive efficacy of these agents for psychosis and agitation. BPSD RCTs also present limitations when they include patients living at home, in senior independent or non-locked assisted living environments rather than patients living in locked assisted living or nursing home facilities. The latter are where the majority of antipsychotics are most commonly used and are where the most severe behaviors are encountered. A further limitation encountered in RCTs may be a lack of equivalence between the antipsychotic doses used, potentially favoring some drugs over others.

To our knowledge, at present no published data from double-blind RCTs on patients with dementia are available for amisulpride, clozapine, paliperidone, asenapine, andziprasidone, which are seldom or never used in BPSD[9].Overall, there is also very limited evidence of any benefit of antipsychotics in the treatment of BPSD over periods longer than 12 weeks, despite the fact that up to 60% of older people with dementia receive treatment with antipsychotics for more than 6 months[25].

1.2. Safety of antipsychotics in dementia

The safety profile of atypical and conventional antipsychotics has been questioned in recent years, as demonstrated by a number of warnings which have been issued by regulatory agencies [16]. Despite all safety warnings, recent studies document a persistent wide use of antipsychotics in dementia due to the lack of alternative pharmacological options. Valiyeva *et al.* demonstrated that the warnings slowed the *growth* in the use of atypical antipsychotics among patients with dementia, but they did not reduce the overall prescription rate of these drugs in Canada[17]. Similarly, other studies in USA and Europe observed a reduction in the use of atypical antipsychotics in dementia as a result of the initial safety alerts[18],[19],[20]. This decreasing trend was however counterbalanced by a switch towards conventional antipsychotics, even though these are reported to have a similar increase in the mortality risk[18],[19].For all these reasons, a re-evaluation of the possible risk minimization effects of the safety warnings as well as a thorough assessment of the long-term mortality of each single antipsychotic in dementia is much needed.

Various safety concerns have been encountered with antipsychotic use, including all-cause mortality, cardiac arrhythmias, peripheral vascular effects, metabolic effects, pneumonia, cerebrovascular accidents. Very little attention has however been given to the safety issues related to antipsychotic withdrawal in BPSD, an area that warrants further investigation particularly because the use of antipsychotics in BPSD is generally recommended in the short-term[26, 27].

The importance of studies targeting antipsychotic use in dementia patients is highlighted by age-related pharmacokinetic changes as well as potential drug-drug interactions that can result in higher and more variable drug concentrations in this population, thus further increasing the risk of toxicity [8],[28]. In addition, age-related pharmacodynamic changes generally require antipsychotic dose adjustment in elderly persons [29]. This is because the clinical effect of a drug is a function of the affinity with the target, the drug concentration at the site of action (depending on the ADME: absorption, distribution, metabolism, excretion) and patient characteristics such as age and sex[30]. Nevertheless, there are few such pharmacokinetic studies which assess the ADME parameters in dementia patients [28]. Drug metabolism and excretion may vary substantially in older persons and current clinical recommendations suggest prescribing only a quarter to half of the defined daily dose of antipsychotics in geriatric patients [30] in the absence of more detailed pharmacokinetic evidence.

In light of the wide use of antipsychotics in dementia patients as well as the uncertainty about their actual safety profile in clinical practice, we conducted an updated review of currently known safety issues of individual antipsychotics.

2. Methods

PubMed was searched for the following terms: ‘antipsychotics’, ‘antipsychotic drugs’, ‘antipsychotic agents’ and ‘mortality’, ‘all-cause mortality’, ‘death’ or ‘cerebrovascular events’, ‘cerebrovascular event’, ‘CVE’, ‘stroke’, ‘ischaemic stroke’, ‘ischemic stroke’, ‘haemorrhagic stroke’, ‘hemorrhagic stroke’, ‘transient ischaemic attack’, ‘transient ischemic attack’, ‘TIA’ or ‘pneumonia’, ‘community-acquired pneumonia’, ‘acute chest infections’, ‘bronchopneumonia’ or ‘hip fracture’, ‘femur fracture’, or ‘deep vein thrombosis’, ‘DVT’, or ‘hyperglycaemia’, ‘hyperglycemias’. Studies were included if they were observational, cohort, case–control or self-controlled studies published in English from 2004 to 2014. Studies were included irrespectively of whether the reference group was unexposed patients or not and with no restrictions related to diagnostic categories.

References of relevant original research as well as review articles were hand-searched to identify further studies. Two investigators (GT and JS) independently examined the titles and abstracts and obtained full texts of potentially relevant papers. Any disagreement was resolved through consensus. Information on study design, setting/data source, study population, outcomes measured, exposure and main findings (risk estimates where possible) were extracted for each study and tabulated. All confidence intervals reported were at the 95% level.

3. Results

3.1. All- cause mortality

In April 2005, the Food and Drug Administration (FDA) issued a warning to inform health professionals that the mortality rate among elderly patients with dementia-related behavioural disorders receiving an atypical antipsychotic was higher than that observed in placebo-treated patients [31]. One of the initial alarm triggers of antipsychotic safety was a pooled analysis of RCTs by the European Medicines Agency (EMA) in 2004, which reported a 2-fold increased risk of all cause-mortality with olanzapine compared to placebo[32]. A more extensive analysis was carried out by the Food and Drug Administration (FDA) shortly after, in 2005. The FDA meta-analysis included 17 RCTs which investigated all-cause mortality in olanzapine, risperidone, quetiapine and aripiprazole and reported a risk which was also approximately two-fold[31]. Further similar

analyses which arrived at similar conclusions were carried out in 2005. A meta-analysis of 5 olanzapine, 5 risperidone, 3 aripiprazole and 3 quetiapine trials which included only elderly dementia patients found that overall, all these drugs carried a risk of excess mortality [33]. In June 2008, the FDA stated that the conventional antipsychotics share a similar risk of increased mortality with the atypical antipsychotics [34].

Several subsequent observational studies investigated the risk of antipsychotic-related all-cause mortality in larger populations than RCTs and over longer exposure periods, and comparing the risk of atypical vs. conventional antipsychotics or non-use (Table 1). One such study was a cohort study published in the USA shortly after the FDA warning and which included 22,890 elderly atypical and conventional antipsychotic users (almost 50% with dementia) [35]. This study found a significant 30% increased risk of mortality with conventional antipsychotics compared to atypical antipsychotics. Similar results were found by a cohort study in British Colombia, namely a 26% increased risk of mortality within 180 days with conventional vs. atypical antipsychotics in elderly patients of whom, however, a lower proportion had dementia [36]. Another cohort study found that there was a 17% lower risk of mortality with atypical APs compared to conventional APs in dementia after 12 months[37]. None of these studies evaluated the risk of all-cause mortality associated with individual antipsychotics. The increasing evidence led the FDA to issue another warning in June 2008 on the high risk of mortality with conventional atypical antipsychotic use [38].

The risk of mortality was found to increase with increasing dose and was highest shortly after exposure[35],[36],[39],[40]. While the expanding research base has highlighted several relevant safety issues, several others such as the differential risk of mortality associated with individual antipsychotics remains unknown. A recent observational study by Huybrechts *et al*. suggested that the risk of mortality is differential, being highest for high dose haloperidol (high dose vs. low dose HR= 1.84 (1.38-2.43), with high and low dose defined using the median daily dose of chlorpromazine equivalent dose as a cut-off point) and lowest for low dose quetiapine (medium vs. low dose HR= 1.02 (0.89-1.18), with medium and low dose quetiapine defined as 50-75 and 0-50mg of chlorpromazine equivalent doses respectively)[41]. However, Huybrechts *et al*. investigated outcomes of only 5 antipsychotics (haloperidol, aripiprazole, olanzapine, quetiapine and ziprasidone, with risperidone as comparator), omitting several others. Two other recently published observational studies supports the finding that mortality risk varies by individual antipsychotic. One study reported that the highest mortality rates were for haloperidol (RR=1.54 (1.38–1.73)) while the lowest were for quetiapine (RR= 0.73 (0.67–0.80)).[42]The other study, which included only vascular dementia patients, reported higher but not statistically significant mortality rates for quetiapine (HR= 1.13 (0.92–1.37)) and lower mortality rates for risperidone (HR= 0.87 (0.60–1.27))[43].

The investigation of antipsychotic-related risk has also been carried out in more vulnerable sub-populations of dementia patients, such as those living in nursing homes[41],[44],[45],[46],[47],[48]. This is of particular importance as elderly persons living in nursing homes are likely to be more frail community-dwelling counterparts[49]. The comparative risk of specific cause mortality for individual antipsychotic agents is also poorly characterised, while more general comparisons between conventional and atypical antipsychotic classes have been investigated [50]. A recent study found a differential risk of specific causes of mortality in nursing homes, but included only one conventional antipsychotic compared to five atypical agent [41]. Huybrechts *et al*. found that haloperidol users in nursing homes had a higher risk of mortality compared with risperidone (HR=2.07 (1.89-2.26)) and quetiapine users had a lower mortality risk (RR=0.81 (0.75-0.88). It should be noted that some studies' findings did not support this higher risk associated with conventional antipsychotics or even any antipsychotics in dementia, but such studies tended to

have very small populations and for this reason should be interpreted in the context of their limitations [51],[52].Several specific causes have been suggested to be at the root of antipsychotic mortality, including cerebrovascular events, pneumonia, peripheral vascular effects and metabolic effects, all of which are explored in further detail below.

A general consideration in these mortality studies and as well as other observational studies described below relates to the comparison group used. As can be seen from tables 1 to 4, the comparison group often consists of non-users of antipsychotics. This may result in the exposed and unexposed groups having important differences in dementia severity and overall frailty that increase the risk of death for exosposed groups independently of antipsychotic use alone.

3.2. Cerebrovascular effects

In October 2002, the marketing authorisation holder of risperidone notified all Canadian healthcare professionals that risperidone users had a higher rate of cerebrovascular events (CVEs) than placebo [53]. In March 2004, the UK Committee on Safety of Medicines recommended that health professionals avoid off-label use of atypical antipsychotics in elderly individuals with BPSD, particularly in those with a high baseline risk of stroke, [54] due to the observed CVE risk associated with these antipsychotics. At that time, information was reported only for olanzapine and risperidone although a similar alert was later released also by the manufacturer of aripiprazole[55].

Following the warning on antipsychotic-related stroke, several observational studies were conducted to compare the risk of stroke between atypical and conventional antipsychotics (Table 2). Most of these studies were conducted in an elderly population [50],[56],[57],[58],[59],[60], [61] but only two were restricted to older patients with dementia [45],[62]. Risperidone and olanzapine were associated with a nearly 3-fold increase in the risk of CVEs in dementia patients [47],[63],[64]. The risk of CVE was extrapolated through the whole class of drugs, despite concerns that this was unjustified [16]. Four observational studies suggest a higher risk of stroke with atypical than with conventional antipsychotics, even in dementia [58],[65],[66],[67]. However, at least four studies found that the risk of CVE was higher for conventional than atypical agents [16],[68],[69],[70]. Although there is very limited data comparing the risk of individual drugs within the class of atypical or conventional antipsychotics, a difference in CVE risk has been reported between phenothiazines (RR=5.79 (3.07–10.9)) and butyrophenones (RR=3.55 (1.56–8.07)) as compared to other atypicals (RR=2.46 (1.07–5.65)) compared to unexposed patients [60]. Another study reported that while conventional antipsychotics as a class were not associated with CVE, sulpiride was associated with CVE[71]. Similarly, as a class atypical antipsychotics were slightly associated with CVE while by individual agent, quetiapine and risperidone were not [71]. Although this study suggests that the difference in risk between class and individual drugs may be important, the results of this study must be interpreted with caution because risk estimates were not statistically significant.

Limited data is available on the dose-effect relationship between antipsychotic dose and stroke [16] although a recently published study reported that higher antipsychotic doses are associated with higher risks of CVE [66]. It was however reported that with regards to the temporal relationship between dose and effect, an elevated risk was found during the first weeks of treatment which decreases over time [72]. Another challenge of these studies was to identify unmeasured predictors of increased risk independently of the drug use. In one study, users of olanzapine and risperidone with several vascular risk factors (which were either not adequately treated or completely untreated)were more likely to develop CVE but it is unclear how much of this excess risk was due to the antipsychotics[73].There can be additional methodological concerns about the

diagnosis of CVE which may or may not be confirmed by radiological evidence. It is also not always clear how uniform or strict the definition of stroke or CVE employed across studies is, which may hinder direct comparison across studies.

The mechanism behind antipsychotic-related stroke in dementia is unknown but has been linked to orthostatic hypotension, hyperprolactinaemia resulting in atherosclerosis, thromboembolic events and excessive sedation [73],[74]. Some antipsychotic agents are known to antagonise alpha-adrenergic receptor which is a pathway for hypotension. Antipsychotic agents most likely to have a hypotensive effect are clozapine, quetiapine, risperidone and olanzapine in decreasing order, while haloperidol and ziprasidone were associated with the lowest risk of hypotension [16]. Atypical and conventional antipsychotics are both associated with venous thromboembolism (VTE) (see section on 'Peripheral vascular effects' below). On the other hand, it has also been hypothesised that the extrapyramidal effects of antipsychotics which lead to stiffness and sedation may later give rise to venous stasis and/or dehydration which could increase the risk of cerebrovascular events. Yet another putative mechanism is the thrombogenic effect due to hyperprolactinaemia which can result in enhance platelet reactivity [75].

Despite these suggested mechanisms, the association between stroke and antipsychotics was questioned because of the absence of a solid and proven biologically plausible explanation, uncertainty about the diagnostic accuracy of either TIA or stroke in the trials considered. The causal relationship between stroke and antipsychotics further questioned because patients were often affected by vascular dementia, which is itself associated with cerebrovascular risk. Cognitive impairment and stroke are very much related and older patients with Alzheimer's disease are more likely to die from cerebrovascular disease than non-demented elderly subjects [16]. Following the warnings on antipsychotic-related stroke, several observational studies were conducted to compare the risk of stroke between atypical and conventional antipsychotics. Most of these studies were conducted in elderly populations[50],[56],[57],[58],[59],[60],[61], but only two were restricted to older patients with dementia [45],[62]. The study by Gill *et al*. reported that long-term care resident status was a risk factor for CVE (RR= 1.15 (0.82-1.6)) for atypical antipsychotics, with conventional antipsychotics being the referent), as was a history of atrial fibrillation factor (RR= 1.23 (0.70-2.02)) [62]. This study did not investigate the differential risk associated with antipsychotic use and provided no information on the duration or dose of antipsychotics used. Liperoti *et al*. reported the dose only descriptively without investigating the association between different doses and risk of CVE, although they provide risk estimates for the hospitalization of elderly nursing home residents with a diagnosis of stroke or transient ischemic attack for two specific atypical antipsychotics: risperidone versus no use (OR =0.87 (0.67-1.12)) and olanzapine versus no use (OR= 1.32 (0.83-2.11)) [45]. Liperoti *et al*. also found that a history of CVE was an effect modifier for atypical antipsychotic use (RR = 4.63 (1.35-32.63)), in particular for olanzapine use (RR= 3.71 (1.55-8.84)) and to a lesser degree for risperidone (RR=1.49 (0.93-2.38). However, no other antipsychotics were considered individually, whether atypical or conventional [45].

3.3. Pneumonia

Infections, primarily pneumonia, have been listed as one of the most prevalent causes of death among elderly demented patients using antipsychotics, both in clinical trials and observational studies [16](Table 3). It is difficult to explore the relationship between antipsychotics and pneumonia since patients with dementia already have a higher risk of aspiration pneumonia, which makes any observational study liable to confounding by indication. Moreover, frail older patients may initially manifest pneumonia with delirium requiring antipsychotic drug treatment, thus also raising the potential for protopathic bias in observational studies [76]. A Dutch study investigating

the association between the hospital-based diagnosis of pneumonia and antipsychotic use reported a 3-fold increased risk during use of atypical and 1.6-fold increase during use of conventional antipsychotics as compared to non-use in an elderly population [76]. Setoguchi *et al*. found a slightly higher rate of fatal pneumonia during conventional antipsychotic use relative to atypical antipsychotic use, but the overall risk of antipsychotic linked to the use was not increased compared to non-use in a cohort of elderly patients [50]. Trifirò *et al.* showed that the use of either atypical or conventional antipsychotics in elderly patients is associated with an increase in the risk of pneumonia in a dose-dependent manner [77]. Looking at individual agents, Trifirò *et al*. found the highest risk of pneumonia was associated with risperidone (OR= 3.51 (1.94–6.36)), followed by zuclopenthixol (OR= 2.25 (1.00–5.08)), haloperidol (OR= 1.95 (1.20–3.17)), olanzapine (OR =1.90 (0.61–5.90)) and paliperidone (OR =1.55 (1.00–2.43)). Given the frequency and poor prognosis of pneumonia in elderly dementia patients, it is important to explore the relationship between use of each single antipsychotic and pneumonia in dementia patients. This has only been explored by one study, to our knowledge, a recently published study which found that, using risperidone as comparator, olanzapine and ziprasidone had a stronger association with pneumonia than quetiapine and aripiprazole; this study was however limited by the small numbers of ziprasidone and aripiprazole users [67].

The possible mechanisms of antipsychotic-induced pneumonia remain speculative. It is likely that antipsychotics may induce aspiration pneumonia in dementia patients through many possible mechanisms involving extrapyramidal adverse events, dysphagia, or sedation, as a result of modulation of dopamine, cholinergic, and H1-histaminergic receptors, respectively [78]. Due to differences in the receptor binding profiles among various antipsychotics, the risk of pneumonia for any single antipsychotic and the underlying mechanism should be further investigated. It has already been shown in one study that the risk of pneumonia is differential between atypical (OR= 5.97 (1.49–23.98)) and conventional antipsychotics (OR= 1.71 (0.76–3.87)), between subclasses such as butyrophenones (OR= 1.42 (0.59–3.37)) and other antipsychotics such as thioxanthene, diphenylbutylpiperidine, and benzamide derivatives (OR= 2.84 (0.74–10.92)) as well as between some individual antipsychotics (see above) [78]. However, this study only considered five antipsychotics individually, leaving doubts about the risk associated with other antipsychotics. In addition, methodological issues such as confounding by indication and protopathic bias obscure the association between antipsychotic drugs and pneumonia and their effect on risk estimates must be considered thoroughly in order to avoid misleading results [78].

3.4. Cardiac arrhythmias

Since the early sixties, sudden cardiac death (SCD) has been reported with conventional antipsychotic use, mostly haloperidol and thioridazine [79]. Particular attention has been paid to the ability of antipsychotic drugs to prolong the QTc interval which may result in Torsade de Pointes and other potentially fatal ventricular arrhythmias[80]. QTc interval prolongation was reported to be highest for thioridazine, sertindole, pimozide, haloperidol, quetiapine and ziprasidone, in decreasing order [81]. Several observational studies have confirmed the signals from spontaneous reports suggesting that conventional antipsychotics are associated with an increased risk of SCD[79],[82],[83],[84]. In particular, thioridazine was withdrawn from the market in some countries due to concerns of cardiac arrhythmia [85]. Recently two large US studies found that the risk of SCD is increased also with the four most frequently prescribed atypical antipsychotics (clozapine, olanzapine, quetiapine and risperidone)[44],[82],[84]. On the basis of this evidence, electrocardiography monitoring would be prudent in routine clinical care if antipsychotics are prescribed to elderly patients[86, 87]. No studies investigated arrhythmogenic potential of antipsychotics in patients with dementia, specifically, and none of the currently available studies

had the statistical power to look at dose and duration effects of individual drugs on the SCD risk.

3.5. Peripheral vascular effects

Antipsychotic use has been associated with the occurrence of venous thromboembolism (VTE), an association that was recently reviewed by the UK Medicines and Healthcare products Regulatory Agency (MHRA)[88]. A relationship between antipsychotic medications and VTE was first suggested around five decades ago[88]. However, despite early descriptions and subsequent reports of VTE associated with antipsychotic use, evidence for a true link has not been clearly established. Reviews of the available data for aripiprazole, clozapine and olanzapine have led to warnings about VTE being added to their Summaries of Product Characteristics (SPCs)[88]. There are now several studies on VTE and antipsychotics[89],[90],[91],[92],[93],[84], [94],[95],[96],[97],[98],[99], [100]mostly on young patients with schizophrenia and with methodological limitations (small sample size, inadequate control of confounding). Findings about specific drugs were inconsistent, but all studies concluded that an increased risk of VTE with atypical and/or conventional antipsychotics was likely[88]. Very little data is available on the peripheral vascular effects of antipsychotics in dementia, which is highly relevant given the extensive use of other potentially interacting medications acting on serotonin receptors and platelet function in these patients. Only one study investigating the link between antipsychotic use and VTE has been published to our knowledge, a recent nested case-control using the a cohort of 72,591 dementia patients[101]. This study found that among users of antipsychotics from this population, current users had a statistically significant increased risk of VTE (OR= 1.23 (1.01-1.60)) compared to controls, defined as dementia patients at risk of VTE. Within the subgroup of current antipsychotic users, new users had a higher risk of VTE than controls, than prevalent users or than past users. The risk of VTE did not appear to vary between first and second generation antipsychotics when these were analysed as separate groups; the risk of VTE associated with individual antipsychotics was not investigated [101]. No other studies investigate the differential risk of VTE associated with individual antipsychotics.

3.6. Metabolic effects

While mortality, stroke and pneumonia were the main focus of research, several other adverse events related to antipsychotic use are also a source of concern (Table 4). Metabolic effects of antipsychotics are a long-term safety concern and may contribute to further increase the cardiovascular risk in older people with dementia[102]. In patients with either schizophrenia or bipolar disorder, the use of antipsychotics (i.e. olanzapine, clozapine) has been associated with metabolic abnormalities including weight gain, lipid disturbances and altered glucose homeostasis[103]. Whether elderly patients with BPSD receiving antipsychotics develop similar disturbances is still unclear. Metabolic effects of antipsychotics in elderly patients with dementia are difficult to assess in general, as food intake is reduced in these subjects. Only a few and relatively small studies have been published so far on this association. Rondanelli *et al*. concluded, on the basis of 36 nursing home residents with AD, that treatment with low-dose atypical antipsychotics does not lead to weight gain or increase in the risk of type II diabetes or lipid metabolism abnormalities[104]. In contrast, the CATIE-AD trial reported weight gain during use of olanzapine, quetiapine and risperidone in 421 AD patients and the risk increased over time[105]. Beside an increase in body weight, there was no apparent effect on glucose levels, total cholesterol and triglycerides levels, apart from an unfavourable change in HDL cholesterol and girth with olanzapine. Post-hoc analyses of other studies with olanzapine and risperidone were consistent with the CATIE-AD trial[16]. A recently published Canadian study by Lipscombe *et al*., carried out using four administrative databases in Ontario, found that among older patients with

diabetes, the initiation of treatment with antipsychotic drugs was associated with an increased risk hyperglycemias [106].

The risk of hyperglycaemia appeared to be much higher for incident (RR= 15.4(8.12-29.2)) use than prevalent (RR=1.36(1.03-1.79)) antipsychotic use for insulin-treated patients taking any antipsychotic, and slightly higher for atypical AP use (RR=1.4(1.06-1.85)) than for conventional AP use (RR=1.27(0.75-2.12)) among these patients. The overall risk of hyperglycaemia was slightly lower when patients were prescribed oral hypoglycaemic agents and were incident antipsychotic users (RR=14.4(8.71-23.8)) compared to when they were prescribed insulin. Lipscombe *et al*.however, did not investigate the risk of hyperglycaemia associated with individual antipsychotics and this remains unknown at present[106]. At present, the association between antipsychotic use and either hyperglycaemia in elderly diabetic patients with dementia or new onset diabetes in elderly dementia patients requires better investigation[16]. In addition, it should be clarified if such possible metabolic effects (i.e. hyperglycaemia, hypercholesterolemia, hypertriglyceridemia and weight gain) of antipsychotics lead to a clinically relevant increased risk of all-cause mortality in these patients over the period of antipsychotic treatment in dementia patients

4. Directions for future research on antipsychotics in BPSD

The body of scientific evidence regarding the safety and efficacy of antipsychotics in BPSD is expanding; however there are several significant research gaps that still exist. There is very limited data on the safety of individual antipsychotics, as illustrated above. In addition, most antipsychotic safety studies tend to group all BPSD patients together rather than evaluating outcomes by individual BPSD symptoms. Only one study has investigated an outcome (mortality) considering symptoms such as delirium and hallucinations in dementia patients prescribed antipsychotics[107]. The type of dementia associated with BPSD is also likely to influence the safety of antipsychotics, but this has been a somewhat neglected area of clinical research.

So far, comprehensive safety data about long-term use of antipsychotics in dementia patients in various settings and different European countries is missing[108]. Although various clinical trials and observational studies have investigated the post-marketing risk of all-cause mortality [35],[36],[37, 40], [43],[44],[51],[109], cerebrovascular adverse events [45],[50],[56],[57],[58],[59],[60],[61], [62]sudden cardiac death[79],[80],[82],[83],[84], venous thromboembolism/pulmonary embolism[88],[89],[90],[91],[92],[93],[94],[95],[96],[97],[98],[99], diabetes mellitus and other metabolic effects [76],[102],[103],[104],[105] and community-acquired pneumonia[76], [77], [78]associated with atypical and conventional antipsychotics, few of these studies were able to properly assess the short- and long-term risk for each single antipsychotic separately in a well-powered study, despite emerging evidence that their clinical characteristics seem to be different. Of the 16 mortality studies we considered in this review, only 6 investigated the risk of some individual antipsychotics [36],[37],[41],[42], [43], ,[48],[100]; of the 18 stroke studies only 7 investigated individual antipsychotics [45],[56],[57],[61], [71],[67],[110]. Only 1 out of 6 studies investigated the risk of pneumonia with individual antipsychotics [111]; only 2 out of 6 studies investigated the risk of hip fracture with individual antipsychotics [112],[113] and neither of the studies investigating the risk of DVT and hyperglycaemia evaluated the individual risk of antipsychotics. This missing information could have important implications for choosing the drug of least risk in populations particularly prone to specific ADRs. The optimal dose associated with least risk of various ADRs is also not well-investigated with regards to antipsychotic use in BPSD, a potentially important aspect of antipsychotic safety given that the dose of APs in BPSD is lower than that in schizophrenia or bipolar disease. This is particularly relevant and factoring given the pharmacokinetic and pharmacodynamic characteristics of dementia patients. Most observational

studies were focused on elderly populations rather than elderly dementia patients specifically. Moreover, these studies were conducted in a specific region or country (mostly USA), which restricts heterogeneity in exposure, thus resulting in lack of statistical power to evaluate the entire range of individual antipsychotics and prevent generalizability of the findings to dementia patients from other Countries. For instance, results from US observational studies can be hardly generalized to the European setting due to the differences about the prescribing pattern of antipsychotics in dementia between USA and Europe.

Individual RCTs were powered on efficacy outcomes and could not provide useful insights on safety outcomes. In addition, systematic reviews and meta-analyses of randomized data were not able to disentangle the absolute and relative risk of each antipsychotic versus placebo and versus other antipsychotics. For some newer atypical antipsychotics, findings have not been systematically reviewed yet. Furthermore, the safety of antipsychotics in BPSD is rarely compared to other off-label medications, such that the risks cannot be compared to other therapeutic options.

The long-term safety of antipsychotics in BPSD in particular presents a critical limitation in BPSD research so far, as there is very limited evidence of any benefit of these drugs for the treatment of BPSD over periods longer than 12 weeks. Most dementia patients discontinue antipsychotic treatment after a few weeks, yet a relevant proportion of them take these drugs for much longer periods. The AGIT and DART studies did not demonstrate any advantage for antipsychotics compared to placebo over six months[114],[115],[116],[117], and the CATIE study described no overall benefit[22]. However the CATIE trial did indicate that antipsychotics were less likely to be discontinued because of perceived ineffectiveness over nine months than placebo[22]. Furthermore, there is very limited data comparing antipsychotics to other off-label drugs in BPSD and similarly, limited data on the withdrawal of individual antipsychotic agents.

5. Conclusion

There are few observational studies that report the risk of adverse events with individual antipsychotics in elderly dementia patients. The highest risk of mortality was reported for haloperidol [36],[39] and chlorpromazine [48] while the lowest risk was reported for olanzapine [36], quetiapine [41], [42] and ziprasidone [41]. The evidence is much less clear-cut for stroke, with some studies reporting an increased [56],[61] or decreased [45],[71], [67],[110] risk with risperidone, increased [61],[110], or decreased [57],[71] risk with quetiapine and increased [57] or decreased [110] risk with haloperidol. Only one study investigated the risk pneumonia with individual antipsychotics but this did not provide a risk estimate nor was it sufficiently powered [111]. The risk of fracture was highest for zuclopenthixol [113] and haloperidol [112],[113] although too few studies investigated this outcome for these results to be conclusive. Only one study investigated DVT [101] and hyperglycaemia [106] respectively, neither of which considered the individual risk of antipsychotics.

While research on antipsychotic efficacy and safety in BPSD has expanded, research on the efficacy of individual antipsychotics in specific BPSD symptoms and the safety issues of individual antipsychotic use in BPSD has lagged behind. There are several studies suggesting a difference between the safety profile of atypical and conventional antipsychotics but there are only few studies on individual antipsychotic safety, suggesting that inter-drug difference in this respect are indeed being over-looked.

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Table1: Observational studies investigating the risk of mortality associated with antipsychotic use in elderly dementia patients. AAP: atypical antipsychotics; Adj.: adjusted; AP: antipsychotic; CAP: conventional antipsychotic; CD: community dwelling; HR: hazard ratio; LCT: long-term care; OR: odds ratio; RR: relative risk; PY: person years.

Author, year	Study design	Setting	Population	Outcome	Exposure	Main findings
Suh and Shah, 2005 [52]	Prospective cohort study	Semi-hospitalized, long-term care nursing home in Seoul	Dementia patients (N=273)	All-cause mortality	All APs (non-use as comparator):	Adj. RR -1.28 (1.13–1.44)
Wang *et al.*, 2005 [35]	Retrospective cohort study	Pennsylvania Medicare	Patients ≥65 (N=22,890)	All-cause mortality	CAPs vs. AAPs	Adj. RR - within 180days: 1.37 (1.27–1.49) - within 40 days: 1.56 (1.37–1.78) - 40–79 days: 1.37 (1.19–1.59) - 80–180 days: 1.27 (1.14–1.41)
Nonino *et al.*, 2006 [118]	Cohort study	Dementia Registry of Local Health Care Unit of Modena	Dementia patients >65 (N=2,314)	All-cause mortality	Incident use of AAPs Vs. non-use	Mortality rate: - AAP: 0.52/1,000 PY; - Non-use: 0.55/1,000PY
Trifirò *et al.*, 2007 [109]	Nested case-control study	Dutch general practice database (IPCI)	Dementia patients ≥65 (N=2,385)	All-cause mortality	Current use of AAP or CAP (non-use of respective class as comparator unless otherwise specified)	Adj. OR -current use of AAP vs. current use of CAP: 1.3 (0.7–2.4) -current AAP use: 2.2 (1.3–2.9) -current CAP use: 1.7 (1.3–2.2)

Gill *et al*., 2007 [40]	Retrospective cohort study	Four administrative databases in Ontario: -Ontario Drug Benefit program -Canadian Institute for Health Information Discharge Abstract Database -Ontario Health Insurance Plan - Registered Persons Database	Dementia patients ≥66 (N=27,259)	All-cause mortality at 30, 60, 120 and 180 days after the initial dispensing of antipsychotic medication	Incident use of AAPs (non-use as comparator) and CAPs (AAP as comparator) stratified in CD LTC cohorts	Adj. RR after 30 days of AAP vs. non-use: -CD: 1.31 (1.02–1.70); -LTC: 1.55 (1.15–2.07) Adj. RR after 30 days of CAP use -CD :1.55 (1.19–2.02) -LCT: 1.26 (1.04–1.53)
Schneeweiss *et al*., 2007 [36]	Retrospective cohort study	Linked administrative data from the British Columbia Ministry of Health, PharmaNet database and British Columbia	Patients ≥65 year old with an AP prescription (N= 37,241)	180 day all-cause mortality	Incident use of AAPs and CAPs (risperidone as comparator)	Mortality rate -CAP: 14.1% -AAP: 9.6% Adj. RR -haloperidol: 2.14 (1.86–2.45) -loxapine: 1.29 (1.19–1.40) -olanzepine: 0.94 (0.80–1.09)
Kales *et al*., 2007 [37]	Retrospective cohort study	US Department of Veteran Affairs registries	Dementia patients ≥65 year old with an AP prescription (N= 10,615)	1 year all-cause mortality from National Death Index	Incident use of AAPs, CAPs and combination of both types (CAP as comparator):	Mortality rate - AAP: 22.6% -CAP: 25.2% -combination: 29.1% Adj. RR - AAP: 0.93

						(0.75–1.16) - combination: 1.33 (0.94–1.86)
Hollis *et al.*, 2007 [39]	Retrospective cohort study	Australian Department of Veteran Affairs claims-based pharmaceutical database	Veterans and war-widows ≥65 (N=16,634)	All-cause mortality	Incident use of antipsychotics, carbamazepine and valproate (incident use of olanzapine as comparator)	RR -incident haloperidol use: 2.26 (2.08–2.47) -incident chlorpromazine use: 1.39 (1.15–1.67) -incident risperidone use: 1.23 (1.07–1.40)
Raivio *et al.*, 2007 [51]	Cohort study	7 Finnish nursing homes and 2 hospitals	Frail elderly patients (N=254)	All-cause mortality during a 2-year follow-up	Incident/prevalent use of AAPs and CAPs (non-use as comparator)	Two- year mortality rate: - AAP: 32.1% - CAP: 45.3% - non-use:49.6% RR - AAP: 0.49 (0.24–0.99) -CAP: 0.68 (0.46–1.03)
Hollis *et al.*, 2007 [48]	Cohort study	Department of Veterans' Affairs database and Medicare Australia	Incident users of APs	All-cause mortality	CAPs (chlorpromazine, haloperidol, pericyazine, trifluoperazine) AAPs (quetiapine, olanzapine, risperidone) (olanzapine as comparator)	RR within 60 days -chlorpromazine: 2.72 (1.84-4.01) -haloperidol: 2.17 (1.86-2.53)
Musicco *et al.*,	Retrospective	Milan Health	Patients ≥60	All-cause	AAPs or	Adj. HR

2011 [119]	cohort study	information database	years prescribed an anticholinesterase inhibitor (N= 4,369)	mortality	CAPs (no AP as comparator unless otherwise specified)	-CAPs: 3.7 (2.6–5.1) -AAPs: 2.5 (2.0–3.0) -CAPs vs. AAPs: 1.5 (1.1–2.1)
Aparasu *et al*., 2012 [49]	Retrospective cohort design matched on propensity score	Medicare and Medicaid data from Texas, Florida, New York and California	Nursing home residents ≥65 years (N=7,218)	All-cause mortality	AAPs vs. CAPs (AAP as comparator)	Adj. HR -CAPs: 1.41 (1.27-1.57) -< 40 days after start of CAPs: 1.81 (1.49-2.18) -40-180 days after start of CAPs: 1.24 (1.09-1.42)
Kales *et al*., 2012 [42]	Retrospective cohort study	U.S. Department of Veteran Affairs database	Dementia patients ≥65 years old (N= 1,932)	180-day mortality	Risperidone, haloperidol, olanzapine, quetiapine (risperidone as comparator)	Propensity-weighted HR -haloperidol: 1.57 (1.39-1.78) -olanzapine: 1.03 (0.92-1.16) -quetiapine: 0.74 (0.67-0.81)
Huybrechts *et al*., 2012 [41]	Cohort study	Linked data from Medicaid, Medicare, the Minimum Data Set, the National Death Index, and a national assessment of nursing home quality.	Nursing home patients ≥65 (N= 75,445)	All-cause mortality (excluding cancer mortality) and cause-specific mortality	Incident use of haloperidol, aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone (risperidone as comparator)	Adj. HR for all non-cancer mortality -haloperidol: 1.81 (1.65-1.98) -aripiprazole: 0.95 (0.78-1.15) -olanzapine: 1.01 (0.95-1.08) -quetiapine: 0.83 (0.77-0.89)

						-ziprasidone: 0.90 (0.69-1.17)
Rafaniello *et al.*, 2013 [107]	Prospective cohort study	Dementia Evaluation Unit of Campania Region to which consultant prescribers are affiliated	Dementia patients with BPSD ≥65 years who were incident antipsychotic users (N=1,618)	All-cause-mortality	AAPs(non-use as comparator)	Rate per 100PY -quetiapine: 5.8 (4.4–7.7) -risperidone: 7.3 (4.8–11.1) -olanzapine: 4.6 (2.5–8.3) -clozapine: 7.7 (1.9–30.9) -aripiprazole: 17.6 (2.5–125.0)
Sultana *et al.*. 2014 [43]	Retrospective cohort study	South London and Maudsley NHS Foundation Trust (SLaM) Biomedical Research Centre database, Clinical Record Interactive Search (CRIS)	Vascular dementia patients (N=1531)	All-cause mortality	AAPs(non-use as comparator)	Adj. HR: -prescription of olanzapine, quetiapine or risperidone ever: 1.05 (0.87–1.26) -quetiapine: 1.13 (0.92–1.37) -risperidone: 0.87 (0.60–1.27)

Table 2: Observational studies investigating the risk of stroke due to antipsychotic use in dementia or in elderly patients. AAPs: atypical antipsychotics; APs: antipsychotics; Adj.: adjusted; BPSD: behavioral and psychological symptoms in dementia; CAP: conventional antipsychotics; CVE: cerebrovascular events; NHS: National Health Service; OR: odds ratio; RR: risk ratio; TIA: transient ischaemic attack.

Author, year	Study design	Setting	Population	Outcome	Exposure	Main findings
Herrmann *et al*., 2004 [56]	Retrospective cohort study	Administrative healthcare database in Ontario	Subjects >65 years (N= 11,400)	Hospital admission due to stroke	Use of risperidone, olanzapine and conventional antipsychotics (CAPs as comparator)	Adj. RR: -risperidone: 1.4 (0.7–2.8) -olanzapine: 1.1 (0.5–2.3)
Gill *et al*., 2005 [62]	Retrospective cohort study	Administrative healthcare database in Ontario	Subjects ≥65 years with dementia (N= 32,710)	Hospital admission due to ischemic stroke	New users of AAPs (risperidone, quetiapine and olanzapine) and CAPs (CAPs as comparator)	Adj. RR of AAP vs. CAP: 1.01 (0.81–1.26)
Liperoti *et al*., 2005 [45]	Case–control study	Nursing homes in Ohio, Maine, Illinois, Mississippi, South Dakota, and New York	Residents of nursing homes in 6 US states (SAGE database) with dementia (N= 1,130 cases and N= 3,658 controls)	Hospital admission for stroke or TIA	Current use of AAPs and CAPs (non-use as comparator)	Adj. OR -risperidone: 0.87 (0.67–1.12) -olanzapine 1.32 (0.83–2.11) -other AAPs: 1.57 (0.65–3.82) -CAPs: 1.24 (0.95–1.63)
Finkel *et al*., 2005 [57]	Retrospective cohort study	USA-wide Medicaid data	Dementia patients (N=18,987)	New case of acute inpatient admission for CVE	Incident use of AAPs (risperidone, olanzapine, quetiapine and	Adj. RR -olanzapine: 1.05 (0.63–1.73) (b) - quetiapine:

					ziprasidone) and haloperidol (risperidone as comparator)	0.66 (0.23–1.87) - haloperidol: 1.91 (1.02–3.60)
Layton *et al.*, 2005 [61]	Prescription event monitoring study	NHS UK prescription data as supplied by Prescription Pricing Authority	Patients of all ages, including patients with dementia (N= 7,684 patients on risperidone; N= 8,826 on olanzapine; N= 1,726 on quetiapine)	Any CVEs within first 180 days therapy	Incident use of risperidone, quetiapine and olanzapine (olanzapine as comparator)	Adj. RR -risperidone: 1.2 (0.5–3.0) -quetiapine: 2.1 (0.6–7.7)
Percudani *et al.*, 2005 [58]	Case–control study	Administrative healthcare database in Lombardy, Italy	Patients ≥65 years (N=35,604)	Hospital admission due to any CVE	Previous use (as monotherapy) of AAPs (risperidone, olanzapine, quetiapine and clozapine) and CAPs (CAPs as comparator)	Adj. OR -CAPs vs. AAPs 1.42 (1.24–1.64)
Wang *et al.*, 2007 [68]	Retrospective cohort study	The Pharmaceutical Assistance Contract for the Elderly Information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE)	Patients >65 with at least one prescription for an antipsychotic (N= 22,890)	CVE	CAPs (AAPs as comparator)	Adj HR: 1.09 (1.02 -1.16)

		and Pennsylvania Medicare				
Barnett *et al.*, 2007 [59]	Retrospective cohort study	Veteran Administration and Medicare database	Subjects ≥65 years with dementia (N=14,029)	Hospital admission due to any CVE	Incident use of AAPs and CAPs (non-use as comparator)	Adj. RR -CAPs: 1.29 (0.48–3.47) -AAPs: 1.20 (0.83–1.74)
Sacchetti *et al.*, 2008 [60]	Retrospective cohort study	Italian general practice database	Patients 65 years or older (N=74,162)	First ever stroke	Incident use of AAPs, butyrophenones, phenothiazines, benzamides (non-use as comparator)	Adj. RR -AAP: 2.46 (1.07–5.65) -butyrophenones: 3.55 (1.56–8.07) -phenothiazines: 5.79 (3.07–10.9) -benzamides: 2.2 (0.98–4.90)
Setoguchi *et al.*, 2008 [50]	Cohort study	Healthcare utilization database in community setting containing all British Columbia residents aged 65 and older	New APs users (N= 37,241), of whom 4,337 had dementia	All-cause mortality and specific-cause mortality	AAPs and CAPs (AAP as comparator)	Adj. HR for all non-cancer deaths -CAPs: 1.27 (1.18–1.37)
Douglas *et al.*, 2008 [65]	Self controlled case series	UK-based electronic primary care records in the general	All patients registered in GPRD with a recorded incident stroke	Stroke	All antipsychotic drugs available in database (non-use as	RR -all APs: 1.73 (1.60-1.87) -CAPs: 1.69 (1.55-

		practice research database (GPRD)	and at least one prescription for any antipsychotic (N= 6790)		comparator)	1.84) for and -AAPs: 2.32 (1.73-3.10) -all APs in dementia patients: 3.50 (2.97-4.12) -CAPs only in dementia patients: 3.26 (2.73-3.89) -AAPS only in dementia patients: 5.86 (3.01-11.38)
Chan *et al.*, 2010 [71]	Retrospective cohort study	Patients in the Department of Psychiatry of the Pamela Youde Nethersole Eastern Hospital, China	Patients ≥ 65 diagnosed with Alzheimer's disease, vascular or mixed dementia with BPSD (N= 1,741)	CVE	All APs (non-use as comparator)	Adj. HR -CAPs: 0.96 (0.58–1.59) -haloperidol: 0.92 (0.53–1.60) -trifluoperazine: 0.79 (0.18–3.47) -sulpiride: 1.48 (0.69–3.18) -AAPs: 1.04 (0.35–3.07) -quetiapine: 0.901 (0.12–6.93) -amisulpride: 7.60 (0.62–92.26) -risperidone: 0.42 (0.05–3.29)

						-olanzapine 5.22 (0.57–47.73)
Laredo *et al.*, 2011 [69]	Case-control study	UK-based electronic primary care records in the General Practice Research Database (GPRD)	Patients over 65 within the database (N=26,885)	CVE	CVE in users versus non-users of AAP/CAP (non-use as comparator unless otherwise specified)	Adj. OR -Any AP: 0.96 (0.89–1.04) -only CAPs: 1.16 (1.07–1.27) -Only AAPs: 0.62 (0.53–0.72) (AAPs as comparator)
Huybrechts *et al.*, 2012 [67]	Cohort study	Medicaid, Medicare, Minimum Data Set and Online Survey Certification and Reporting data for patients from nursing homes in 45 US states	Medicaid eligible residents ≥65 who initiated antipsychotic treatment in nursing homes (N=83,959)	Hospitalization for CVE (stroke/TIA), within 180 days of treatment initiation	AAPs (AAPs as comparator when comparing classes; risperidone as comparator when comparing individual APs)	Propensity-adj. HR -CAPs: 0.81 (0.65-1.01) -aripiprazole: 0.99 (0.72-1.35) -olanzapine: 0.94 (0.84-1.05) -quetiapine: 0.91 (0.80-1.03)
Wu *et al.*, 2013 [66]	Case-cross over study	National Health Insurance Research Database (NHIRD) in Taiwan	Patients over 18 with incident stroke within NHIRD (N= 14,584)	Stroke	All APs available in database (CAPs as comparator)	Adj. OR -AAPs: 1.91 (1.67-2.18)
Wang *et al.*, 2013 [70]	Case–case–time–control design study	USA Veterans Health Administration database	Patients stroke ≥60 with a diagnosis of stroke (N= 511)	Ischaemic stroke	All APs (non-use as comparator)	Adj. OR -1.8 (1.7–1.9)
Liu *et al.*, 2013	Cohort study	National Health	Dementia	Stroke	All APs (no AP	Adj. HR

[120]		Insurance Research Database (NHIRD) in Taiwan	patients ≥65 years		use in dementia patients as comparator)	for AP use in dementia): 1.17 (1.01–1.40)
Shin *et al.*, 2013 [110]	Case-crossover study	Korean Health Insurance Review and Assessment Service database	Patients >64 years	Stroke	Risperidone, quetiapine and olanzapine (non-exposure as comparator)	Adj. OR for outcome within 30 days of starting AP -AAP: 3.9 (3.3–4.6) -risperidone: 3.5 (2.9–4.2) -quetiapine: 2.7 (2.0–3.6) -olanzapine: 1.2 (0.7–2.0)

Table 3: Observational studies investigating the risk of pneumonia associated with antipsychotic use in the dementia or in the elderly. AAPs: atypical antipsychotics; Adj.: adjusted; APs: antipsychotics; CAPs: conventional antipsychotics; OR: odds ratio; RR: risk ratio.

Author, year	Study design	Setting	Population	Outcome	Exposure	Main findings
Trifirò *et al.*, 2010 [77]	Nested case-control	Dutch general practice database (IPCI)	Patients (≥ 65) newly treated with antipsychotics (N=258)	Fatal and nonfatal community-acquired pneumonia	AAP or CAP (past use of any AP as comparator)	Adj. OR Fatal/nonfatal pneumonia: - AAPs: 2.61 (1.5–4.6) -CAPs: 1.8 (1.2–2.5) Fatal pneumonia: - AAPs: 6.0 (1.5–24.0) -CAPs: 1.7 (0.8-3.9)
Knol *et al.*, 2008 [76]	Nest case-control	Dutch PHARMO database	Patients (≥ 65) newly treated with antipsychotics (N= 22,944; n= 543 cases)	Hospital admission due to pneumonia	AAP or CAP (non-use as comparator)	Adj. OR -current use of AAP: 3.1 (1.9–5.1) -current use of CAPs: 1.5 (1.2–1.9)
Gau *et al.*, 2010 [121]	Case-control study	Rural community hospital in Ohio (USA)	Patients aged 65 years or older (N=194)	Hospital admission due to community-acquired pneumonia	AAP (non-use as comparator)	Adj. OR -AAP: 2.26 (1.23–4.15)
Star *et al.*, 2010 [122]	Self-controlled cohort	UK IMS Health Disease Analyzer database	Adults aged 65 years or older (number of patients not provided)	Acute chest infections, bronchopneumonia, hypostatic pneumonia	Distribution over time of AAPs and CAPs with respect to date of diagnosis of the study outcomes	In elderly patients (≥ 65): - higher rate of acute chest infections following AAPs and much less CAPs

						-higher rate of bronchopneumonia following either AAP or CAP prescriptions.
Barnett *et al.*, 2006 [59]	Retrospective cohort study	US Veterans Administration database	Patients hospitalized due to pneumonia (N= 16,931)	In-hospital mortality	AAP or CAP (no use of neuropsychiatric drugs as comparator)	Adj. OR -CAP: 1.5 (1.0–2.2) -AAPs: 1.2 (1.0–1.5)
Hatta *et al.*, 2013 [111]	Prospective observational study	Thirty-three general hospitals, where at least one psychiatrist worked full time	Patients who developed delirium during hospital admission and received antipsychotics for delirium (N= 2,453 of which 30% had dementia)	Serious adverse events including aspiration pneumonia	All APs prescribed	Aspiration pneumonia, n (%): -with all APs 17 (0.7) -with risperidone 7 (0.8) -with quetiapine 4 (0.5) -with perospirone 0 (0) -with olanzapine 2 (2.3) -with aripiprazole 0 (0) -with haloperidol 3 (0.6) -with 'other' antipsychotics 1 (0.8)

Table 4: Observational studies investigating the risk of other adverse events associated with antipsychotic use in dementia or in elderly persons. AAPs: atypical antipsychotics; Adj.: adjusted; APs: antipsychotics; CAPs: conventional antipsychotics; DVT: deep vein thrombosis; ICD: international classification of diseases IRR: incidence rate ratio; OR: odds ratio; RR: risk ratio.

Hip or femur fracture						
Author, year	**Study design**	**Setting**	**Population**	**Outcome**	**Exposure**	**Main findings**
Liperoti *et al.*, 2007 [112]	Case-control studies	Systematic Assessment of Geriatric drug use via Epidemiology (SAGE) database	Nursing home residents in 6 U.S. states	Hospitalization for hip fracture; Hospitalization for hip fracture ICD9 820-821	CAPs as a class, haloperidol, other conventional agents; AAPs as a class, risperidone, olanzapine, other atypical agents (non-use as comparator)	OR hospitalization for hip fracture: - CAP: 1.35 (1.06-1.71) -haloperidol: 1.53 (1.18-2.26) hospitalization for hip fracture ICD9 820-821: -AAP: 1.37 (1.11-1.69) -risperidone:1.42 (1.12-1.80) -olanzapine: 1.34 (0.87-2.07)
Kolanowski *et al.*, 2006 [123]	Case-control studies	Health claims database	Health care insured dementia patients aged>70 (N=959)	Diagnosis of hip fracture	AAPs or CAPs (non-use as comparator)	OR -AAP: 1.47 (0.82-2.65) -CAP: 2.33 (1.08-5.03)
Pouwels *et al.*, 2009 [113]	Case-control studies	All patients, PHARMO Database (Netherlands) (age>18) Dutch PHARMO	Patients >18 with a hip/femur fracture during the study period (N=6,763	Hospitalization for hip fracture	AAPs and CAPs (non-use as comparator)	Adjusted OR -CAPs: 1.76 (1.48, 2.08) -pipamperone: 1.54 (1.15-2.06) -haloperidol:

		Record Linkage System	cases; N=26,341 controls)			2.33 (1.72-3.18) -zuclopenthixol: 2.44 (1.59-3.75) -thioridazine: 1.51 (0.60-3.78) -levomepomazine: 0.80 (0.35-1.82) -others: 1.19 (0.79-1.78) -AAPs: 0.83 (0.42-1.65) -risperidone: 0.84 (0.38-1.88) -quetiapine, olanzapine, clozapine: 0.83 (0.23-3.02)
Jalbert *et al*., 2010 [124]	Case-control studies	NHs in California, Florida, Illinois, New York, and Ohio	Long stay Medicaid-eligible residents age >65 living in nursing homes with at least 20 beds (N= 764 cases; N=3,582)	Hospitalization for hip fracture ICD-9 820 Hospitalization for hip fracture	AAPs and CAPs (non-use as comparator)	Adj. OR -new use of AAP: 1.36 (0.95-1.94) -prevalent use of AAP: 1.33 (1.08-1.63) -prevalent use of CAP: 1.28 (0.7-2.34)
Pratt *et al*., 2011 [125]	Self-controlled case series studies	Australian Government Department of Veterans'	Veterans/spouses aged ≥65 hospitalised for hip fracture	Hospitalization for hip fracture ICD-10 S720, S721	CAPs (non-use as comparator)	IRR -1 week: 1.04 (0.40-2.70) -2-8 weeks: 2.2

		Affairs Health Care Claims Database	(N=8,285)			(1.65-3.02) -9-12 weeks: 1.79 (1.12-2.84) ->12 weeks: 2.19 (1.62-2.95)
Wang *et al*., 2001 [126]	Case-control study	Medicare, New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled administrative database	Patients ≥65 (N=1,222 cases: N= 4,888 controls)	Hospitalization for hip fracture ICD-10 S720, S721 (non-hip fracture patients as comparators)	Any AP use	Adj. OR for any AP use: 1.60 (p-value: 0.0001)
Deep vein thrombosis						
Schmedt and Garbe, 2013 [101]	Nested case-control study	German Pharmacoepidemiological Research Database	Dementia patients >65	Hospitalization with a main discharge diagnosis for DVT (ICD-10 GM codes I80.1, I80.2, I80.3) or pulmonary embolism (PE) (ICD-10 CM code I26.x).	CAPs and AAPs (non-use as comparator)	Adj. OR -current AP use 1.23 (1.01-1.50) -prevalent AP use: 1.09 (0.87-1.36) -new AP use: 1.63 (1.10-2.40) -past user: 0.75 (0.53-1.05) -AAPs: 0.89 (0.64-1.24) CAPs: 0.94 (0.74-1.20) All APs as a group: 1.62 (1.15-2.27)

Hyperglycemia						
Lipscombe *et al.*, 2009 [106]	Nested case-control study	Four administrative databases in Ontario: Ontario Drug Benefit database, National Ambulatory Care Reporting System database, Canadian Institute for Health Information Discharge Abstract Database, Ontario Health Insurance Plan	Diabetic patients ≥66 (N=13 817)	Occurrence of hyperglycemia		Adj. RR for patients treated with insulin: -any current AP: 1.40 (1.06-1.85) -incident AP use: 15.4 (8.12-29.2) -prevalent AP use: 1.36 (1.03-1.79) -AAP use: 1.4 (1.06-1.85) -incident AAP use: 16 (8.26-31.1) -prevalent AAP use: 1.38 (1.04-1.82) -CAP use: 1.27 (0.75-2.12) -incident CAP use: 11.6 (4.75-28.3) -prevalent CAP use: 1.01 (0.52-1.98) Adj. RR for patients treated with oral hypoglycaemic agents: -any current AP use: 1.36 (1.12-1.66)

						-incident AP use: 14.4 (8.71-23.8) -prevalent AP use: 1.31(1.08-1.60) -AAP use: 1.37 (1.12-1.67) -incident AAP use: 15.4 (9.08-26.0) -prevalent AAP use: 1.35 (1.10-1.64) -CAP: 1.31 (0.90-1.90) -incident CAP use: 11.7 (5.81-23.4) -prevalent CAP use: 0.95 (0.58-1.57)

2.2. Antipsychotic use in elderly patients and the risk of pneumonia. Gambassi G[1], Sultana J[2], Trifirò G[2]. Expert Opin Drug Saf. 2015 Jan;14(1):1-6.

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Abstract

Antipsychotics are frequently and increasingly prescribed off-label for the treatment of behavioural and psychological symptoms associated with dementia despite their modest efficacy. Instead, the safety profile of antipsychotics has been questioned repeatedly in recent years with various concerns, including death. Meta-analyses of randomized controlled trials found that one of the major causes of death associated with atypical antipsychotics use was pneumonia. Only few observational studies, however, have investigated the risk of pneumoniain elderly patients, especially among those receiving conventional antipsychotics. The aim of this editorial is to synthesize the current evidence from observational studies regarding the risk of pneumonia in elderly patients receiving either conventional or atypical antipsychotics. The studies conducted so far document that the risk of pneumonia is 2 to 3 fold increased in a dose-dependent fashion with both classes compared to non-use, with a possibly higher risk attributable to atypical antipsychotics. The risk seems to peak at the beginning of treatment (e.g., 7-30 days), and dissipates over time for both conventional and atypical antipsychotics. The risk-benefit ratio suggests that there will be 1 excess hospitalization for pneumonia for every 2 to 5 patients receiving any clinical improvement in symptoms. Considering the modest improvement in terms of efficacy, the risks associated with antipsychotics in elderly patients may outweigh their benefit.

Antipsychotics are commonly prescribed in both community and nursing home setting. These drugs are traditionally classified as conventional or atypical agents. The two classes differ in terms of pharmacological profile: conventional antipsychotics (such as haloperidol) are D2-receptor antagonists while atypical antipsychotics (such as quetiapine, olanzapine and risperidone) are 5HT-receptor antagonists although they may also bind to other receptor types.

In the United Kingdom psychiatric drugs made up nearly 9% of all prescriptions in 2010, with olanzapine, quetiapine and risperidone accounting for 24%, 23% and 17% of all prescriptions, respectively [1]. Antipsychotics are primarily indicated in the treatment of schizophrenia and in the manic phases of bipolar disorder. However, these drugs are also frequently used off-label. In particular, in the last years there is an increasing use of antipsychotics worldwide for the treatment of behavioural and psychological symptoms of dementia (BPSD). Only risperidone is approved for the treatment of aggression, one of the several symptoms of BPSD.

The safety of antipsychotics when used in elderly people with dementia has been seriously questioned. The Food and Drug Administration (FDA) issued a warning in April 2005 about an almost two-fold increased risk of all-cause mortality when antipsychotics were used to control BPSD, with pneumonia being one of the leading causes of death [2]. The FDA later extended such warning to conventional antipsychotics, inferring that the risk of pneumonia may be similarly increased by conventional agents [3].

After the initial warning, several observational studies have investigated the association between antipsychotics use in elderly patients and pneumonia (**Table 1**).In the Netherlands, Knol et al. assessed the risk of pneumonia leading to hospitalization using a record-linkage administrative database[4], while Trifirò et al. investigated fatal and non-fatal pneumonia using a nationwide general practice database [5]. Interestingly, both studies found an increased risk of pneumonia with antipsychotic use, although twice as high with atypical as compared to conventional antipsychotic agents. The higher risk of pneumonia associated with atypical antipsychotics has been confirmed by Huybrechts et al. in North America[6, 7]. Similarly, a differential risk of pneumonia associated with antipsychotic class was also observed by Barnett et al. using a retrospective cohort study design [8].Others studies found no differential risk or provided insufficient information [9, 10].

While these and other findings indicate an increased risk of pneumonia with antipsychotics, observational studies are liable to confounding by indication because dementia patients have a higher baseline risk of aspiration pneumonia [11]. In addition, frail elderly persons may experience delirium as a prodromal symptom of pneumonia and, as a consequence, receive antipsychotic treatment. This increases the risk of protopathic bias in observational studies, i.e. wrong attribution of the onset of pneumonia to antipsychotic administration [4]. Nevertheless, Trifirò et al.[5] and Huybrechts et al. [7] observed that the risk of pneumonia appears to be dose-dependent, strengthening the hypothesis that antipsychotics are involved in the causality pathway.

As regards the temporal pattern of pneumonia associated with antipsychotics, current findings suggest that the risk peaks initially and decreases over time. Wang et al. [12] reported that the risk is higher within 30 days of antipsychotic initiation, [HR 1.11 (95%CI: 0.76–1.63)], decreases after 60 days [HR1.03 (95%CI: 0.76–1.38)] and it is not further evident after 120 days of continuous treatment [HR0.84 (95%CI: 0.66–1.05)]. However these findings were not statistically significant. Most specifically, Trifirò et al. [5] documented that the risk of pneumonia in elderly patients treated with antipsychotics appears to be higher during the very first week of treatment[OR 4.62 (95% CI: 2.05-10.38)] and decreases thereafter. Similarly reduced risk with continuous treatment was found in a self-case controlled series by Pratt et al. [13], but only for atypical antipsychotics.

The evaluation of antipsychotic-associated risk of pneumonia by class is limited by the heterogeneity of individual antipsychotics. Based on the different receptor-binding profile of antipsychotic drugs, it has been hypothesized that the risk of pneumonia might differ by individual agent[13]. However, there are only few studies investigating the risk of pneumonia with individual antipsychotic agents. A nested case-control study in 2,560 elderly patients observed that the risk of pneumonia was highest for risperidone [OR 3.51 (95% CI: 1.94–6.36)], followed by haloperidol [OR 1.95 (95% CI: 1.20–3.17)][5]. A similar study using risperidone as a comparator, however, found no statistically significant differences in the risk of pneumonia for ziprasidone [HR1.45 (95% CI:0.62-3.38)], olanzapine [HR1.20 (95% CI:0.94-1.53)], quetiapine [HR1.20 (95% CI:0.94-1.53)] and aripiprazole [HR0.64 (95% CI:0.23-1.78)][7].

More evidence is needed to confirm that the risk of antipsychotic-associated pneumonia varies with individual antipsychotics.

The biological pathways underlying antipsychotic-induced pneumonia are not currently known although plausible hypotheses exist. Antipsychotics may lead to aspiration pneumonia in elderly patients through extrapyramidal adverse events, dysphagia or sedation, as a result of modulation of dopaminergic, muscarinic, and H1-histaminergic receptor systems, respectively[5]. It should be noted, however, that in most of the observational studies there were insufficient information about the severity of the underlying condition and inconsistent data regarding co-morbidities. [14] Nonetheless, the use of antipsychotics has been linked to an increased risk of pneumonia also in large nationwide cohorts of much younger patients affected by schizophrenia, and by bipolar disorder with a substantially lower burden of comorbid conditions [15, 16]. In these patients, lithium and other mood stabilizers are not associated with the risk of pneumonia. Receptor affinities for histaminergic and muscarinic are considered the most plausible explanation for the association seen with antipsychotics in such cohorts. To further support this biological mechanism, it is a consistent finding that the concomitant use of more than one antipsychotic drug is far more dangerous.

Expert opinion

The studies conducted so far suggest an association between antipsychotic drug use in elderly persons and pneumonia. Three studies demonstrated that the risk of pneumonia varies by antipsychotic class, with a higher risk being attributed to atypical antipsychotics [4, 6-9]. A more recent finding is the demonstration of a differential risk associated with individual antipsychotic drugs [5, 7]. Further studies are needed to confirm whether there are differences in risk of pneumonia associated with individual antipsychotics and to identify possible risk factors of antipsychotic-induced pneumonia, particularly in frail elderly with dementia. The role of severity of dementia as a risk factor was generally not considered in any of the studies.

As pneumonia associated with antipsychotic in elderly patients is more likely to occur at higher dosage, it is important to start the therapy with the lowest dosage possible, followed by careful dose titration.

In addition, the evidence about the temporal relation between the initiation of an antipsychotic and the onset of pneumonia suggests that a more intense patient monitoring is needed immediately after initiation and during the early phases of antipsychotic treatment, particularly among nursing home residents.

It is currently not known which clinical risk factors predispose elderly patients prescribed antipsychotics to develop pneumonia. This lack limits clinicians in their ability to identify elderly persons for whom the risks of antipsychotic treatment exceed the benefit.

Future research should provide more detail on individual antipsychotics, the lowest-risk dose and the role of severity of dementia and other possible risk factors in the antipsychotic-pneumonia association. To conclude, the risk of pneumonia associated with antipsychotics has been quantified by several studies and these have provided valuable information. Any antipsychotic use is associated with an increased risk of pneumonia compared to non-use but atypical antipsychotics were often found to be associated with a higher risk of pneumonia compared to conventional agents. Considering the modest improvement in terms of efficacy, the risks associated with antipsychotics in elderly patients may outweigh their benefit.

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Table 1: Observational studies investigating pneumonia as an outcome following antipsychotic exposure in elderly persons.

Author, year	Study design	Setting - Population	Outcome	Exposure	Main risk estimates
Trifirò et al., 2010 [5]	Nested case-control	Dutch general practice database – older people (≥ 65) newly treated with AP (N=258)	Fatal and non-fatal community-acquired pneumonia	AAP or CAP (past use of any AP as comparator)	Adj. OR Fatal/nonfatal pneumonia: - AAPs: 2.61 (1.5–4.6) -CAPs: 1.8 (1.2–2.5) Fatal pneumonia: - AAPs: 6.0 (1.5–24.0) -CAPs: 1.7 (0.8-3.9)
Knol et al., 2008 [4]	Nested case-control	Dutch PHARMO database - Patients (≥ 65) newly treated with antipsychotics (N= 22,944; n= 543 cases)	Hospital admission due to pneumonia	AAP or CAP (non-use as comparator)	Adj. OR -current use of AAP: 3.1 (1.9–5.1) -current use of CAPs: 1.5 (1.2–1.9)
Gau et al., 2010 [9]	Case-control study	Rural community hospital in Ohio (USA) - Patients aged 65 years or older (N=194)	Hospital admission due to community-acquired pneumonia	AAP (non-use as comparator)	Adj. OR -AAP: 2.26 (1.23–4.15)
Star et al., 2010 [17]	Self-controlled cohort	UK IMS Health Disease Analyzer database - Adults aged 65 years or older (number of patients not provided)	Acute chest infections, bronchopneumonia, hypostatic pneumonia	Distribution over time of AAPs and CAPs with respect to date of diagnosis of the study outcomes	In elderly patients (≥ 65): -higher rate of acute chest infections following AAPs and much less CAPs -higher rate of bronchopneumonia following either AAP or CAP prescriptions.
Pratt et al., 2011[13]	Self-controlled case series	Australian Government Department of Veterans' Affairs Health Care Claims Database - Elderly patients≥65 years (N=13,324 patients hospitalised for	Hospitalisation rates for hip fracture and pneumonia	AAPs or CAPs (non-use as comparator)	Adj. IRR -CAPs at 1 week: 1.51 (1.07-2.14) -CAPS at 2-8 weeks: 1.62 (1.37-1.92) -CAPS at 9-12

		pneumonia)			weeks:1.69 (1.32-2.16) -CAPS at over 12 weeks: 1.63 (1.36-1.96) AAPs at 1 week: 1.73 (1.31-2.29) AAPs at 2-8 weeks: 1.70 (1.48-1.95) AAPs at 9-12 weeks: 1.67 (1.37-2.04) AAPs at over 12 weeks: 1.70 (1.51-1.93)
Huybrechts et al., 2012 [7]	Retrospective cohort study	Medicaid, Medicare, Minimum Data Set and Online Survey Certification and Reporting data for patients from nursing homes in 45 US states - Medicaid eligible residents ≥65 who initiated antipsychotic treatment in nursing homes (N=83,959)	Hospitalization for myocardial infarction, cerebrovascular events, serious bacterial infections (including pneumonia), and hip fracture within 180 days of antipsychotic initiation.	AAPs (AAPs as comparator when comparing classes; risperidone as comparator when comparing individual APs)	Propensity-adj. HR -CAPs: 0.81 (0.65-1.01) -aripiprazole: 0.99 (0.72-1.35) -olanzapine: 0.94 (0.84-1.05) -quetiapine: 0.91 (0.80-1.03)
Huybrechts et al. 2011[6]	Retrospective cohort study	Administrative data from the British Columbia Ministry of Health - Elderly persons ≥65 newly admitted to a nursing home(N=10,900)	All non-cancer deaths, including pneumonia	AAPs, CAPs (AAPs as comparator when comparing AP classes), benzodiazepines and antidepressants	Propensity-adj. RR: -CAPs: 0.94 (0.56–1.58)
Wang et al., 2007 [12]	Retrospective cohort study	The Pharmaceutical Assistance Contract for the Elderly Information from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) and Pennsylvania Medicare - Patients ≥65 with at least one prescription for an	Acute myocardial infarction; ventricular arrhythmia; cerebrovascular events; congestive heart failure; pneumonia; other serious bacterial infections	CAPs (AAPs as comparator)	-Adj. HR in 30 days: 1.11 (0.76–1.63) -Adj. HR in 60 days: 1.03 (0.76–1.38) -Adj. HR in 120 days: 0.84 (0.66–1.05)

		antipsychotic (N= 22,890)			
Barnett et al., 2006 [8]	Retrospective cohort study	US Veterans Administration database - Patients hospitalized due to pneumonia (N= 16,931)	In-hospital mortality	AAP or CAP (no use of neuropsychiatric drugs as comparator)	Adj. OR -CAP: 1.5 (1.0–2.2) -AAPs: 1.2 (1.0–1.5)
Aparasu et al., 2013 [10]	Retrospective cohort study	Dual eligible (Medicare Medicaid) nursing home patients new antipsychotic users in 4 US states (N= 49,904)	Hospital claim for pneumonia within 6 months of treatment	CAPs (AAPs as comparator)	Adj. HR 1.24 (0.94-1.64) Adj. HR <50 days: 1.17 (0.83-1.66) Adj. HR 50-180 days: 1.36 (0.87-2.14)
Hatta et al., 2013 [19]	Prospective observational study	Thirty-three general hospitals, where at least one psychiatrist worked full time - Patients who developed delirium during hospital admission and received antipsychotics for delirium (N= 2,453 of which 30% had dementia)	Serious adverse events including aspiration pneumonia as secondary outcome	All APs prescribed	Aspiration pneumonia, n (%): -with all APs 17 (0.7) -with risperidone 7 (0.8) -with quetiapine 4 (0.5) -with risperidone 0 (0) -with olanzapine 2 (2.3) -with aripiprazole 0 (0) -with haloperidol 3 (0.6) -with 'other' antipsychotics 1 (0.8)

Abbreviations- AAPs: atypical antipsychotics; Adj.: adjusted; APs: antipsychotics; CAPs: conventional antipsychotics; IRR: incidence rate ratio; OR: odds ratio; RR: risk ratio. Risk estimates are reported with 95% confidence intervals.

3. Drug utilisation studies

The two papers presented in this chapter address the need to understand antipsychotic prescribing trends in elderly persons with dementia in the United Kingdom, Italy and the Netherlands. The first paper describes a study carried out using THIN (UK) and HSD (Italy) while the second paper describes a study carried out using IPCI (the Netherlands).

3.1. The Effect of Safety Warnings on Antipsychotic Drug Prescribing in Elderly Persons with Dementia in the United Kingdom and Italy: A Population-Based Study. Janet Sultana[a,g], Andrea Fontana[b], Francesco Giorganni[a], Alessandro Pasqua[c], Claudio Cricelli[c], Edoardo Spina[a], Giovanni Gambassi[d], Jelena Ivanovic[e], Carmen Ferrajolo[f,g], Mariam Molokhia[h], Clive Ballard[i], Samantha Sharp[i], Miriam Sturkenboom[g], Gianluca Trifirò* [a,g,j] CNS Drugs. 2016 Nov;30(11):1097-1109.

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Abstract

Background: Antipsychotic (AP) drugs are commonly used to manage behavioural symptoms of dementia. Nevertheless, international (European Medicines Agency - Europe) and national (Medicines and Healthcare products Regulatory Agency – UK and the Italian Drug Agency) regulatory agencies issued safety warnings against antipsychotic (AP) use in dementia in 2004 and 2009.

Objective: The aim of this study is to investigate short- and long-term impact of safety warnings on AP use in UK and Italian persons with dementia using two nationwide databases, The Health Improvement Network (THIN) from the UK and Health Search Database-Cegedim-Strategic Data-Longitudinal Patient Database (HSD-CSD-LPD) from Italy.

Methods: The quarterly prevalence of AP use was calculated overall, by class and by individual drug in persons with dementia aged ≥65 years. Generalized linear models were used to explore the effect of the safety warnings.

Results: Over the period 2000-2012, 58,497 and 10,857 persons ≥65 years with dementia were identified from the THIN and HSD-CSD-LPD databases. After the 2004 warnings, atypical AP use decreased while conventional AP use increased in Italy and the UK until 2009; however, the trend for APs individually showed that risperidone/olanzapine use decreased while quetiapine increased in both countries. After the 2009 warnings (until 2012), atypical and conventional AP use decreased in the UK (11% to 9%, and 5% to 3%, respectively), but such use increased in Italy (11% to 18% and 9 to 14%, respectively).

Conclusion: The 2004 warnings led to a reduction in olanzapine and risperidone use and increased quetiapine/conventional AP use in both countries. From 2009, AP use fell in UK but not Italian persons with dementia. Possible reasons for the difference in AP use between the two countries include a more proactive approach towards reducing AP use in the UK compared to Italy.

Key points

- This study is the first to present the short- and long-term effects of the safety warnings on the use of antipsychotic (AP) drugs in dementia in the UK and in Italy in a general practice setting on a national level.
- The safety warnings combined with proactive national initiatives in the UK may have contributed to the significant reduction in AP use since 2009. Equally, the less proactive approaches to reduce AP prescribing in Italy may be one reason why AP prescribing did not decrease in this country.

1. Introduction

Over 90% of people with dementia experience behavioural and psychological symptoms of dementia (BPSD), including aggression, confusion and hallucinations [1], for which antipsychotics s (APs) are commonly prescribed, usually off-label [2]. Eighteen placebo-controlled randomized clinical trials (RCTs) have shown significant but modest improvement of aggression (Standardized Effect Size: 0.22) and smaller but significant benefits in psychosis (Standardized Effect Size 0.18) over 6-12 weeks of treatment with risperidone and olanzapine in persons with BPSD in a systematic review by Ballard et al. [3]. In contrast, quetiapine appears ineffective according to the same systematic review as well as a meta-analysis [3-4]. In Europe, risperidone is the only AP indicated for the treatment of BPSD [for short-term (≤6 weeks) management of severe aggression in dementia, if unresponsive to other treatments] [5]. Severe AP-related adverse effects in persons with dementia include pneumonia, stroke and all-cause mortality [6-8].

Following a pooled analysis of RCTs in 2004, the European Medicines Agency (EMA) reported an almost 2-fold increased risk of all cause-mortality and 3-fold increase in cerebrovascular events in persons with dementia treated with risperidone and olanzapine [9]. Thereafter, a series of safety warnings about AP use in dementia were launched by international/national agencies (**Table 1**). While the initial warnings pertained specifically to the atypical APs risperidone and olanzapine, in 2009 the regulatory safety warnings were extended to all APs. During this period there were also high-profile reports in England from the Alzheimer's Society and the All Party Parliamentary Group on Dementia targeting inappropriate AP prescribing [10]. An English Department of Health-commissioned review in 2009 indicated that unnecessary AP use was potentially leading to an additional 1,600 strokes and 1,800 deaths in older persons with dementia, annually [11]. Following the publication of this report, there was a proactive initiative in England with the government committing to reduce AP use in dementia by two-thirds by 2011. A ministerial working group was established and the reduction of AP prescribing became a key target of English dementia policy strategies [12]. The Dementia Action Alliance, formed between key stakeholders (government, professional bodies, and charities representing people with dementia) launched a call to action on inappropriate AP prescribing in June 2011. Toolkits were produced to support health/social care professionals in using alternative approaches [13].

Table 1: List of safety warnings issued by the UK and Italian health regulatory bodies and by the European Medicines Agency (for the European Union).

Drug agency	Communication date and type	Target drug	Safety concern	Target patient population	Advice/Directive
MHRA	Letter to all healthcare professionals in March 2004	Olanzapine and risperidone, but warning cautioned against the use of any antipsychotic	Stroke	Elderly persons with dementia	Olanzapine and risperidone should not be used to treat non-cognitive symptoms of dementia; treatment with these drugs should be short-term; the need for atypical antipsychotics should be reviewed in persons with dementia prescribed these drugs
MHRA	Communication published in Drug Safety Update (MHRA webpage) in March 2009	Risperidone, but warning cautioned against the use of any antipsychotic	All-cause mortality and stroke	Elderly persons with dementia	Prescribers should weigh the benefits of risperidone treatment in persons with dementia carefully, particularly persons with risk factors for stroke.
MHRA	Communication published in Drug Safety Update (MHRA webpage) in May 2012	All antipsychotics	All-cause mortality and stroke	Elderly persons with dementia	Prescribers should review the need for antipsychotic use in persons with dementia
AIFA	Pharmacovigilance initiative launch addressed mainly to prescribers working within centres specializing in the care of persons with dementia, published on the AIFA webpage, July 2005	All antipsychotics	No clear mention of a particular safety concern- prescribers were cautioned to limit the use of antipsychotics	Elderly patients with dementia, particularly patients with cerebrovascular risk factors	Physicians working at centres specializing in the care of persons with dementia should compile a pharmacovigilance data sheet if they prescribe any antipsychotic to a person with dementia; this information will be used to build a pharmacovigilance database. These physicians should review their patients every two months and are reminded that antipsychotic prescriptions should not last more than 60-90 days. These prescribers were also encouraged to report any antipsychotic-related adverse events.
AIFA	Translation of EMA 2008 warning on the increased risk of all-cause mortality with conventional antipsychotics addressed to all prescribers, published on the AIFA webpage, November 2008	Conventional antipsychotics but caution on use of any antipsychotic	All-cause mortality	Elderly patients with dementia	Physicians were advised that the increased risk of mortality with atypical antipsychotics does not justify a switch from atypical to conventional antipsychotic use in persons with dementia.
AIFA	Reminder of legal requirements regarding antipsychotic prescribing in dementia, published on the AIFA webpage, May 2009	All antipsychotics	No clear mention of a particular safety concern; prescribers were cautioned of potential grave harm to patients' health	Persons with dementia	Prescribers were reminded that the informed consent of persons with dementia or their legal representatives is required by law for the first antipsychotic prescription. This is waived for repeat prescriptions. Prescribers were also advised to use antipsychotics only when deemed strictly necessary in persons with dementia
AIFA	Confirmation of the validity of the previously-issued antipsychotic prescribing in dementia guidance, published on the AIFA webpage, July 2013	Atypical antipsychotics	No clear mention of a particular safety concern	Persons with dementia	AIFA confirmed that the previously instated antipsychotic prescribing guidance is still valid.
AIFA	Communication on antipsychotic prescribing in specialized dementia centres, published on the AIFA webpage, September 2013	All antipsychotics	No clear mention of a particular safety concern	Persons with dementia	This communication superseded the one issued in July 2013. It states that antipsychotic prescribing in dementia should be carried out through centres specializing in the care of persons with dementia.
EMA	Urgent modification to product information, March 2004	Olanzapine	All-cause mortality and cerebrovascular events	Elderly persons with dementia	Olanzapine summary of product characteristics were updated to include a risk of all-cause mortality and stroke with olanzapine use in dementia. It was highlighted that olanzapine is not approved to treat non-cognitive symptoms of dementia.
EMA	Modification of Summary of Product Characteristics and Package Leaflet for aripiprazole, olanzapine, paliperidone, and risperidone, September 2005	Atypical antipsychotics	All-cause mortality	All users of olanzapine with a particular warning on the use of this drug in elderly persons with dementia	Prescribers warned about increased risk of all-cause mortality with atypical antipsychotic use in dementia.
EMA	Warning on the increased risk of mortality with conventional antipsychotic use in persons with dementia, November 2008	Conventional antipsychotics but caution on use of atypical antipsychotics too	All-cause mortality	Elderly persons with dementia	Physicians were advised that the increased risk of mortality with atypical antipsychotics does not justify a switch from atypical to conventional antipsychotic use in persons with dementia.

Abbreviations: AIFA-*Agenzia Italiana del Farmaco*; MHRA: Medicines and Healthcare Products Regulatory Agency; EMA: European Medicines Agency

The UK Department of Health commissioned National Dementia and AP Prescribing (DAP) audit suggested a reduction in AP prescribing by half between 2008 and 2011 [14] but participation in the audit was voluntary, leading to potential biases. On the other hand, in 2005 the Italian Drug Agency launched an active pharmacovigilance initiative, targeted at Italian specialist dementia centers, but no assessment of AP prescribing trends was planned [15]. This activity involved completing a pharmacovigilance data sheet if APs were prescribed to a person with dementia. In Italy, the same warning in 2005 advised physicians to review their patients every two months and reminded them that the duration of AP use in persons with dementia should not exceed 90 days. Other AP-related initiatives in Italy were more advice-oriented rather than directly action-oriented compared to the UK initiatives while some had a technical-legal and/or a clinical nature. For example, the communication by AIFA in 2009 reminded prescribers that informed consent is required by law before the first AP is prescribed to a person with dementia. This warning also advised that APs should be used only where strictly needed in persons with dementia.

The effectiveness of risk minimization measures requires careful monitoring through observational studies [16]. The effect of safety warnings on AP prescribing has been investigated in several countries within [17-19] and outside Europe (**Appendix 1**) [20-21]. The two available Italian studies investigated only short-term effects of the warnings and one of those was limited to a restricted geographic area [22-23]. No nationwide studies have been conducted in the UK so far although a study by Guthrie et al. has described AP use after the Medicines and Health Products Regulatory Agency (MHRA) warnings in 2004 and 2009 using data from 87 Scottish general practices [24].

Given the lack of information on recent trends in AP utilisation in Italy and the UK, the aim of this population-based study was to investigate and compare the short and long-term effects of the safety warnings issued by international/national drug regulatory agencies on AP prescribing in older people with dementia in UK and Italy. Additionally, this study explored whether a 50% reduction in AP use in UK dementia people between 2008 and 2011, as documented by the DAP audit, was confirmed in a nationwide population.

2. Methods

2.1. Setting

Two nationwide, general practice databases were used for this retrospective population-based study: The Health Improvement Network (THIN, UK) and Health Search Database -Cegedim-Strategic Data-Longitudinal Patient Database (HSD-CSD-LPD, Italy). THIN currently contains anonymized clinical data for 11 million persons with 3.7 million active patients (covering approximately a 6.2% representative sample of UK population) registered with 562 general practices across the UK. Data in HSD-CSD-LPD are recorded by approximately 900 general practitioners (GPs) from all over Italy, covering a population of 1,166,076 persons (approximately a 2% representative sample of the Italian population). Both THIN and HSD-CSD-LPD contain data on patient demographics, diagnoses (coded using Read codes in THIN and International Classification of Diseases, 9th revision, clinical modification (ICD-9 CM) in HSD-CSD-LPD) and drugs prescribed (coded using British National Formulary (BNF)/Multilex codes in THIN and Anatomical Therapeutic Chemical (ATC) classification in HSD-CSD-LPD). Both databases have been used extensively for pharmacoepidemiological research [25-30].

2.2. Participants

Persons registered in both databases were considered eligible for inclusion if they were alive and had at least one year of database history. The study period ranged from January 1st 2000 to

December 31st, 2012 in HSD-CSD-LPD and May 31st, 2012 in THIN, based on last data drawn at the time the study was conducted. Person contribution to the cohort was censored at the end of the study period, transfer out of database or death, whichever came first. Eligible persons from both databases who were ≥65 years and had a diagnosis of dementia (**Appendix 2**) were identified.
Persons who were <65 years and those ≥65 years, irrespective of dementia diagnosis, were also identified in order to allow a broad comparison of crude prevalence of AP use in these two populations with respect to those ≥65 years with dementia. We also hypothesised that more marked change in drug utilisation among persons ≥65 years with dementia compared to the other two populations would suggest whether the safety warnings were specific to the former population.

2.3. Drug exposure

AP prescriptions were identified using specific Multilex/BNF codes in THIN (**Appendix 3**) and ATC codes (N05A*, except for lithium: N05AN*) in HSD-CSD-LPD. APs were grouped by therapeutic class: a) atypical APs (amisulpride, aripiprazole, asenapine, clozapine, olanzapine, paliperidone, quetiapine, risperidone, sertindole, zotepine); b) conventional APs (all other APs). Prescribing patterns for the most commonly prescribed APs (quetiapine, risperidone, olanzapine and haloperidol) were also analysed individually.

2.4. Statistical analysis

The effect of safety warnings on the prevalence of AP use was assessed using generalized linear models (GLMs) for longitudinal data, which account for the effect of multiple measures over time collected by the same individual (cluster-level covariate) using the logit formula (specifically, the link function) and assuming a binomial distribution with first-order autoregressive covariance structure as regards subject error term. GLMs were used to model the probability of receiving an AP and included the time covariate as the main exposure. To account for the hierarchical data structure, a generalized estimating equation was used to calculate the parameters of GLMs and provided model-based robust standard errors. By means of GLMs, two main evaluations were carried out: 1) whether the mean prevalence of AP use changes 3, 6 and 12 months before and after the warnings (i.e. to assess whether the onset of the warning effect was immediate and whether the effect persisted); 2) whether the prevalence of AP use changes over each unitary increase of a quarter year, performing a test for linear trends within each time interval between two consecutive safety warnings. For instance, using THIN data, four possible time intervals can be defined: 1) from the start of the study until the first quarter of 2004, when the first EMA/MHRA warning was issued; 2) between the first quarter of 2004 and the third quarter of 2005, when the second EMA warning was launched; 3) between the third quarter of 2005 and the first quarter of 2009, when the second MHRA warning was launched and 4) from the first quarter of 2009 until the end of the study.

To assess the change in mean prevalence of AP use before and after the warnings, separate GLMs (overall, within each AP drug class for the most commonly used APs) were built. These GLMs included an intercept term (this quantifies the logit of the estimated overall mean AP prevalence) and a categorical time variable where categories were ordered and defined according to the corresponding quarter year from the beginning to the end of the study (e.g. for THIN data, the time variable assumes value 0 for the first quarter of 2000, the value of 1 for the second quarter of 2000, and so on, until the end of the study). Comparisons between the estimated means of AP prevalence of use before and after each warning occurrence were statistically assessed using suitable comparisons (i.e. statistical contrasts), within the estimated GLMs, with respect to the quarter year at

which each warning occurs (i.e. setting null coefficients for time points that must be ignored and setting contrasting non-null coefficients, with opposite sign and sum of zero, for all time points involved in the comparison with respect the time point at which each warning occurs).

To evaluate whether the prevalence of AP user changes with every passing quarter year, separate GLMs were run which included the persons' presence in a specific time interval as a dummy covariate (e.g. three possible dummies if four time intervals are considered), the time covariate (i.e. the slope of the GLM, treated as continuous variable) and lastly, time-by-interval interaction terms. The person's presence in both databases was defined as the time between the person's registration in the database and their date of transfer out of the database, death or if none of these dates are registered, the end of the study. For each unitary increase of quarter year, the mean change in the log odds of AP use (i.e. log odds ratio) was estimated within each time interval between the warnings using the time-by-interval interaction terms. The presence of linear trends was identified by testing the statistical significance of the log odds ratios. Having included a continuous time covariate and the interaction terms, this model successfully mimicked a segmented regression analysis using longitudinal data, as different slopes were estimated with respect to each specific time interval, the start of which is marked by the launch of a warning.

Furthermore, to assess how much the expected prevalence of AP use changes in absolute terms within each defined time interval, the following approach was adopted: 1) the expected prevalence of AP use was derived from GLMs for each quarter year, using the inverse formula of the logit link function; 2) the absolute difference of expected prevalence between two consecutive quarters was calculated within each defined time interval; 3) the median (along with the 2.5 and 97.5 percentiles) of the distribution of all such differences, i.e. the slope representing the quarterly prevalence of AP use from the beginning to the end of one time interval, was estimated. This information complements that provided by the previously defined GLMs and may be more easily interpretable. As the corresponding 2.5 and 97.5 percentiles of the medians cannot formally represent a 95% confidence interval, their statistical significance was deduced from the corresponding log odds ratio. Plots of the observed and estimated quarterly prevalence of AP user over time were further reported.

Finally, to put the above findings in a broader context, the annual prevalence rate of AP use in the time interval between one warning and another was calculated by 1) summing all patients' follow-up time (this represents the denominator in terms of person-years); 2) estimating the expected number of AP users (i.e. the numerator) by summing each persons' AP exposure time and dividing this by the person's total follow-up time for the whole population; 3) dividing the numerator by the denominator.

2.4.1. Sub-analysis

Persons aged ≥80 were identified irrespectively of a dementia diagnosis for a *post-hoc* descriptive analysis in order to compare the prevalence of AP use between the oldest old in the Italian and UK populations. AP use is very likely to be related to dementia even in absence of a dementia diagnosis in this population. In addition these persons are likely to have more severe dementia than their younger counterparts triggering more AP prescribing. Given these two assumptions, we hypothesised that a comparison of the prevalence of AP use in persons $\geq$80 in the Italian and English databases could indicate whether there was a differential use of these drugs in the two

countries that could partly explain significant differences in drug utilisation pattern in the two countries.

A p value <0.05 was considered for statistical significance. All statistical analyses were performed using SAS Release 9.3 (SAS Institute, Cary, NC, USA).

2.5. Ethical approval

The use of THIN and HSD-CSD-LPD for this study was approved by the THIN Scientific Review Committee (ref: SRC 13-085) and the Ethical Committee of the University of Messina respectively.

3. Results

Overall, 58,497 and 10,857 persons with dementia ≥65 years were identified in THIN and HSD-CSD-LPD, respectively. The gender distribution and mean age in the two databases was similar (**Table 2**).

Table 2: Cohort characteristics of persons identified in THIN (UK) and HSD-CSD-LPD (Italy).

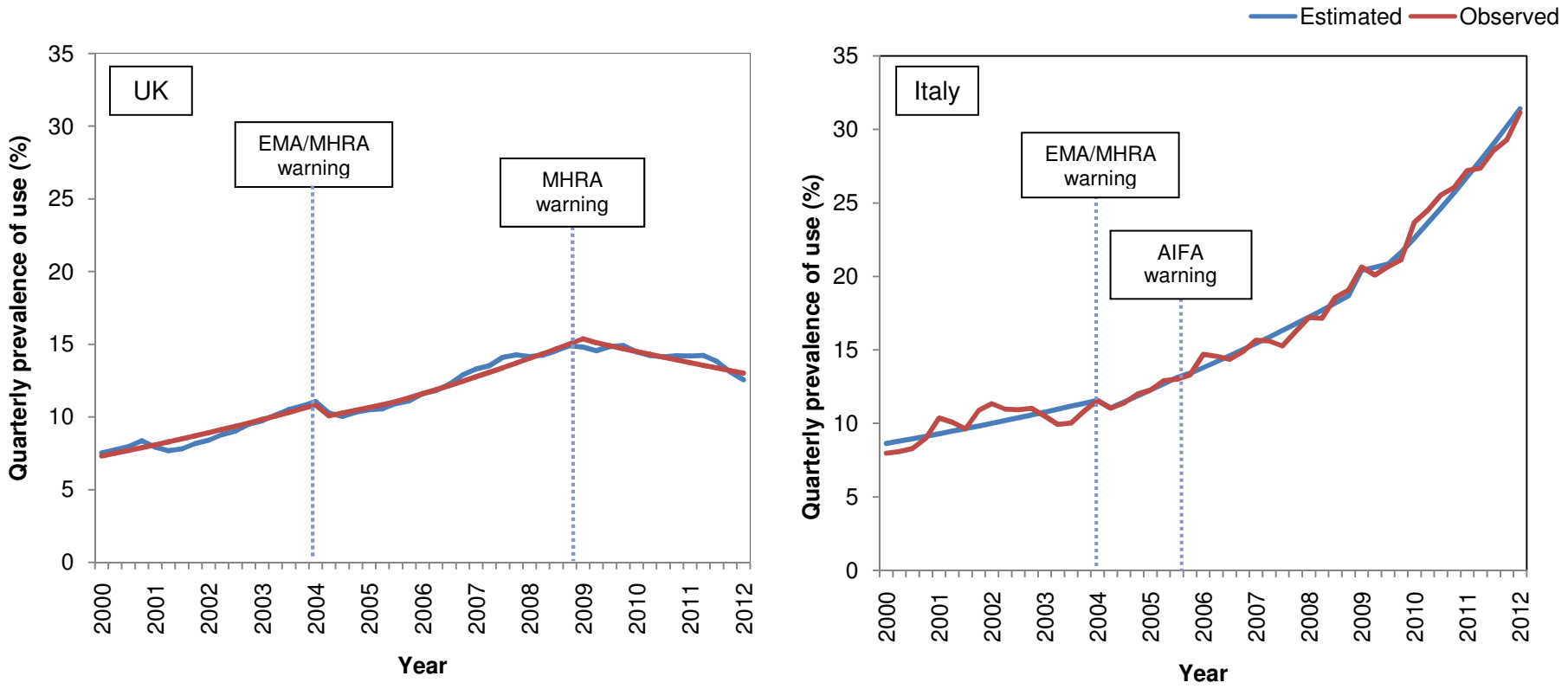
	THIN		HSD=CSD-LPD	
	N (%)	**Mean ± SD**	**N (%)**	**Mean ± SD**
All persons ≥ 65 with dementia	58,497	80.29 ± 7.56	10,857	77.84 ± 6.75
Female	40,963 (70.03)	-	7,433 (68.46)	-
Male	17,534 (29.97)	-	3,424 (31.54)	-

Abbreviations: HSD-CSD-LPD- Health Search Database -Cegedim-Strategic Data-Longitudinal Patient Database; SD- standard deviation; THIN- The Health Improvement Network

The crude quarterly prevalence of AP use in persons <65 years throughout the study period was approximately 0.6% in both countries (**Appendices 4 and 5**), increasing to approximately 2% in the general population ≥65 years in both countries (**Appendices 6 and 7**).

The quarterly prevalence of AP use in older people with dementia was initially similar in both countries: approximately 7% in 2000, followed by a comparable gradual increase up to around 10% in 2004 (**Figure 1**). The effect of the safety warnings on AP use in persons with dementia from 2004-2009 and 2009-2012 is described in more detail in the following sections.

Figure 1: Quarterly prevalence rates of any antipsychotic use in persons with dementia ≥65 years old in the UK (THIN) (left panel) and Italy (HSD-CSD-LPD) (right panel) from the first quarter of 2000 to the first quarter of 2012. Major warnings issued by international (EMA) and national (MHRA and AIFA) drug agencies are indicated.



Abbreviations: AIFA-*Agenzia Italiana del Farmaco*; MHRA- Medicines and Healthcare Products Regulatory Agency; EMA- European Medicines Agency

3.1. Effects of the safety warnings on AP use in older people with dementia from 2004-2009

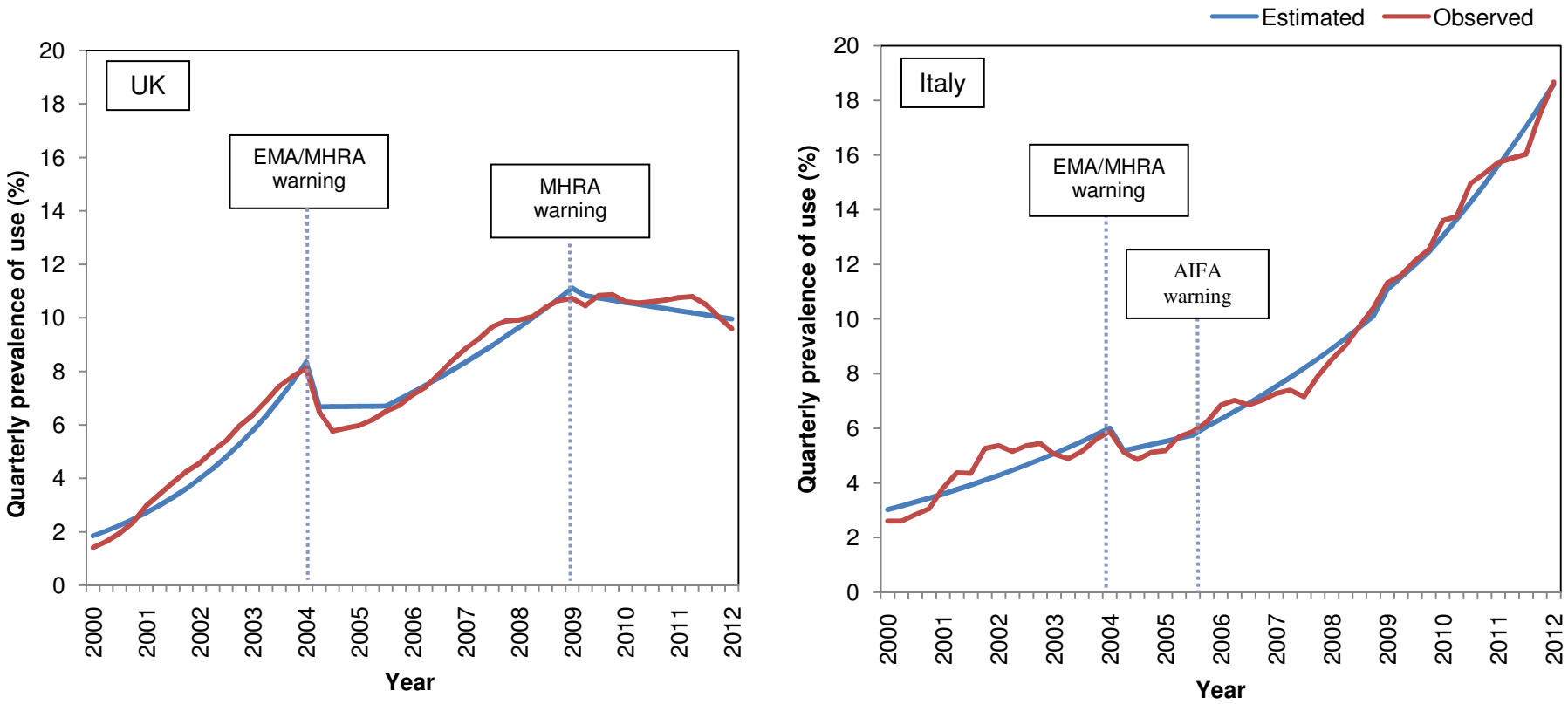
The 2004 warnings in the UK and Italy were associated with a marked short-term reduction of atypical AP use (**Figure 2**). In the UK, the quarterly prevalence of atypical AP use decreased rapidly from a pre-warning peak of 8% to 6% within less than one year following the warning; in Italy, there was a similar pattern with a decrease from 6% to 5% over the subsequent year. In contrast there was an increase in prescribing of conventional APs in both countries. The prevalence of conventional AP use in the UK increased from 3.5% to almost 4.5% within less than one year after the warning, while remaining stable thereafter (**Figure 3**).

In Italy, there was a more sustained increase in conventional AP use from 6% at the time of the warning to 10% in 2009. The overall prevalence of AP use returned to pre-warning levels by 2005 in Italy and by 2007 in the UK. AP use continued to increase in both countries until 2009, more markedly so in Italy (**Figure 1**).

Statistical comparisons

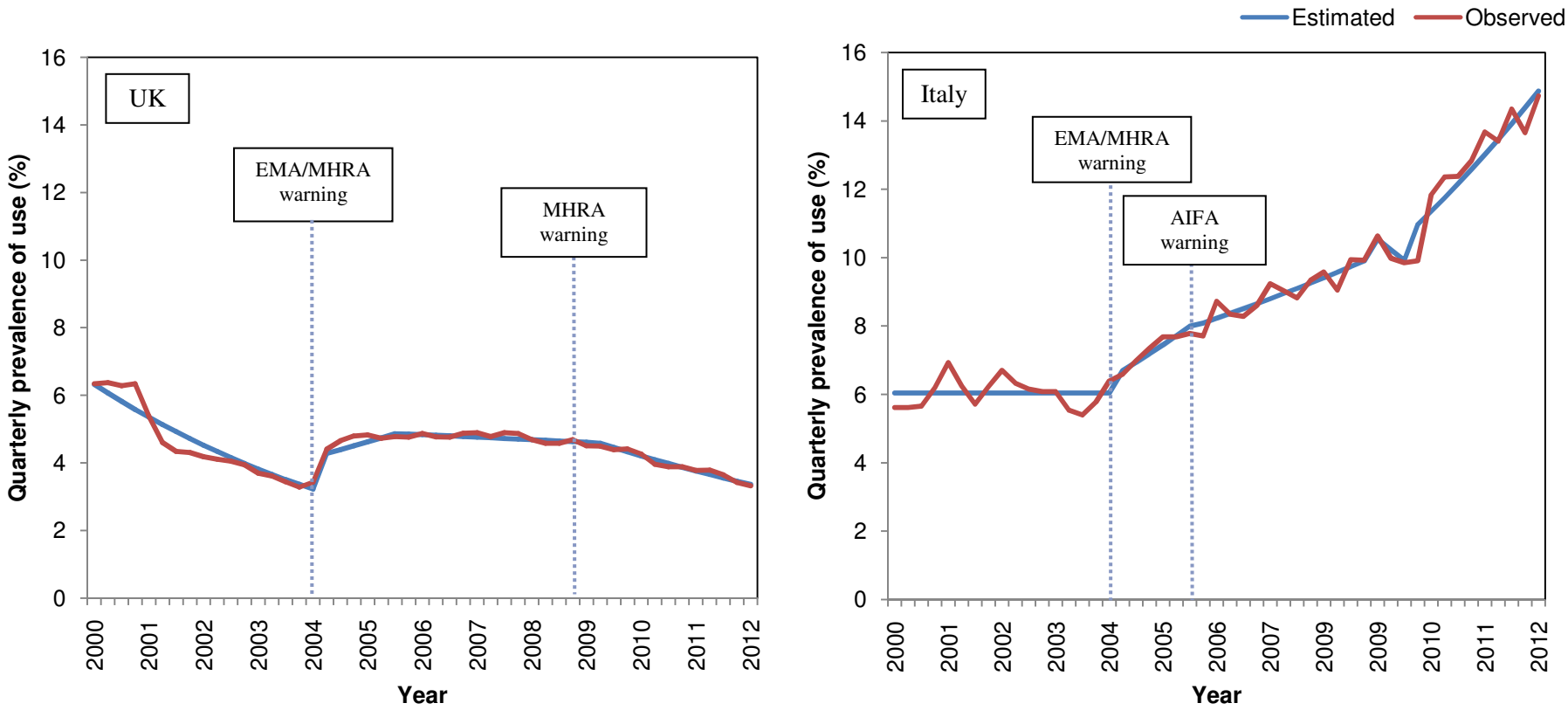
The statistical comparison of the prevalence of AP use at 3, 6 and 12 months before and after the warnings allowed the identification of the onset of the warning effect (i.e. a decrease in the prevalence of AP use) and whether this was statistically significant (**Tables 3 and 4**). At 3, 6 and 12 months after the warning in the UK, atypical AP use decreased from 7% to 6% (p-value <0.001), while conventional AP increased significantly from 3% to 4% (p-value <0.001). In Italy conventional AP use increased at 3, 6 and especially 12 months after the warning (from 5.7% to 7.2% at 12 months; p-value <0.001), while atypical AP use did not significantly decrease at any of the time-points evaluated.

Figure 2: Quarterly prevalence rates of atypical antipsychotic use in persons with dementia ≥65 years old in the UK (THIN) (left panel) and Italy (HSD-CSD-LPD) (right panel) from the first quarter of 2000 to the first quarter of 2012. Major warnings issued by international (EMA) and national (MHRA and AIFA) drug agencies are indicated.



Abbreviations: AIFA-*Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; HSD-CSD-LPD- Health Search Database -Cegedim-Strategic Data-Longitudinal Patient Database MHRA- Medicines and Healthcare Products Regulatory Agency; THIN- The Health Improvement Network

Figure 3: Quarterly prevalence rates of conventional antipsychotic use in persons with dementia ≥65 years old in the UK (THIN- left panel) and Italy (HSD-CSD-LPD- right panel) from the first quarter of 2000 to the first quarter of 2012. Major warnings issued by international (EMA) and national (MHRA and AIFA) drug agencies are indicated.



Abbreviations: AIFA-*Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; HSD-CSD-LPD- Health Search Database -Cegedim-Strategic Data-Longitudinal Patient Database MHRA- Medicines and Healthcare Products Regulatory Agency; THIN- The Health Improvement Network

3.2. Effects of the safety warnings on AP use in older people with dementia from 2009-2012

AP use among persons ≥65 years with dementia was approximately 5% higher in Italy compared the UK in 2009 (**Figure 1**). The 2009 MHRA warning, EMA recommendations and parallel report from the UK Department of Health had a different impact as compared to the 2004 warning in the UK. There was a smaller change over the year following the warning, but over a 4 year period atypical AP use in the UK dropped from approximately 11% to 9%. In contrast to the pattern observed after the 2004 warning, the AP use did not increase again after the 2009 MHRA warning. Conventional AP use also decreased from approximately 5% to 3% over the same period in the UK. In contrast, atypical AP use in Italy increased steadily from 11% in 2009 to 18% in 2012, while conventional AP use also increased from 9% in 2009 to 14% in 2012 (**Figures 2 and 3**).

Statistical comparisons

No significant changes in the prevalence of AP use overall or by class was seen within 6 months after the 2009 warning in the UK, although atypical and conventional use by class increased slightly within 1 year (p-value 0.0011 and 0.01 respectively) (**Table 3**).

AP use overall and atypical AP use increased slightly but significantly within 6 months after the warning in Italy. AP use overall also changed significantly 12 months after the warning when the prevalence increased from 19% to 22% (p-value <0.001) (**Table 4**), as a result of an increase of both conventional (from 10% to 11%) and atypical APs (from 10% to 13%).

3.3. Prescribing trend of individual APs in older people with dementia

In the UK and Italy, the prevalence of olanzapine use after the 2004 warnings decreased from approximately 2% to 1% (**Appendix 8**). After the 2009 warning, olanzapine use in the UK started decreasing modestly but kept increasing in Italy. The prevalence of risperidone use before the 2004 warning was higher in the UK (5%) than in Italy (2%), but both decreased to roughly 1% after the 2004 warnings (**Appendix 9**). The use of risperidone did not appear to change after the 2009 warnings either in the UK or Italy. The prevalence of quetiapine use in the UK increased from 1% to 7% after the 2004 warnings, while gradually decreasing after the 2009 warning (**Appendix 10**). In contrast, quetiapine use increased steadily from its marketing year (2000) up to 14% in 2012 in Italy. The prevalence of haloperidol use in the UK remained stable at approximately 1% from 2000 to 2004, increasing rapidly thereafter from 1% to almost 2%, decreasing back to 1% after the 2009 warning (**Appendix 11**), while in Italy haloperidol use increased continuously from 2000 (1.5%) to 2012 (6%). The GLM statistical comparisons of individual AP prevalence 3, 6 and 12 months after the warnings confirmed the above results (**Appendix 11 and 12**).

The analysis of estimated mean changes in the prevalence of AP use and annual prevalence of use after the warning occurrences confirmed all the above findings (**Appendix 13 to 16**).

3.4. Sub-analyses

The results of the sub-analysis comparing AP use in persons ≥80 showed a comparable use of APs in the UK and Italy. Conventional APs initially had a higher prevalence of use (3% and 2% in the UK and Italy respectively in 2000) while atypical AP use was much lower (<1% in both countries in 2000); thereafter the use of both classes remained between 1%-2% in the UK and Italy (**Appendix 17**).

Table 3: Prevalence of antipsychotics use in patients 65 and over with dementia in UK (THIN) at 3, 6 and 12 months before and after the warnings.

Antipsychotic	Time window before and after warnings	Warning occurrence	Prevalence of AP use before the warning (%)	Prevalence of AP use after the warning (%)	Comparison between the two prevalences (p-value)
Any AP	3 months	1st quarter 2004	10.7	10.3	0.042*
		1st quarter 20091	14.9	14.6	0.271
	6 months	1st quarter 2004	10.6	10.1	0.004*
		1st quarter 2009	14.7	14.7	0.912
	12 months	1st quarter 2004	10.3	10.3	0.999
		1st quarter 2009	14.5	14.7	0.131
Conventional APs	3 months	1st quarter 2004	3.3	4.4	<0.001*
		1st quarter 2009	4.7	4.5	0.303
	6 months	1st quarter 2004	3.4	4.5	<0.001*
		1st quarter 2009	4.6	4.4	0.146
	12 months	1st quarter 2004	3.5	4.7	<0.001*
		1st quarter 2009	4.6	4.4	0.009*
Atypical APs	3 months	1st quarter 2004	7.8	6.5	<0.001*
		1st quarter 2009	10.6	10.4	0.463
	6 months	1st quarter 2004	7.6	6.1	<0.001*
		1st quarter 2009	10.5	10.6	0.524
	12 months	1st quarter 2004	7.1	6.0	<0.001*
		1st quarter 2009	10.2	10.7	0.001*

*Statistically significant (p-value <0.05). **Abbreviation:** AP- antipsychotic; THIN- The Health Improvement Network

Table 4: Prevalence of antipsychotic use in patients 65 and over with dementia in Italy (HSD-CSD-LPD) at 3, 6 and 12 months before and after the warnings.

Antipsychotic	Time window before and after warnings	Warning occurrence	Prevalence of AP use before warning (%)	Prevalence of AP use after warning (%)	Comparison between the two prevalences (p-value)
Any antipsychotic	3 months	1st quarter 2004	10.8	11.0	0.707
		2nd quarter 2009	20.6	20.7	0.957
	6 months	1st quarter 2004	10.4	11.2	0.019
		2nd quarter 2009	19.8	20.9	0.033*
	12 months	1st quarter 2004	10.3	11.6	<0.001*
		2nd quarter 2009	18.8	22.5	<0.001*
Conventional APs	3 months	1st quarter 2004	5.8	6.6	0.024
		2nd quarter 2009	10.6	9.8	0.136
	6 months	1st quarter 2004	5.6	6.8	<0.001*
		2nd quarter 2009	10.3	9.9	0.283
	12 months	1st quarter 2004	5.7	7.1	<0.001*
		2nd quarter 2009	9.9	11.0	<0.001
Atypical APs	3 months	1st quarter 2004	5.6	5.1	0.174
		2nd quarter 2009	11.3	12.1	0.149
	6 months	1st quarter 2004	5.4	5.0	0.107
		2nd quarter 2009	10.9	12.3	0.002*
	12 months	1st quarter 2004	5.2	5.1	0.554
		2nd quarter 2009	10.1	13.0	<0.001*

*Statistically significant (p-value <0.05). **Abbreviation:** AP- antipsychotic; HSD-CSD-LPD- Health Search Database -Cegedim-Strategic Data-Longitudinal Patient Database.

4. Discussion

To our knowledge, this is the first population-based, nationwide study which explored short- and long-term effects of the safety warnings on AP use in dementia from two European countries, Italy and the UK. The comparative pattern of change of AP use in dementia in both countries provides key insights. The initial EMA/MHRA warning regarding stroke and mortality risk associated with risperidone and olanzapine led to a significant short-term reduction in atypical AP use over 12 months, but with increased conventional AP use. By 2005, AP use was again increasing in both the UK and more so in Italy. Although the safety warnings in 2009 had a limited immediate impact on AP prescribing, there was a sustained 25% reduction in AP use between 2010 and 2012 in the UK (from a quarterly prevalence of 14% to 11%), while a substantial increase in total AP use (to 32% in 2012) was observed in Italy. The prolonged reduction of AP use after the 2009 warning in the UK and the divergent pattern of AP use comparing the UK and Italy suggests that at a national level, the safety warning along with independent policy initiatives and proactive strategies of entities such the National Dementia Alliance may exert a greater influence on curbing AP use in dementia than the safety warnings launched by regulatory agencies alone.

The elevated use of APs in dementia remains a concern in both countries and cannot be explained by changes in the yearly prevalence of dementia in persons 65 and over (**Appendices 18 and 19**). Although present data support a significant reduction of AP use in people with dementia since 2009 in the UK, the observed reduction was 25% rather than the 50% presented in the DAP audit results [14], and the level of AP reduction achieved is still considerably less than the target of a two thirds reduction that was proposed in the Bannerjee report for the UK Department of Health [11]. Nevertheless, it is clear that the change in AP use the UK is much more favourable than that seen over the last decade in Italy, where 1 in 3 people with dementia were still prescribed APs in 2012. This increased pattern of use in Italy is also consistent with reports from other European countries (**Appendix 1**), emphasizing the need for coordinated action at a national level, if sustained reductions in AP use in people with dementia are to be achieved. The reason why the warnings in the UK appeared to be relatively more successful in reducing AP use in dementia can only be speculated but may be related to several factors such as the mode of dissemination, directness of appeal to appropriate healthcare professionals, clarity and action-oriented nature of the directive and the clarity with which the risk in question is communicated. For example, the 2004 warning by the MHRA was clearly action-oriented, recommending immediate review of patients because of “an important concern” on the increased risk of stroke, and was sent to all healthcare professionals as an “Urgent message” encouraging them to spread the word. In Italy on the other hand, the risk communication in 2004 was conveyed only through EMA and not by the national regulatory agency, AIFA. The first AIFA communication on the topic was issued a year later in 2005 but the warning of drug-related risk as well as information on the associated pharmacovigilance project appeared to target mainly prescribers in specialist dementia centres rather than all prescribers potentially responsible for the care of persons with dementia. Other warnings in Italy such as the 2009 AIFA communication was a reminder of the legal context of AP prescribing in dementia but did not highlight a concrete drug safety risk associated with these drugs leading to more cautious prescribing (e.g., increased risk of stroke) and was not action-oriented. Similarly, the 2009 MHRA warning was not action-oriented but was limited to advice on drug prescribing; in addition it was not actively disseminated but was published on the MHRA webpage. Nevertheless, the combined effect of this relatively passive regulatory action supplemented by other continued actions aiming to reduce AP use in dementia is likely to have led to a sustained reduction in AP use among dementia patients in the UK.

This study has several strengths. The databases used allowed us to sample a large number of primary care patients that can be considered representative of the two national populations. In

addition, both countries have a universal healthcare system which further increases the comparability of findings in the two countries. GLMs were used to estimate the prevalence of AP use accounting for clustered data (i.e. multiple measures over time per individual), an approach similar to the interrupted time-series analysis. GLMs have several advantages compared to time-series analysis. For example, time-series analysis is limited with regards to data fitting and requires the assumption of the stationary condition of the stochastic process, whereas this assumption is not required for GLMs. Interrupted time-series analysis may also be reliable in predicting future observations, provided that the model represents the stochastic process very well. However, GLMs can provide statistical evaluations based on robust statistical inference of comparisons between the prevalence of AP use in different time windows using statistical comparisons, whereas these evaluations are not possible using time-series analysis. The present study also has various strengths when compared to similar studies. Some published studies considered the effect of the safety warnings only on risperidone and olanzapine use [19], while others did not consider APs by class in their analysis [19,24]. In addition, other studies had a shorter observation period compared to the present study [19,22,23], did not use nationwide data [19,22] or did not consider haloperidol individually, the most commonly prescribed conventional AP [18,19,24].
A limitation of this study is that no information was available on AP dispensing in both countries [17, 18]. In Italy, the use of atypical APs may be partly under-estimated since prescription drugs may be made available directly from Italian National Health Service (NHS) hospitals, thus by-passing GPs. The AP prescribing patterns described in the present study mainly reflect GP prescribing to elderly persons living in the community setting rather than nursing homes. Nevertheless we were able to trace the living arrangements of 3,746 persons $\geq$65 years with dementia, of whom 3,554 were living in nursing home in THIN. No information on whether persons were living in a nursing home were found in HSD-CSD-LPD although given the structure of the Italian NHS it is likely that GP prescribing in nursing homes is similarly partially covered in HSD-CSD-LPD. Another limitation is that the diagnoses of dementia as found in THIN and HSD-CSD-LPD were not validated in the present study; nevertheless, the prevalence of dementia in THIN was found to be comparable with national estimates in the UK [31]. The validity of dementia diagnoses in both databases was not tested in the present study.

It should also be noted that in an observational study such as the present one, findings can point to an association but not a causal link between changes in AP prescribing pattern and the safety warnings. The influence of other factors on AP prescribing apart from the warnings, such as the DAP audit or initiatives by the National Dementia Alliance in the UK, may have influenced prescribing activities. In addition, comparisons between the warning effects should consider the different content and different dissemination methods used, however this cannot be taken into account in the statistical analysis used.

5. Conclusion

The initial warnings targeting olanzapine and risperidone use in older people with dementia generally reduced the prescribing of these drugs in the short-term, but resulted in a shift towards quetiapine and conventional AP use. Although the warnings led to a decrease in overall AP use in more recent years in the UK, this was more modest than stipulated by the DAP audit. Nevertheless, this reduction suggests that the pressure exerted in the UK to decrease AP prescribing in dementia achieved a substantial impact as compared to Italy, where AP prescribing continued increasing throughout the study.

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Appendices

Appendix 1: European studies carried out investigating the effect of drug safety warnings on antipsychotic use in older people.

Author, year	Setting	Population	Exposure	Outcomes	Findings
Galling et al., 2014	EGB database (France)	Elderly patients with and without dementia	All APs, APs by class and olanzapine and risperidone individually from 2003 to 2011	Monthly prevalence of AP use as a function of the 2004 and 2009 EMA warnings	-The monthly use of all APs decreased steadily from 2003-2011 from 16-11% and did not appear to be associated with the warnings. -Atypical APs decreased from 12% in 2003 to 5% in 2011 but the trend was already decreasing before the warning; after the 2009 warning this decrease stopped. -Conventional AP use increased from 3% in 2003 to 5% in 2011. Minimal changes in drug utilization were seen after both warnings. -Olanzapine use remained stable at 0.5% from 2003-2011; no change in trend was seen after the warnings. -Risperidone use increased from 2% in 2003 to 4% in 2011; use of this drug increased slightly after the 2004 warnings and decreased slightly after the 2009 warning.
Schulze et al., 2013	GEK database (Germany)	Elderly dementia patients	All APs and APs by class from 2004 to 2009	Change in yearly prevalence of AP use, number of AP packages and DDD per person per year as a function of the 2004 drug safety mails in Germany, the 2005 FDA safety warning on atypical AP use and the 2008 FDA/EMA warning on conventional AP use.	-The yearly prevalence of any AP use changed minimally after the 2004 warning (from 35% before to 34% the year after). Similarly small changes were seen after the 2005 warning, where the prevalence of use changed from 34% to 32% in the year after. No changes were seen after the 2008 warning, with the prevalence remaining stable at 32%. -The trend for conventional AP use was very similar to that of AP use overall, starting at 27% before to 26% after the 2004 warning, decreasing to 23% after the 2005 warning. The prevalence of use remained at 23 % before and after the 2008 warning. -The yearly prevalence of atypical AP use remained relatively constant at 17-18% over the observation period.
Guthrie et al., 2013	PCCIU database (Scotland)	Elderly dementia patients	All APs and risperidone, olanzapine, quetiapine individually from 2001–2011	Quarterly prevalence of oral AP prescribing, initiation and discontinuation; prescription of hypnotics, anxiolytics or antidepressants	-In 2001 15% of dementia patients were prescribed any oral AP, increasing to 23% just before the 2004 warning. Levels dropped back to 15% after the 2004 warning. The 2009 warning was associated with a reduction from 17% to 14% after the 2009 warning. -Risperidone use decreased from 12% before the 2004 warning to 4% shortly after. No decrease was seen after the 2009 warning. -Olanzapine use decreased from 3% before the 2004 warning to 1% shortly after. No change was seen after the 2009 warning. -Quetiapine use increased steadily after the 2004 warning, up to a peak of 8% just before the 2009 warning. There was a short-term decrease in quetiapine use after the 2009 warning which decreased back to pre-warning levels within 1 year.
Franchise et al., 2012	Lombardy Region Drug Administrative Database (Italy)	Elderly dementia patients treated with Aches	All APs, APs by class and olanzapine, quetiapine, haloperidol, clotiapine and risperidone	Number of AP prescriptions per person and gap between AP prescriptions as a function of the 2004 EMA warning and the 2006 AIFA warning;	-The yearly prevalence of AP use decreased from 23% before the 2004 warning to 17% a year after the 2004 warning. AP use decreased from 17% to 16% after the 2006 warning but levels rose back up to 17% 1 year later. -Atypical AP use decreased from 20% before the 2004 warning to 16% in the year after. Following the 2006 warning, atypical AP use decreased from 16% to 14% within a year but rose back to 15% the year later.

			individually from 2002 to 2008	yearly prevalence of AP use, probability of continuing antipsychotic treatment.	-Conventional AP use decreased slightly following the 2004 warning, from 4% to 3% over 2 years. Levels rose to almost 5% after the second warning in 2006. -Olanzapine use decreased from 5% to 3% within a year of the 2004 warning but no change was seen after the 2006 warning. -Risperidone use was very similar to olanzapine but levels decreased by approximately 1% after the 2006 warning. -Quetiapine use was already increasing before the 2004 warning and continued to do so after, albeit at a lower rate (from 9% before to 11% a year after). After the 2006 warning, there was a short-term decreased in use from 13% to 10% after a year, which rose to 12% a year later. -The use of haloperidol did not seem to change with the warnings, the prevalence of which remained below 2% from until 2007, increasing to 3% in 2008.
Trifiró et al, 2010	HSD-CSD LPD Italian nationwide database	General population, elderly persons and elderly persons with dementia	AP use by class, and by individual APs (haloperidol, promazine, quetiapine, chlorpromazine, risperidone, olanzapine, clotiapine and thioridazine) among elderly persons with dementia from 2000 to 2005.	One-year and monthly prevalence of AP use as a function of the 2004 MHRA warning and the 2005 FDA warning.	-The monthly prevalence of conventional AP use increased from 12% to 14% after the 2004 warning and did not appear to change after the 2005 warning. - The monthly prevalence of atypical AP use decreased from 8% to 6% after the 2004 warning but started increasing again after the 2004 warning.
Sanfelix-Gimeno et al., 2009	Valencia Health Agency pharmacy claims database (Spain)	Elderly patients and younger adults	Risperidone and olanzapine use (stratified by strength) from 2000 to 2006	Monthly prevalence of risperidone and olanzapine use in DDD as a function of three warnings issued by the Spanish drug agency: March and May 2004 (considered as one warning) and February 2005	-Low-strength risperidone use among pensioners decreased from 95,000 DDDs per month before the 2004 warnings to 90,000 after. This dropped to 65,000 DDDs after the 2005 warning. No change was seen for high-dose risperidone use among pensioners which increased throughout the study. -Low-strength olanzapine use among pensioners decreased from 15,000 DDDs before the 2004 warnings to 9,000 DDDs within a year. No change was seen after the 2005 warning. High-dose olanzapine use increased steadily throughout the study.

Abbreviations: AChеEI: acetylcholinesterase inhibitor; AIFA: *Agenzia Italiana del Farmaco* (Italian Drug Agency); EGB: *Echantillon Généraliste de Bénéficiaires*; EMA: European Medicines Agency; DDD: defined daily dose; FDA: Food and Drug Administration; GEK: *Gmünder Ersatz Kasse*, a German nationwide health insurance company database; HSD-CSD-LPD: Health Search Database - Cegedim Strategic Data, Longitudinal Patient Database; MHRA: Medicines and Healthcare Products Regulatory Agency; PCCIU: Primary Care Clinical Information Unit.

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Schulze J., van den Bussche H., Glaeske G., Kaduszkiewicz H., Wiese B., Hoffmann F., 2013. Impact of safety warnings on antipsychotic prescriptions in dementia: nothing has changed but the years and the substances. Eur. Neuropsychopharmacol. 23(9): 1034–42.

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Appendix 2: Dementia diagnoses in THIN (UK) and HSD (Italy).

Dementia Read codes	A410.00, A411.00, E00..00, E00..11, E00..12, E000.00, E001.00, E001000, E001100, E001200, E001300, E001z00, E002.00, E002000, E002100, E002z00, E003.00, E004.00, E004.11, E004000, E004100, E004200, E004300, E004z00, E012.00, E012.11, E012000, Eu00.00, Eu00000, Eu00011, Eu00012, Eu00013, Eu00100, Eu00111, Eu00112, Eu00113, Eu00200, Eu00z00, Eu00z11, Eu01000, Eu01200, Eu01300, Eu01y00,Eu01z00, Eu02000, Eu02100, Eu02400, Eu02z00, Eu02z11, Eu02z12, Eu02z13, Eu02z14, Eu02z15, Eu02z16, F110.00,F111.00, F116.00, F11x700, F21y200, F21y211, Fyu3000
ICD9-CM dementia codes	290, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.2, 290.21, 290.20, 290.3, 290.4, 290.40, 290.41, 290.42, 290.43, 290.8, 290.9, 294.1, 331.0, 331.1

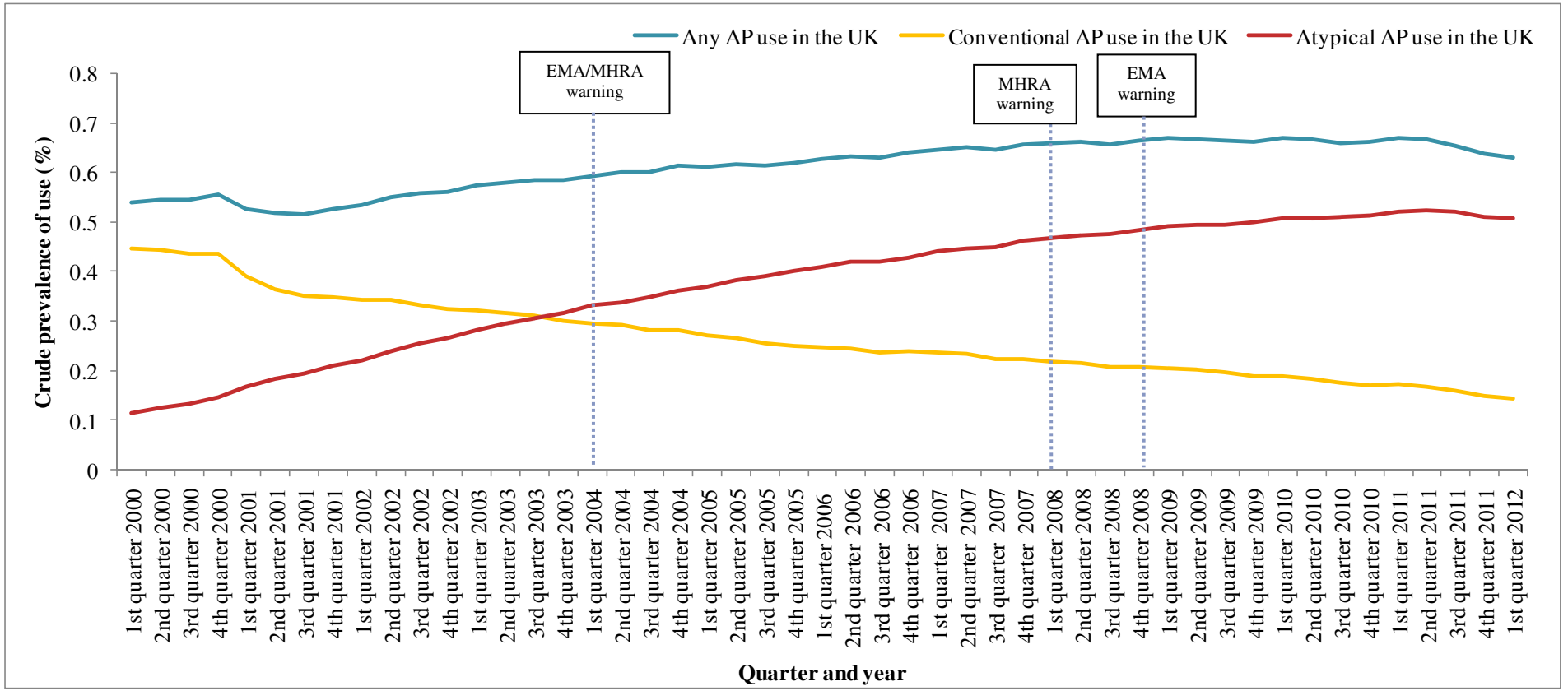
Abbreviations: ICD9-CM- international classification of diseases with clinical modification

Appendix 3: Multilex codes for antipsychotic drugs in THIN (UK). All antipsychotics have the BNF code '4020100'.

Drug name	Multilex Code
Amisulpride	91077998, 91425998, 88383997, 88383996, 88383998, 90209998, 86433998, 91083998, 94545990, 94845990, 88387997, 94544990, 94844990, 88387996, 88387998, 94846990
Aripiprazole	85834998, 87450998, 85833998, 87449998, 85832998, 87448998, 87089998, 83903998, 85835998, 85837998, 85836998, 87453998, 87452998, 87451998, 87090998
Benperidol	82225998, 88885998, 95979998, 95980998
Chlorpromazine	97871998, 82892998, 96689996, 97879998, 95200992, 97877998, 97880998, 97134992, 96689998, 97880997, 93242998, 97132992, 96689997, 97880996, 97129992, 96614992, 94111992, 94821992, 96102992, 94107992, 98186990, 96690998, 96691996, 99007990, 93587998, 93593998, 98062989, 95687990, 96690996, 98062990, 96690997, 96691997, 96919989, 97236988, 98192989, 96691998, 94761998, 95365990, 97236990, 98189990, 98192988, 94761997, 95364990, 96919990, 97236989, 98192990, 99010990
Chlorprothixene	96686997
Clozapine	87019998,87340998, 93596997, 82800998, 87020998, 87341998, 93596998, 82802998, 82799998, 93595997, 82801998, 93595998, 82803998
Dartalan (Thiopropazate)	94891992
Droperidol	97343998, 97343997, 93674998, 97334992, 93675998, 96303997, 96303998
Flupenthixol	98766998, 98766997, 99775998, 97516998, 99776998, 86421998, 86420998, 85613998, 96502997, 96502998, 86422998, 96502996, 85614998, 94879998, 86423998, 96503998
Fluphenazine	85300998, 96342992, 85295998, 98759998, 85294998, 85299998, 85298998, 99414998, 93032992, 96498997, 96498998, 85296998, 85303998, 85302998, 96286990, 96742990, 85297998, 85301998, 99408998, 96500998, 99411998, 99411997, 99411996, 97466992, 96501998, 96501997, 96501996
Fluspirilene	99189998, 96494998
Haldoperidol	95086992, 96265992, 97946997, 96307992, 97344997, 97346997, 97945998, 97345997, 96242998, 97945997, 96758992, 97944997, 96242997, 97346996, 97945996, 97568992, 97946998, 96244998, 97344998, 97346998, 97946996, 83786998, 97944998, 96245997, 96245998, 96246998, 93695997, 83787998, 93695998, 98155990, 96247997, 96248996, 98131989, 98625989, 92815996, 96247998, 98625990, 91921998, 92815998, 98080990, 96247996, 98625988, 92815997, 96115990, 96249997, 97135989, 98131990, 8360988, 98544990, 96248998, 96248997, 96249998, 97135990, 96249996, 96889990, 98154990, 98544988
Levomepromazine	95918998, 98853997, 98853998, 95919998, 95919997, 82709998, 87504998, 87505998
Loxapine	94007998, 94007997, 94007996, 94006998, 94006997, 94006996
Olanzapine	91618997, 89569996, 91364998, 97433998, 90664998, 86324998, 85376998, 91618998, 89569998, 89569997, 90659996, 97995998, 86325998, 90659997, 87647998, 89567996, 7111998, 90659998, 85377998, 89567998, 89567997
Paliperidone	84524998, 84523998, 84527998, 84526998, 84525998
Pericyazine	83019998, 99362997, 98865998, 97878992, 83020998, 99362998, 99362996, 95576998, 95577997, 95577998, 95577996
Perphenazine	99651998, 99651997, 98587998, 97877992, 94164992, 95575998, 97786998, 97786997, 95575997, 95575996
Pimozide	97342996, 97342998, 97342997, 95516996, 95516998, 95516997
Pipotiazine	85409998, 98622998, 85410998, 85411998, 85413998, 95503998
Promazine	99117998, 98783998, 96750992, 93708997, 93708998, 97406989, 95385998, 95386998, 95386996, 95386997, 98063990, 95385997, 98063989, 93476998, 98786996, 93477998, 98786998, 99093990, 93477997, 98786997, 99093988
Quetiapine	88734996, 81923998, 88733997, 83492998, 88733998, 88734998, 88734997, 83491998, 87907998, 83490998, 83493998, 81924998, 83995998, 83994998, 83993998, 83996998, 82773998, 82772998, 88737998, 88737996, 88736997, 88736998, 88737997, 87908998

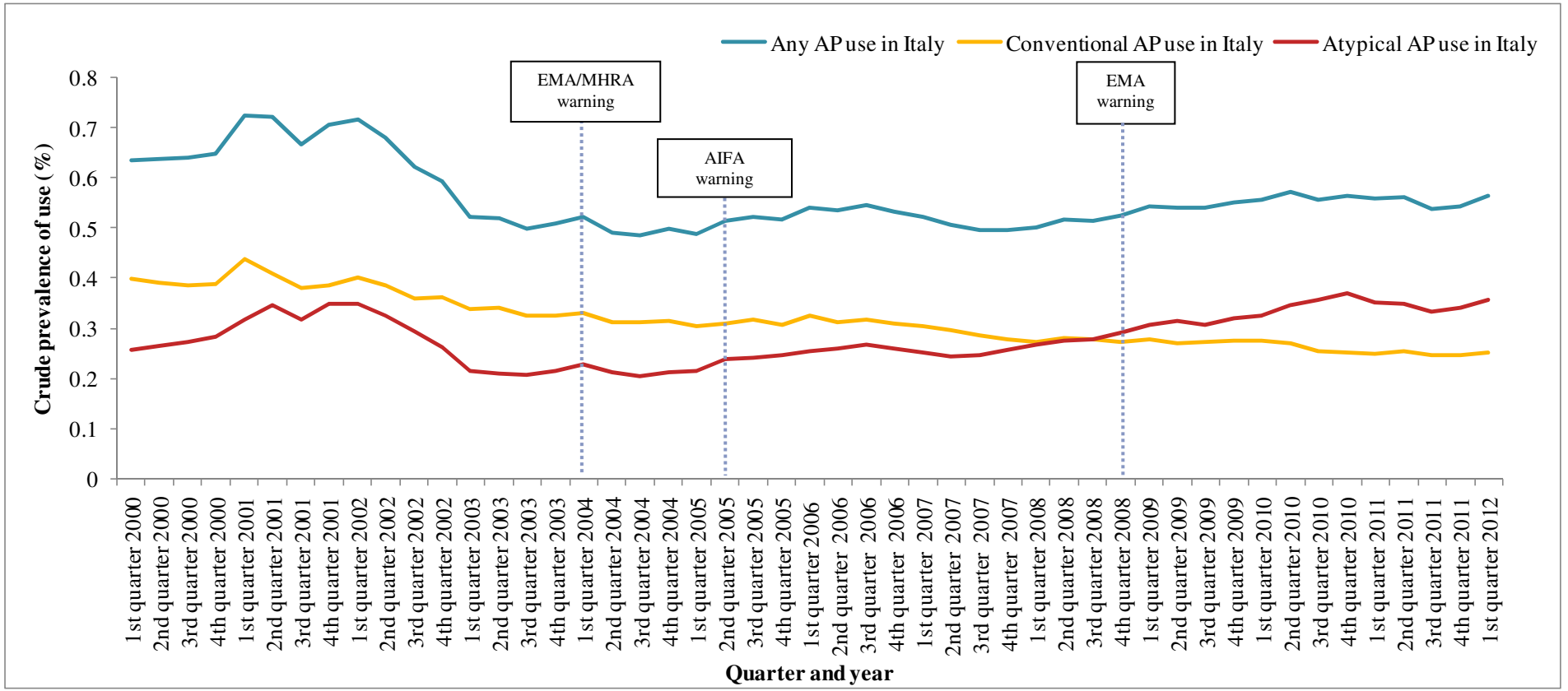
Risperidone	86983998, 92023998, 90395998, 99649998, 93240997, 91676998, 92107998, 99649997, 92089998, 85039998, 96914992, 99649996, 85038998, 93240998, 89908998, 93240996, 99637997, 91374998, 90396998, 85042998, 85040998, 86984998, 92491990, 88164998, 88163998, 95519998, 91968998, 92957990, 98585998, 98585997, 98585996, 92953990, 99637998, 99637996
Sertindole	89809997, 89809996, 89809998, 89812997, 89812996, 89811998, 89812998
Sulpiride	90805998, 97176998, 98796998, 90158998, 98796997, 98149992, 95226997, 95226998, 97163990, 97858990, 97966990, 95226996, 97163989
Thiopropazate	98174992
Thioproperazine	96492992, 98173992
Thioridazine	99436998, 98899997, 99437998, 99437997, 98899998, 98899996, 99437996, 96570992, 92821997, 95173996, 95174996, 95174997, 95173997, 98403989, 95173998, 98003989, 98403990, 92821998, 95174998, 98404988, 95175998, 95175997, 97715990, 98003990, 98404990, 95175996, 97715989, 98003988, 98404989
Trifluoperazine	99108996, 99107998, 95607992, 99109998, 99107997, 99109996, 99108997, 98203992, 99109997, 98206992, 95119998, 99108998, 95118997, 95119996, 95118998, 92623996, 95118996, 92623997, 92623998, 98052989, 98400990, 95119997, 98052990, 87435998
Trifluperidol	95116997, 98204992, 95116998, 95117998, 95117997
Zotepine	98190996, 98190998, 98190997, 99337996, 99337998, 99337997
Zuclopenthix Decanoate	85607998, 95071998, 85609998, 96628998, 96628997, 98767998
Zuclopenthixol Acetate	93519998, 86332998, 86334998, 86333998, 86335998, 93520998
Zuclopenthixol Dihydrochloride	99821997, 99821996, 99821998, 96629997, 96629996, 96629998

Appendix 4: Crude prevalence of antipsychotic use in patients under 65 years in the UK (THIN) per quarter year during the study period from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.



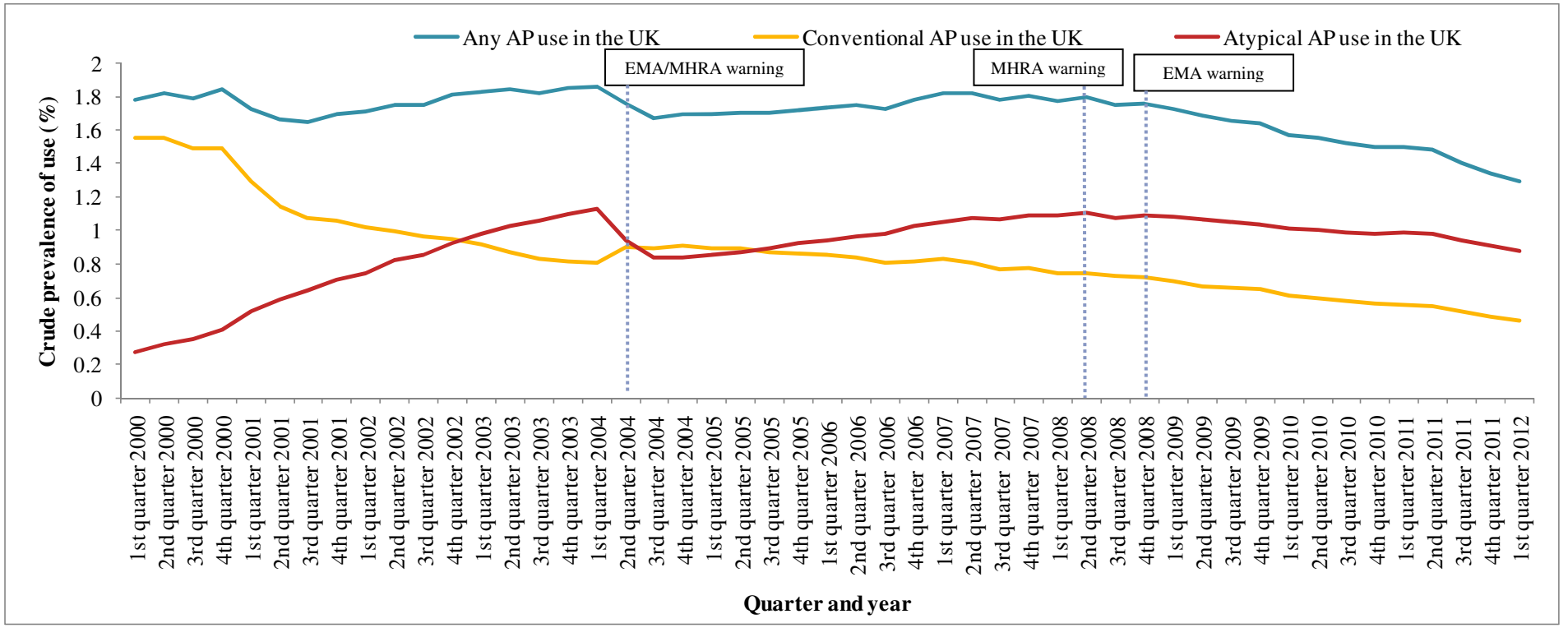
Abbreviations: AP- Antipsychotic; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

Appendix 5: Crude prevalence of antipsychotic use in patients under 65 years per quarter year in Italy (HSD-CSD-LPD) from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.



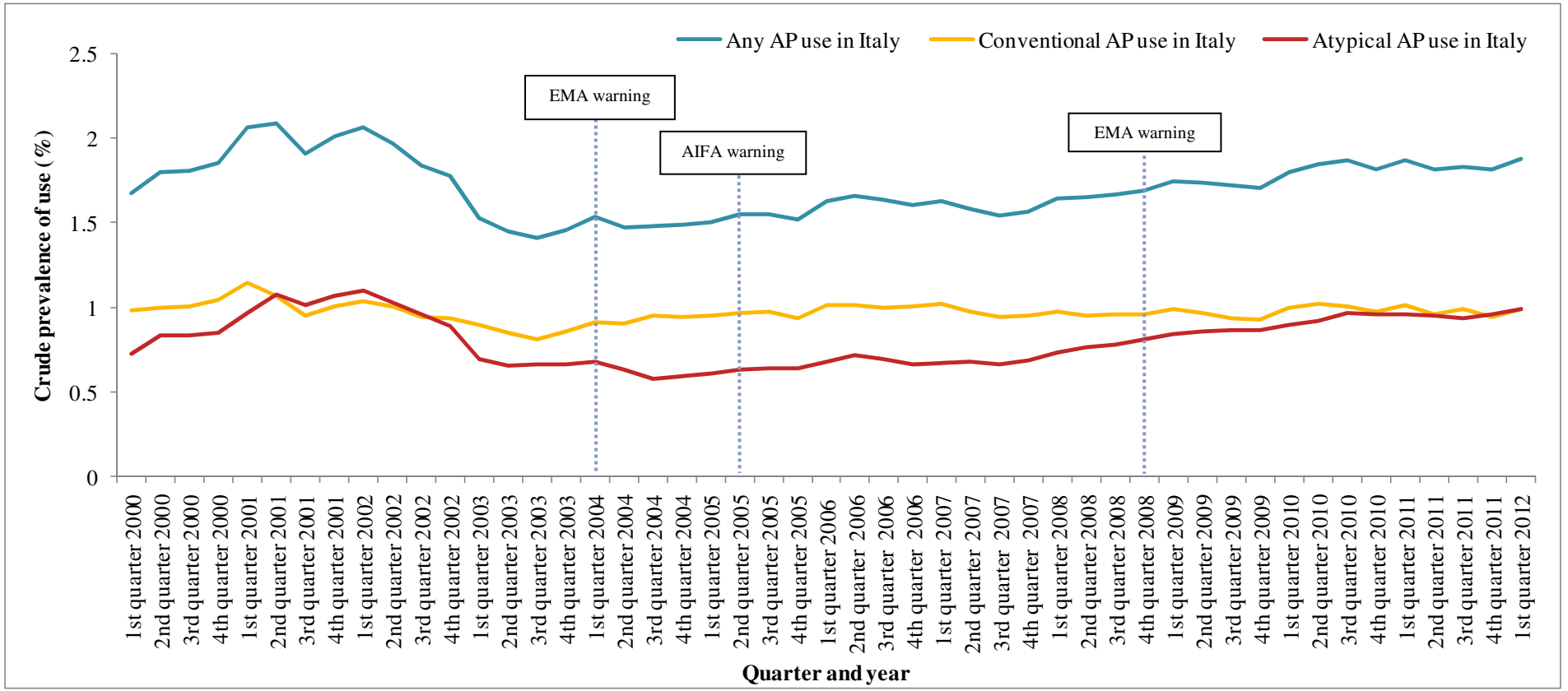
Abbreviations: AP- Antipsychotic; AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency

Appendix 6: Crude prevalence of antipsychotic use in patients ≥65 years (irrespective of dementia diagnosis) per quarter year in the UK (THIN) from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.



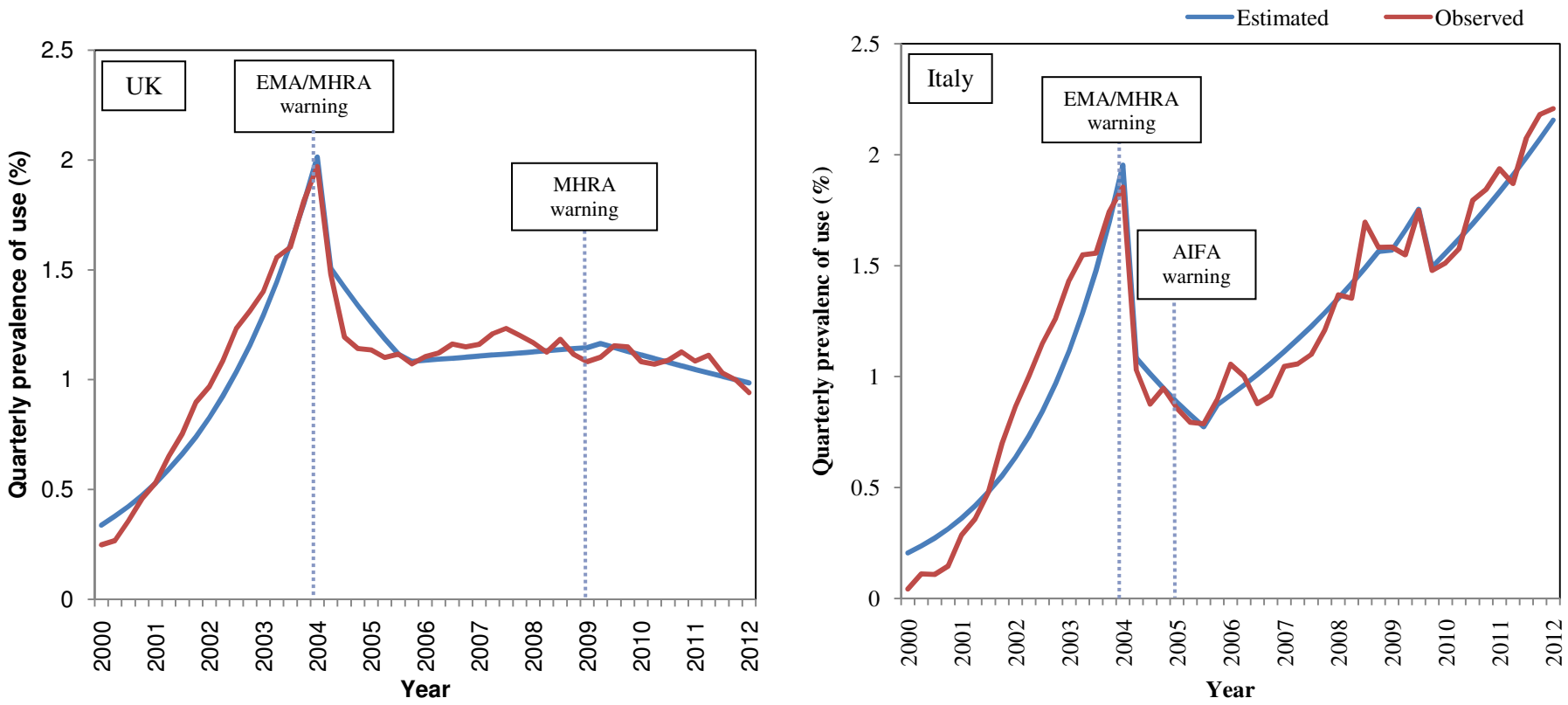
Abbreviations: AP- Antipsychotic; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

Appendix 7: Crude prevalence of antipsychotic use in patients ≥65 years (irrespective of dementia diagnosis) per quarter year in Italy (HSD-CSD-LPD) from the 1st quarter of 2000 to the 1st quarter of 2012, with main warnings labelled.



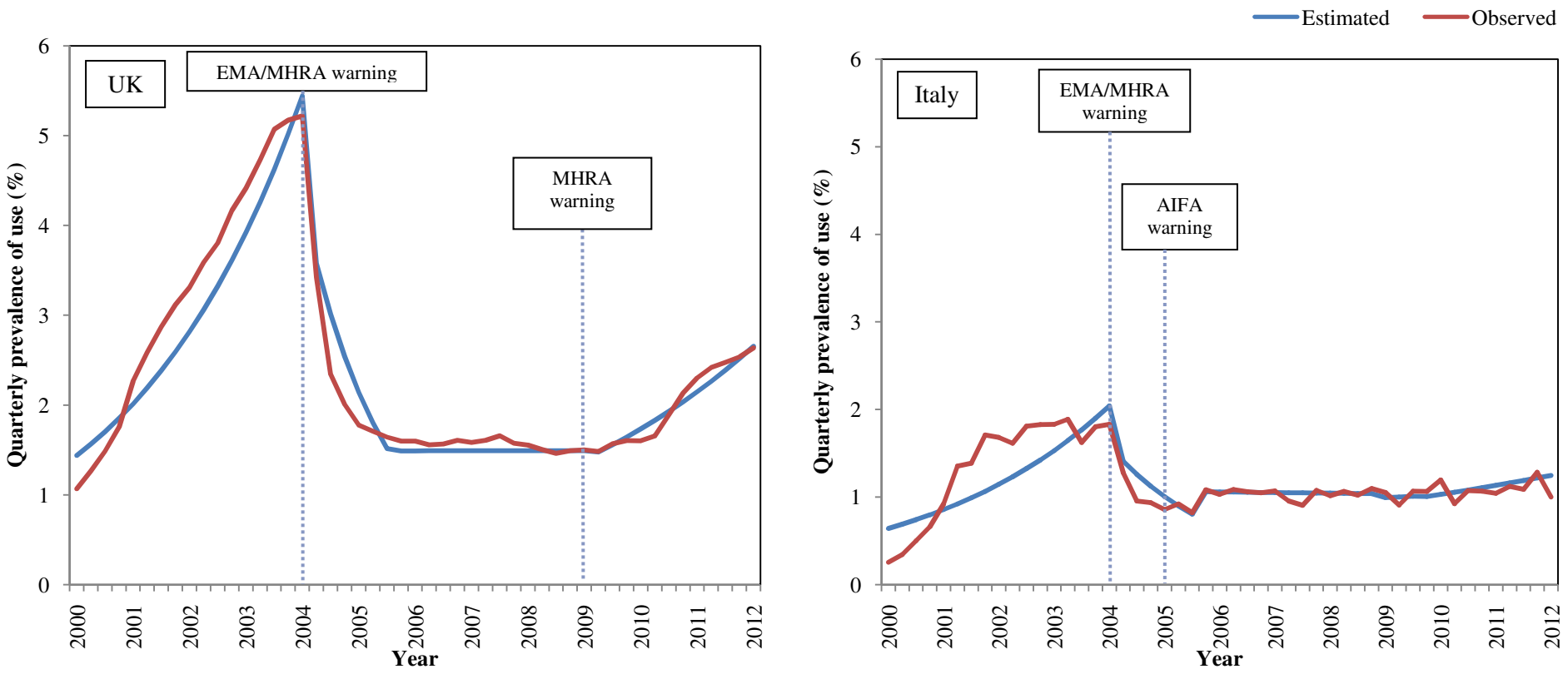
Abbreviations: AP- Antipsychotic; AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency

Appendix 8: Quarterly prevalence rates of olanzapine use in dementia patients ≥65 years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD- right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.



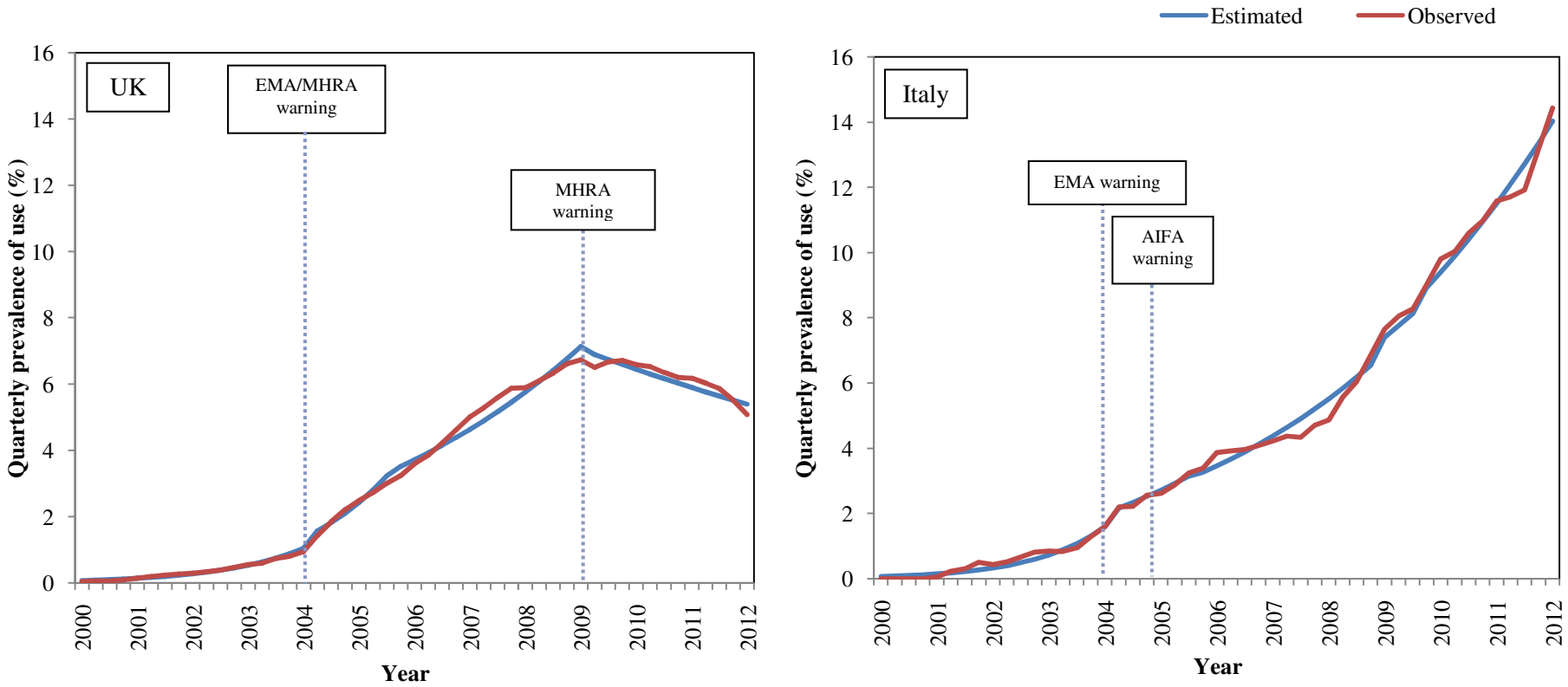
Abbreviations: AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

Appendix 9: Quarterly prevalence of risperidone use in dementia patients ≥65 years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD -right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.



Abbreviations: AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

Appendix 10: Quarterly prevalence of quetiapine use in dementia patients ≥65 years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD- right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.



Abbreviations: AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

Appendix 11: Quarterly prevalence of haloperidol use in dementia patients ≥65 years old in the UK (THIN- left panel) and Italy (HSD-CSD LPD- right panel) from the first quarter of 2000 to the first quarter of 2012, with main warnings labelled.

Abbreviations: AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

Appendix 11: Prevalence of antipsychotics use in patients 65 and over with dementia in the UK (THIN) at 3, 6 and 12 months before and after the warnings.

Antipsychotic	Time window before and after warnings	Warning occurrence	Prevalence of AP use before the warning (%)	Prevalence of AP use after the warning (%)	Comparison between the prevalences (p-value)
Olanzapine	3 months	1st quarter 2004	1.8	1.5	<0.001*
		1st quarter 2009	1.1	1.1	0.893
	6 months	1st quarter 2004	1.1	1.3	<0.001*
		1st quarter 2009	1.1	1.1	0.756
	12 months	1st quarter 2004	1.6	1.2	<0.001*
		1st quarter 2009	1.1	1.1	0.573
Quetiapine	3 months	1st quarter 2004	0.8	1.4	<0.001*
		1st quarter 2009	6.6	6.5	0.612
	6 months	1st quarter 2004	0.8	1.6	<0.001*
		1st quarter 2009	6.5	6.6	0.457
	12 months	1st quarter 2004	0.7	2.0	<0.001*
		1st quarter 2009	6.2	6.6	<0.001*
Risperidone	3 months	1st quarter 2004	5.2	3.4	<0.001*
		1st quarter 2009	1.5	1.5	0.939
	6 months	1st quarter 2004	5.1	2.9	<0.001*
		1st quarter 2009	1.5	1.5	0.529
	12 months	1st quarter 2004	4.9	2.4	<0.001*
		1st quarter 2009	1.5	1.6	0.262
Haloperidol	3 months	1st quarter 2004	0.9	1.5	<0.001*
		1st quarter 2009	2.0	1.8	0.100
	6 months	1st quarter 2004	0.9	1.6	<0.001*
		1st quarter 2009	2.0	1.8	0.061
	12 months	1st quarter 2004	0.9	1.7	<0.001*
		1st quarter 2009	2.0	1.8	0.004*

*Statistically significant (p-value <0.05). **Abbreviation:** AP- antipsychotic

Appendix 12: Prevalence of antipsychotic use in patients 65 and over with dementia in Italy (HSD-CSD-LPD) at 3, 6 and 12 months before and after the warnings.

Antipsychotic	Time window before and after warnings	Warning occurrence	Prevalence of AP use before warning (%)	Prevalence of AP use after warning (%)	Comparison between the two prevalences (p-value)
Olanzapine	3 months	1st quarter 2004	1.7	1.0	<0.001*
		2nd quarter 2009	1.6	1.7	0.460
	6 months	1st quarter 2004	1.6	0.9	<0.001*
		2nd quarter 2009	1.6	1.6	0.872
	12 months	1st quarter 2004	1.6	0.9	<0.001*
		2nd quarter 2009	1.5	1.6	0.808
Quetiapine	3 months	1st quarter 2004	1.3	2.2	<0.001*
		2nd quarter 2009	7.7	837	0.195
	6 months	1st quarter 2004	1.1	2.2	<0.001*
		2nd quarter 2009	7.3	8.6	<0.001*
	12 months	1st quarter 2004	1.0	2.4	<0.001
		2nd quarter 2009	6.5	9.3	<0.001*
Risperidone	3 months	1st quarter 2004	1.8	1.3	0.005*
		2nd quarter 2009	1.0	1.1	0.925
	6 months	1st quarter 2004	1.7	1.1	<0.001*
		2nd quarter 2009	1.1	1.1	0.952
	12 months	1st quarter 2004	1.8	1.0	<0.001*
		2nd quarter 2009	1.1	1.1	0.996
Haloperidol	3 months	1st quarter 2004	2.3	2.7	0.066
		2nd quarter 2009	4.7	4.4	0.417
	6 months	1st quarter 2004	2.1	2.7	<0.001*
		2nd quarter 2009	4.5	4.5	0.980
	12 months	1st quarter 2004	2.1	3.0	<0.001*
		2nd quarter 2009	4.3	4.9	0.003*

*Statistically significant (p-value <0.05). **Abbreviation:** AP- antipsychotic

Appendix 13: Median change in prevalence of antipsychotic use, along with 2.5 and 97.5 percentiles, for each quarter year in each time window in elderly people in the UK with dementia.

		Start of study (1st quarter 2000) to first EMA/MHRA warning (1st quarter 2004)	First EMA/MHRA warning (1st quarter 2004 to second EMA warning (3rd quarter 2005)	Second EMA warning (3rd quarter 2005) to second MHRA warning (1st quarter 2009)	Second MHRA warning (1st quarter 2009) to end of study (1st quarter 2012)
Median changes in prevalence (%) per quarter year	All APs	0.0044% (-0.018, 0.241%)*	0.0016% (-0.005, 0.196%)*	0.0013% (-0.005, 0.337%)*	-0.0017% (-0.197, 0.002%)*
	Conventional APs	0.0042% (-0.228, 0.241%)*	0.0020% (-0.005, 0.196%)*	0.0007% (-0.019, 0.330%)	-0.0019% (-0.197, 0.002%)*
	Atypical APs	0.0044% (-0.220, 0.513%)*	0.0024% (-0.005, 0.196%)	0.0013% (-0.019, 0.350%)*	-0.0041% (-0.197, 0.002%)*
	Olanzapine	0.0055% (-0.220, 0.513%)*	0.0020% (-0.083, 0.196%)*	0.0039% (-0.019, 0.350%)	-0.0071% (-0.195, 0.002%)*
	Quetiapine	0.0071% (-0.220, 0.513%)*	0.0024% (-0.083, 0.374%)*	0.0040% (-0.019, 0.352%)	-0.0078% (-0.195, 0.002%)*
	Risperidone	0.0093% (-0.211, 0.470%)*	0.0020% (-0.475, 0.374%)*	0.0039% (-0.019, 0.352%)	-0.0071% (-0.195, 0.117%)*
	Haloperidol	0.0110% (-0.211, 0.470%)*	0.0024% (-0.402, 0.325%)*	0.0040% (-0.019, 0.352%)*	-0.0078% (-0.195, 0.117%)*

*The corresponding log odds ratio change of AP use for each unitary increase of a quarter year (test for linear trend) was statistically significant. The percentiles reported in brackets cannot be interpreted as the conventional 95% confidence intervals. **Abbreviations:** APs- antipsychotics; MHRA- Medicines and Healthcare Products Regulatory Agency; EMA: European Medicines Agency

Appendix 14: Estimated annual prevalence rate in each time window in elderly people in the UK with dementia.

		Start of study (1st quarter 2000) to first EMA/MHRA warning (1st quarter 2004)	First EMA/MHRA warning (1st quarter 2004) to second EMA warning (3rd quarter 2005)	Second EMA warning (3rd quarter 2005) to second MHRA warning (1st quarter 2009)	Second MHRA warning (1st quarter 2009) to end of study (1st quarter 2012)
Annual prevalence rate in person-years (%)	All APs	4.5%	8.4%	7.1%	8.7%
	Conventional APs	2.2%	3.6%	2.6%	2.5%
	Atypical APs	2.4%	5.2%	4.8%	6.5%
	Olanzapine	0.5%	1.1%	0.5%	0.6%
	Quetiapine	0.2%	1.6%	2.8%	3.8%
	Risperidone	0.0%	0.0%	0.1%	0.2%
	Haloperidol	1.7%	2.2%	0.9%	1.3%

Abbreviations: APs- antipsychotics; MHRA- Medicines and Healthcare Products Regulatory Agency; EMA- European Medicines Agency

Appendix 15: Median change in prevalence of antipsychotic use, along with 2.5 and 97.5 percentiles, for each quarter year in each time window in Italian elderly people with dementia.

		Start of study (1st quarter 2000) to EMA warning (1st quarter 2004)	EMA warning (1st quarter 2004) to AIFA warning (3rd quarter 2005)	AIFA warning (3rd quarter 2005) to EMA/AIFA warning (4th quarter 2008)	EMA/AIFA warning (4th quarter 2008) to AIFA warning (3rd quarter 2009)	AIFA warning (3rd quarter 2009) to end of study (4th quarter 2012)
Median changes in prevalence (%) per quarter year	All APs	0.0009% (-0.017, 0.182%)*	0.0014% (-0.008, 0.398%)*	0.0015% (-0.004, 0.433%)*	0.0011% (-0.017, 0.115%)	0.0005% (-0.005, 1.118%)*
	Conventional APs	0.0008% (-0.017, 0.179%)	0.0015% (-0..008, 0.398%)*	0.0016% (-0.004, 0.423%)*	0.0011% (-0.023, 0.013%)	0.0005% (-0.005, 1.118%)*
	Atypical APs	0.0009% (-0.017, 0.198%)*	0.0015% (-0.008, 0.398%)*	0.0018% (-0.004, 0.423%)*	0.0011% (-0.023, 0.219%)*	0.0008% (-0.005, 1.089%)*
	Olanzapine	0.0010% (-0.017, 0.201%)*	0.0015% (-0.054, 0.386%)*	0.0019% (-0.004, 0.423%)*	0.0011% (-0.023, 0.219%)	0.0012% (-0.005, 1.089%)*
	Quetiapine	0.0012% (-0.017, 0.204%)*	0.0015% (-0.054, 0.386%)*	0.0022% (-0.004, 0.423%)*	0.0011% (-0.023, 0.366%)*	0.0017% (-0.005, 1.089%)*
	Risperidone	0.0014% (-0.017, 0.204%)*	0.0015% (-0.095, 0.386%)*	0.0019% (-0.004, 0.414%)	0.0012% (-0.023, 0.366%)	0.0020% (-0.005, 1.060%)
	Haloperidol	0.0017% (-0.017, 0.203%)*	0.0015% (-0.095, 0.386%)*	0.0022% (-0.004, 0.414%)*	0.0011% (-0.104, 0.366%)	0.0020% (-0.005, 1.060%)*

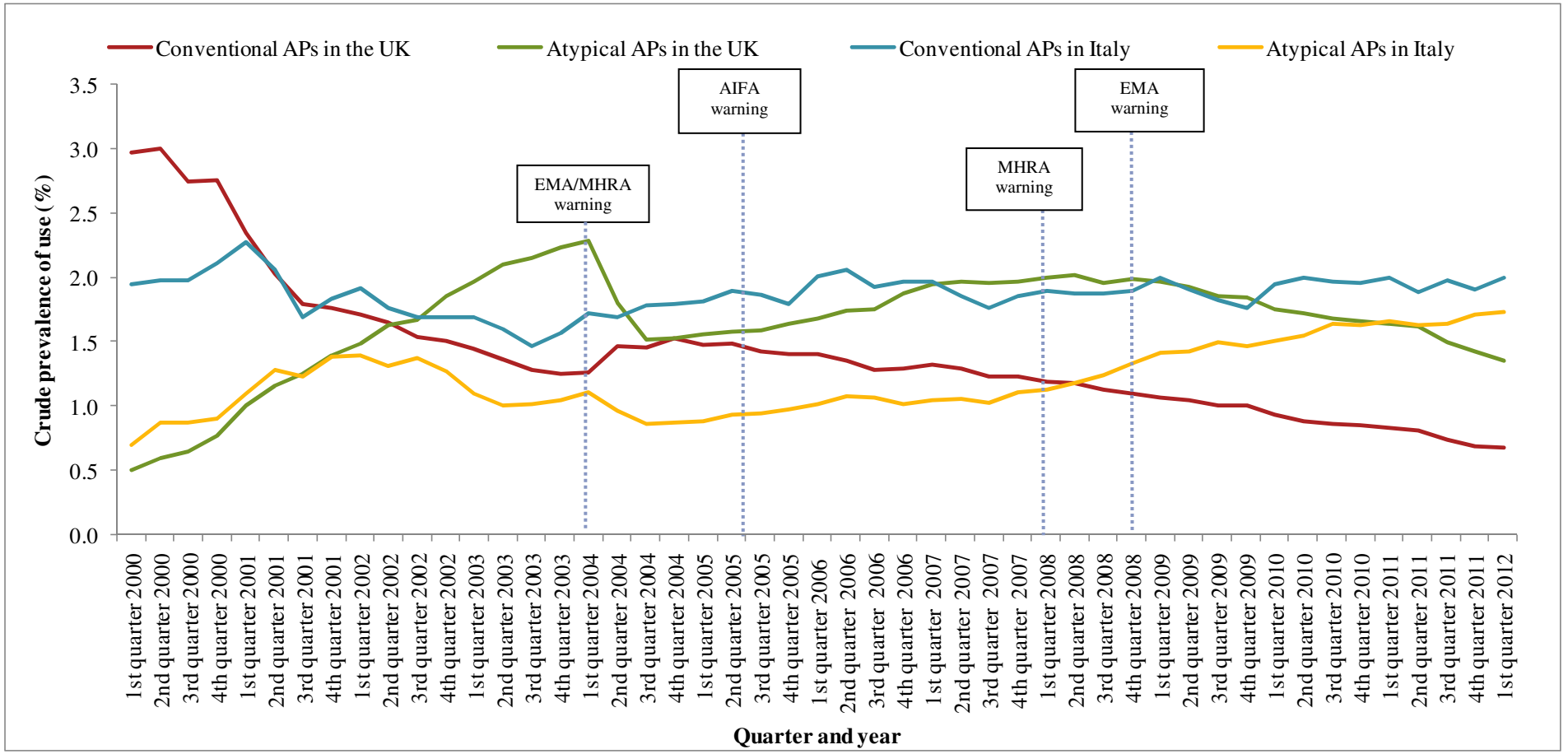
*The corresponding log odds ratio change of AP use for each unitary increase of a quarter year (test for linear trend) was statistically significant. The percentiles reported in brackets cannot be interpreted as the conventional 95% confidence intervals. **Abbreviations:** AIFA- *Agenzia Italiana del Farmaco*; APs- antipsychotics; EMA- European Medicines Agency

Appendix 16: Estimated annual prevalence rate in each time window in Italian elderly people with dementia.

		Start of study (1st quarter 2000) to EMA warning (1st quarter 2004)	EMA warning (1st quarter 2004) to AIFA warning (3rd quarter 2005)	AIFA warning (3rd quarter 2005) to EMA/AIFA warning (4th quarter 2008)	EMA/AIFA warning (4th quarter 2008) to AIFA warning (3rd quarter 2009)	AIFA warning (3rd quarter 2009) to end of study (4th quarter 2012)
Annual prevalence rate in person-years (%)	All APs	3.9%	8.1%	6.3%	21.9%	11.5%
	Conventional APs	2.4%	4.8%	3.7%	11.1%	5.7%
	Atypical APs	1.7%	3.7%	3.0%	12.4%	6.6%
	Olanzapine	0.3%	0.7%	0.4%	1.6%	0.7%
	Quetiapine	0.2%	1.7%	1.8%	8.6%	4.9%
	Risperidone	0.0%	0.0%	0.0%	0.0%	0.0%
	Haloperidol	0.5%	0.8%	0.4%	1.1%	0.5%

Abbreviations: AIFA- *Agenzia Italiana del Farmaco*; APs- antipsychotics; EMA- European Medicines Agency

Appendix 17: Prevalence of use of conventional and atypical antipsychotic use in patients ≥80 per quarter year in the UK (THIN) and Italy (HSD-CSD-LPD) year during the study period from the 1st quarter of 2000 to the 1st quarter of 2012.



Abbreviations: AIFA- *Agenzia Italiana del Farmaco*; EMA- European Medicines Agency; MHRA- Medicines and Healthcare Products Regulatory Agency

Appendix 18: Yearly prevalence of dementia in THIN in persons aged ≥65 years old (UK).

Year	Numerator	Denominator	Prevalence of dementia (95% CI)
2000	3,616	916,087	0.4 (0.39-0.41)
2001	4,985	984,875	0.5 (0.49-0.51)
2002	6,457	1,059,397	0.6 (0.59-0.61)
2003	8,153	1,134,980	0.7 (0.68-0.72)
2004	10,095	1,211,921	0.8 (0.78-0.82)
2005	11,922	1,287,350	0.9 (0.88-0.92)
2006	14,077	1,364,504	1 (0.98-1.02)
2007	15,986	1,450,876	1.1 (1.08-1.12)
2008	17,878	1,539,736	1.2 (1.18-1.22)
2009	19,874	1,636,149	1.2 (1.18-1.22)
2010	21,833	1,728,766	1.3 (1.28-1.32)
2011	23,721	1,839,240	1.3 (1.28-1.32)

Abbreviation: 95% CI- 95% confidence intervals

Appendix 19: Yearly prevalence of dementia in HSD-CSD-LPD in persons aged ≥65 years old (Italy).

Year	Numerator	Denominator	Prevalence of dementia (95% CI)
2000	1,558	639,586	0.2 (0.19-0.21)
2001	2,180	721,107	0.3 (0.29-0.31)
2001	2,841	811,929	0.3 (0.29-0.31)
2003	3,335	871,157	0.4 (0.39-0.41)
2004	3,849	895,588	0.4 (0.39-0.41)
2005	4,348	907,515	0.5 (0.49-0.51)
2006	4,727	923,875	0.5 (0.49-0.51)
2007	5,032	938,065	0.5 (0.49-0.51)
2008	5,281	940,408	0.6 (0.58- 0.62)
2009	5,471	944,122	0.6 (0.58- 0.62)
2010	5,718	948,496	0.6 (0.58-0.62)
2011	5,519	944,784	0.6 (0.58-0.62)

Abbreviation: 95% CI- 95% confidence intervals

3.2. Antipsychotic use in dementia patients in a general practice setting: a Dutch population-based study. J. Sultana[1,2], I. Leal[2], M. de Ridder[2], M. Sturkenboom[2], G. Trifiro'[1,3]*. Epidemiol Psychiatr Sci. 2016 Aug;25(4):403-6.

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Introduction

Antipsychotic (AP) prescribing in elderly persons has been a focus of attention from drug regulatory agencies in the past decade. These drugs are commonly prescribed off-label for behavioral and psychological symptoms in dementia (BPSD). Risperidone is specifically approved for persistent aggression in patients with moderate to severe Alzheimer's dementia for up to 6 weeks but other commonly used antipsychotics such as olanzapine, quetiapine and haloperidol do not have a specific indication for dementia-related symptoms. The lack of more effective pharmacological options led to a widespread over-use of antipsychotics in dementia, including specific drugs such as quetiapine for which there is very limited evidence supporting its efficacy in BPSD based on clinical trial data (Ballard & Waite, 2006).

In 2004, the European Medicines Agency (EMA) launched a first safety warning informing healthcare providers that the use of olanzapine and risperidone was associated with an increased risk of stroke as well as all-cause mortality(European Medicines Agency, 2004) and by August 2009 EMA extended the warning to all antipsychotic use in dementia (European Medicines Agency, 2009). Observational studies investigating AP use in dementia within Europe suggest that international and national safety warnings may have had only a short-term impact on AP prescribing (Schulze et al., 2013; Gallini et al., 2014; Sanfelix-Gimeno et al., 2009; Franchi et al., 2012; Trifiro' et al., 2010; Guthrie et al., 2013). Such warnings may also have prompted the use of other antipsychotics, replacing those used previously, rather than reducing the excess use of these drugs.

In the Netherlands, recent investigations of antipsychotic use in older persons focused on institutionalized elderly persons (van der Putten et al., 2014; Kleijer et al., 2014; van der Speck et al., 2013; van de ven-Vakhteva et al., 2013; Sterk et al., 2012). The prevalence of antipsychotic use in community-dwelling Dutch elderly persons with dementia in recent years has not been estimated. Nevertheless, two nested case-control studies using the Dutch Integrated Primary Care Information (IPCI) database suggest that both atypical and conventional antipsychotics are associated with increased risk of death and community-acquired pneumonia in elderly persons (Trifiro' et al., 2010; Trifiro' et al., 2007) and a case-control study using the Dutch PHARMO record linkage system found an increased risk of cerebrovascular events in elderly persons (Kleijer et al., 2009). The aim of this population-based study was therefore to explore whether the prevalence of AP use changed in a cohort of dementia patients in a Dutch general practice database after the warning launched by EMA in August 2009.

Methods

Data source

The Integrated Primary Care Information (IPCI) database is a Dutch general practice database containing complete electronic health records from 466 general practices. There are around 1,786,000 patients registered in IPCI, who are representative of the Dutch general population in terms of age and sex distribution. Available data includes medical diagnoses, coded using International Classification of Primary Care codes, prescription data, coded using (Anatomical Therapeutic Chemical (ATC) classification system and additional medical information (e.g. laboratory measurements, functionality status variables etc.) among others, as well free text clinical notes. IPCI has been used extensively for pharmacoepidemiology research (Trifiro' et al., 2007; Trifiro' et al., 2010; Straus et al., 2004).

Population

Persons in IPCI were considered eligible if they had a minimum one year of database history, were alive and aged 65 years or older and had a diagnosis of dementia over the observation period 1st January 2008-31st December 2013. Patient contribution to the study was censored at the end of study period, i.e. 31st December 2013, transfer out of database/end of registration in IPCI or death.

Exposure

Prescriptions of APs were identified using ATC codes: N05A (except for N05AN which corresponds to lithium). The antipsychotics identified were grouped by class as atypical (ATC: N05AX08, N05AX11, N05AX12, N05AX13, N05AX14, N05AE03, N05AE04, N05AE05, N05AH02, N05AH03, N05AH04, N05AH05, N05AL05) and conventional (all others N05A, except for N05AN). The prevalence of the commonly used antipsychotics risperidone, quetiapine, olanzapine and haloperidol were investigated separately.

Analysis

The trimester prevalence of AP use was calculated dividing the number of persons receiving at least one AP prescription (numerator) by the number of persons registered in the database in the same trimester. Data management and analysis were carried out using SAS Release 9.3 (SAS Institute, Cary, NC, USA).

Review board approval

The study was approved by IPCI Review Board (IPCI Raad van Toezicht).

Results

From 2008 to 2013 314,191 patients aged 65 and over were identified in IPCI. Of these, 14,396 (4.6%) had a diagnosis of dementia. At the start of the observation period (2008), the trimester prevalence of any APs was 13% in elderly dementia patients, decreasing to 11% just before the warning in the third trimester of 2009 (Figure 1). The use of any APs increased mildly in the 3 months after the warning (from 10 to 11%), thereafter decreasing gradually to 8%. The trend for conventional APs was very similar to that for APs overall over the observation period, starting at 10% in 2008 decreasing to 7% in the second trimester of 2009. There was briefly a small increase in prevalence from 6 to8% 3 months after the warning, after which there was a general decrease to 7% at the end of the observation period. The trimester prevalence of atypical APs was much lower, at approximately 4% throughout the pre-warning period; this initially decreased from 4 to 3% over the year after the warning, and remained stable, fluctuating between 3 and 4%. Haloperidol was the most commonly used antipsychotic. The prevalence of haloperidol fluctuated between 4 and -5% before the warning and initially rose slightly from 5 to 6% in the trimester after the warning, after which there was a gradual decrease to 4%. The second most commonly used antipsychotic was risperidone, with a prevalence of 2 to 3% throughout the observation period. Quetiapine and olanzapine had a very low prevalence of use, remaining stable at 1% throughout the observation period.

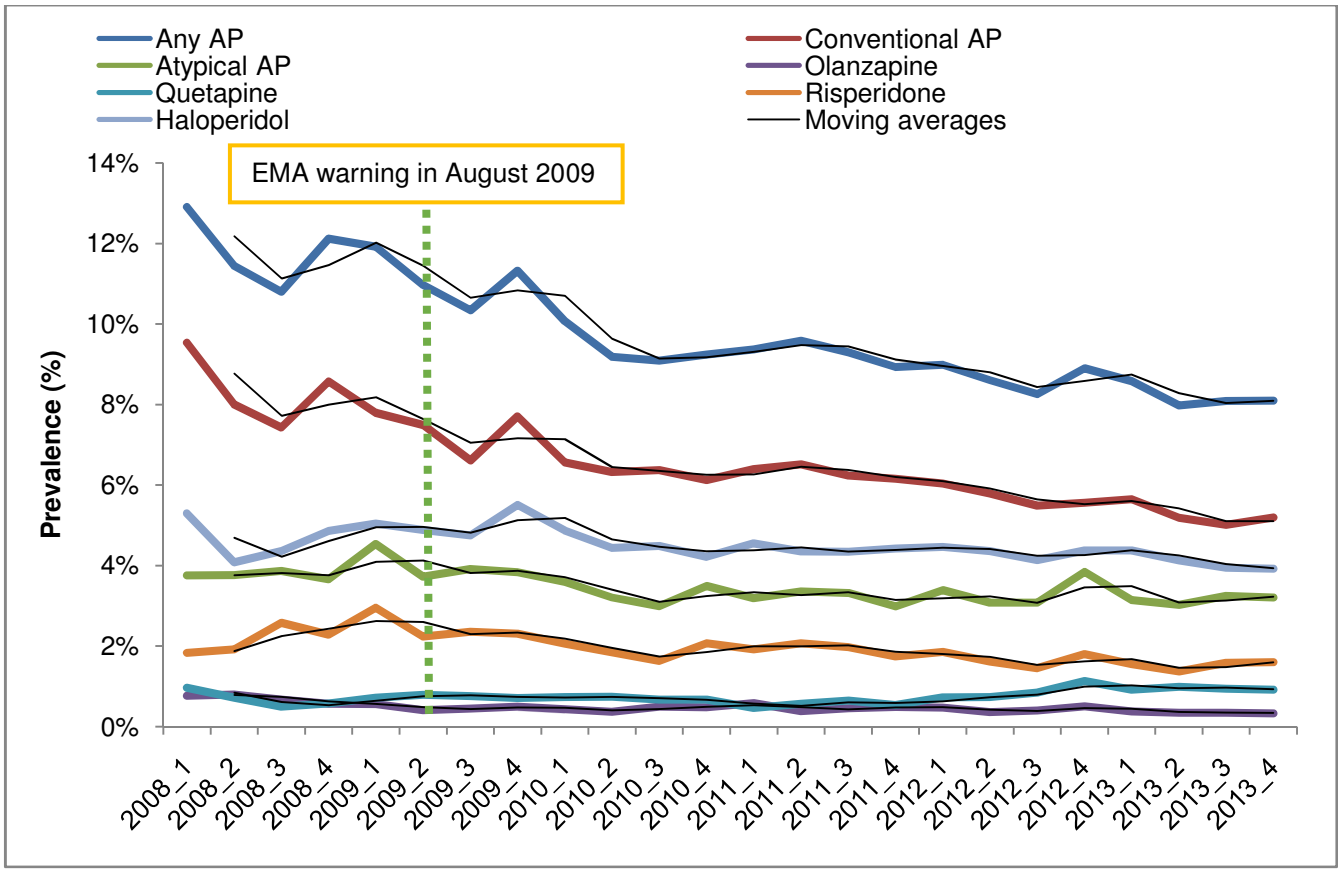

Figure 1: Prevalence of antipsychotic use in elderly dementia patients in a Dutch general practice setting. Abbreviation- AP: antipsychotics

Discussion

The most commonly prescribed antipsychotics among elderly patients with dementia in Dutch general practice between 2008 and2013 were haloperidol and risperidone. This is in line with Dutch clinical guidelines for General Practitioners (GPs) for dementia (Dutch College of General Practitioners, 2015) suggesting that haloperidol and risperidone can be used in cases of acute psychosis and/or aggression if non-pharmacological approaches are not successful. The low prevalence of quetiapine (approximately 1% during the whole study period) is consistent with the less convincing evidence supporting the efficacy of this drug in BPSD. In other countries quetiapine was found to be prescribed in older people with dementia more frequently than other antipsychotic drugs (Franchi et al., 2012; Guthrie et al., 2013). In their study carried out using the Lombardy Administrative Database (Italy) from 2002 to 2008, Franchi et al. found that by 2008, quetiapine was by far the most commonly prescribed drug in elderly persons taking anti-cholinesterase inhibitors (a proxy of dementia), with an annual prevalence of 12%; to put this in context, this prevalence could be compared that of the next most commonly prescribed antipsychotic in Lombardy, haloperidol, of 3% in 2008. The quarterly prevalence of use of quetiapine in Scottish persons with dementia peaked to 10% in 2010 but gradually decreased to 6% by 2011 (Guthrie et al., 2013).

The higher use of conventional agents rather than atypical ones in dementia is of clinical significance because randomized clinical trials investigating the effectiveness of antipsychotics did not find evidence favoring the use of conventional APs in dementia. On the other hand, such trials

did find a modest improvement in aggression and smaller but nevertheless significant benefit in psychosis over 6-12 weeks of treatment with risperidone and olanzapine (Ballard & Waite, 2006). After the 2009 EMA warning, the use of both classes of drugs continued to decline.

The elevated use of conventional antipsychotic use in Dutch persons with dementia (6% quarterly prevalence by the end of 2013) compared to atypical antipsychotics (4% quarterly prevalence by the end of 2013) was also seen in dementia patients in France and Germany(Schulze et al., 2013; Gallini et al., 2014). In French community-dwelling persons ≥65 with dementia, the monthly prevalence of conventional antipsychotic use was 15% in 2003 compared to 4% for atypical antipsychotic use (Gallini et al., 2014). However by 2012, both classes of drugs had a similar monthly prevalence at approximately 5%. In Germany, the annual prevalence of conventional antipsychotic use among persons with dementia estimated using health insurance data decreased from 35% in 2004 to 32% in 2009 but remained higher than atypical antipsychotic use which increased marginally from 17% in 2004 to 20% in 2009 (Schulze et al., 2013). In Italy, on the other hand, atypical antipsychotics were more commonly used than conventional ones in persons with dementia, with an annual prevalence of 15% in 2008 compared to 5% for conventional antipsychotics (Franchi et al., 2012). This is most likely explained by the very high use of quetiapine in this population as described above.

The higher use of conventional antipsychotics in some countries may have been at least partly prompted by drug safety warnings which initially cautioned prescribers regarding the increased risk of all-cause mortality and stroke associated with olanzapine and risperidone in 2004 (European Medicines Agency, 2004), although national and international drug regulatory agencies extended the warning to all antipsychotic use in dementia in 2009 (European Medicines Agency, 2009).

The use of antipsychotics overall in the Dutch community setting at the end of the observation period (quarterly prevalence of approximately 9% in 2013) was much lower compared to the use of these drugs in the long-term care setting. A recent study found that 32% of a sample of 290 Dutch long-term care residents were prescribed an antipsychotic (van der Putten et al., 2014). Similar findings were reported in the same year in a larger study (N=1,090 Dutch long-term care residents from 20 long-term care residences), where 31% long-term care residents were prescribed at least one antipsychotic drug (Kleijer et al., 2014).

Further information is needed to understand whether the changes in antipsychotic use in dementia correspond to increase in the appropriateness of drug prescribing. Strategic action is needed to promote the appropriate use of antipsychotics in dementia patients and facilitate adoption of non-pharmacological treatment, the latter currently being under-utilized for reasons that include low awareness among healthcare professionals of their efficacy and implementation as well as non-reimbursable status of non-pharmacological interventions (Kales et al., 2014).

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Conflict of interest: None of the authors have conflicts of interest directly related to the study. MS is heading a research unit that holds unconditional research contracts with some pharmaceutical companies (Eli Lilly, Pfizer, AstraZeneca Novartis, Boehringer, GSK, Servier), none related to this study.

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5. Conclusions

The reviews presented herein show that antipsychotic use in dementia is associated with several adverse outcomes such as all-cause mortality, stroke, pneumonia, venous thromboembolism and hip-fracture. The observational studies considered have several advantages such as the large and often nationally representative patient samples available, which reflect clinical practice. On the other hand such studies may be limited by several biases and are subject to confounding if not well-designed, in addition to residual confounding which cannot be accounted for. Findings from each study must be evaluated based on the merits of the methods employed.

Antipsychotic use in dementia is on the increase in Europe, in particular in Italy. The warnings in the UK seem to have been effective in particular when several entities including MHRA but also the Alzheimer's Society UK and the All Parliamentary Group on Dementia launched their awareness campaigns. On the other hand, a less intensive and more seemingly bureaucratic approach such as that used in Italy did not appear to lead to a decrease in the use of antipsychotics in dementia. Antipsychotic use in the Netherlands appeared to be relatively lower compared to the UK and Italy as well as being in line with national guidance issued.

It should be noted that the drug utilisation studies in question are limited in the sense that it is the use of antipsychotics in dementia that is being described; it was not possible to evaluate whether such use was specifically for BPSD, as diagnoses of the symptoms for which antipsychotics would be used, such as aggression, are not routinely available. Notwithstanding, the fact that to date, according to the summary of product characteristics only risperidone is licensed for the short-term management of aggression in dementia and the fact that all identified populations in the drug utilization studies had a diagnoses of dementia, suggests that the studies carried out in THIN, HSD and IPCI address an important information gap in the description of potentially inappropriate antipsychotic use in this population.

With regards to future antipsychotic safety studies, these should try to account for frailty as a confounder or effect modifier as well as accounting for public health interventions that may modify the pattern of drug use and the associated drug-related risks, giving risk to a "calendar year effect". In addition, identifying and adjusting for potential drug interactions in dementia patients, rather than only adjusting for polypharmacy as a confounder as is often done, may additionally improve the accuracy of the risk estimates obtained in such safety studies.

4. Special topics in drug safety studies

The following sections describe topics of interest in drug safety studies of particular relevance to antipsychotic use in the elderly. The first paper, “Can information on functional and cognitive domains improve short-term mortality risk prediction among community-dwelling older persons? A population-based study using a UK primary care database”, describes a retrospective study aiming to investigate firstly, whether data on frailty in the elderly is registered in THIN database and whether such information is predictive of one-month and one-year mortality. The investigation of frailty can be considered a special topic in this context because frailty may partially account for residual confounding in observational studies in the elderly. The second paper, “Drug safety warnings: a message in a bottle?”, addresses the question of how public health warning such as those issued for antipsychotic use in older persons may affect the underlying risk in exposed persons.

4.1. Can information on functional and cognitive domains improve short-term mortality risk prediction among community-dwelling older persons? A population-based study using a UK primary care database. Janet Sultana[1,5], Andrea Fontana[2], Francesco Giorgianni[1], Giorgio Basile[1], Elisabetta Patorno[3], Alberto Pilotto[4], Miriam Sturkenboom[5] and Gianluca Trifiro'[5,6*] Submitted to European Journal of Epidemiology.

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Abstract

Background: Functional and cognitive domains have been rarely evaluated for their prognostic value in general practice (GP) databases. The aim of this study was to identify functional and cognitive domains in The Health Improvement Network (THIN) and to evaluate their additional value for the prediction of one-month and one-year mortality in elderly persons.
Methods: A retrospective cohort study was conducted in THIN, a UK nationwide general practitioner database. Patients ≥65 years were identified in THIN database during the years 2000-2012. THIN was mined for functional and cognitive domains. Only information on mobility, dressing and accommodation was registered in THIN frequently enough to be analysed further. One-year and one-month mortality risk was predicted using logistic models with following covariates: model 1): age + sex; model 2): age + sex+ a co-morbidity score, i.e., the quality outcomes framework (QOF) score; and model 3): age + sex + QOF score + functional/cognitive domain. The discriminatory power achieved by each model was assessed by computing the area under the Receiver Operating Characteristics (ROC) curve (AUC), using the predicted probabilities carried out by the model (also known as the "c-statistic") along with their 95% confidence interval (CI).
Results: Overall, 1,193,268 subjects aged ≥65 years were identified (median follow-up: 5.5 years, first-third quartile range: 2.5-9.9 years). The most frequently registered functional domains were: mobility (N=55,597 patients, 4.7%, of the whole elderly population), accommodation (N=23,684; 2%) and dressing ability (N=5,197; 0.4%). A significant improvement on one year and one month mortality prediction in elderly people was observed by adding accommodation into Model 3: c-statistics (95% CI) increased from 0.71 (0.70-0.72) to 0.76 (0.75-0.77) and 0.73 (0.71-0.75) to 0.79 (0.77-0.80), respectively. A slight improvement was seen for dressing and mobility for both one-year and one-month mortality. A less notable improvement in the prediction of one-year and one-month mortality was observed when the population was restricted to patients with dementia.
Conclusion: Functional domains were not frequently recorded in the THIN database. Nevertheless, whenever registered, these domains improved the accuracy of a model including age, sex and co-morbidities on the prediction of one month and one year mortality risk among community-dwelling older people.

Keywords: elderly, frailty, electronic healthcare databases, mortality

Introduction

The last two decades have seen a significant increase in the number of observational studies investigating drug safety using electronic healthcare databases, particularly in populations that are more susceptible to adverse drug reactions, such as elderly persons. Of the many pharmacoepidemiologic studies that have been carried out, mortality is a widely explored outcome [1-18]. However the data sources used to carry out such studies usually capture medical information that is limited to demographic traits, medical history (diagnoses and medical procedures) and drug history [19]. As a result, pharmacoepidemiological studies investigating the risk of death and other outcomes associated with drugs may suffer from residual unmeasured confounding. This may be an issue since the clinicians' decision to prescribe a drug to an elderly person is likely to take other prognostic factors such as predictors of a short life-expectancy (e.g. inability to independently carry out activities of daily living, being bed-ridden, severity of dementia) or of an increased susceptibility to adverse drug reactions (e.g. unexplained weight loss, disability, living without a carer) [20]. These factors, which may generically be labelled as components of frailty, can contribute to residual confounding if they remain unmeasured and unaccounted for in the analytical phase. Frailty can be clinically defined as a marked loss of functional reserve capacity and a heightened difficulty in maintaining homeostasis, resulting in increased physical vulnerability and a decreased ability to recover after a noxious event. resulting in increased physical vulnerability and a decreased ability to recover after a noxious event. To date, there is no a gold standard for measuring frailty. In clinical practice, the two most commonly used models of frailty are: the phenotype model, defined by unintended weight loss, fatigue, general weakness, reduced walking speed and limited physical activity [21] and the cumulative deficit model, defined by co-morbidities and impaired functionality/disability [22].

A co-morbidity score, the Quality Outcomes Framework (QOF), has been previously developed and validated in the UK general practice (GP) database The Health Improvement Network (THIN) for mortality prediction. This score is similar to the Charlson co-morbidity score and is composed of diseases which GPs in the UK are incentivised to register. It has been shown that the use of demographic variables and the QOF score is more predictive of mortality in elderly persons than the Charlson co-morbidity scores [23]. This could provide prognostic information on the basis of which clinicians may carry out their prescribing decisions and which may therefore account for some unmeasured confounding. Although a recently published study proposes a composite 'frailty' score using THIN containing disease and non-disease indicators of health [24], the value of individual non-disease indicators of frailty as predictors of mortality remains uncertain.

A recent review of mortality prediction accounting for frailty suggests that a frailty index consisting of co-morbidities and healthcare claims which are indicative of frailty may be the best approach towards adjusting risk estimates in observational studies using claims data [20]. We hypothesise that, provided sufficient data is available, individual functional/cognitive domains registered in THIN should be predictive of mortality in elderly people.

The aim of the present paper was therefore to investigate: (1) which functional and cognitive domains are registered and how commonly such domains are registered in community-dwelling elderly people and (2) if functional and cognitive domains improve the prediction of short-term mortality in addition to age, gender and co-morbidities, compared to age, gender and co-morbidities alone, in a cohort of elderly persons (and with dementia specifically) using the THIN database.

Materials and methods

Data source

The THIN database was used to carry out this study. THIN contains electronic patient records registered by general practitioners (GPs) during routine clinical practice and currently collects anonymized clinical data for 11 million persons (covering approximately 6.2% of the UK population) registered with 562 general practices across UK. All persons in THIN are registered in a patient file with data on patient date of birth, date of death where applicable, sex, date of registration within the database and registration status within the database (i.e. whether the patient is active or has been transferred out of the database). All persons in the database have a unique and de-identified code, which is used to link the patient file with other files such as the medical file. The medical file contains medical diagnoses, related information such as functional and cognitive domains, and the date when this information was registered. Data on medical diagnoses in the medical file is coded using Read codes, the standard clinical terminology system that is used in general practice in the UK. THIN also has a prescription file which contains data on prescribed drugs such as the date of prescription, the generic name, the strength, and the formulation of the prescribed drug. Drug information is coded through British National Formulary (BNF) and Multilex codes.

Study population

We identified two cohorts of patients: a cohort of elderly persons and a cohort of elderly persons with dementia. Patients in the cohort of elderly persons were included in the study if they were aged $\geq$65 with at least one year of database history prior to the start of follow-up over the period from January 1st 2000 to December 31st 2012. The cohort entry date if one year of database history was available before January 1st 2000 was defined as the date between January 1st 2000 and December 31st 2012 when a person reached 65 years, or if already 65 years old before the start of the study period, the cohort entry date was the 1st of January 2000. If a person $\geq$65 years did not have one year of database history prior to the 1st of January 2000, the date at which one year of database history was accumulated was considered the cohort entry date, provided that this fell between the 1st of January 2000 and the 31st of December 2012.

In the dementia cohort, patients were included if they met the previous requirements and in addition had a dementia diagnosis. Patients with a diagnosis of dementia were considered as a separate population since these patients broadly constitute a group of public health interest in current pharmacoepidemiologic research and their functional and/or cognitive status is likely to be more severe compared to persons without dementia.

Covariates

Demographics and clinical history

Demographic characteristics (age and sex) were evaluated at the cohort entry date while the clinical characteristics were evaluated any time prior to the cohort entry date. The co-morbidities chosen to describe the health status of the study population consisted of fifteen diseases that are part of the Quality and Outcomes Framework (QOF) programme, a voluntary scheme available to all GPs in the UK which incentivises GPs to register certain diseases [23]: asthma, atrial fibrillation, cancer (excluding non-melanotic skins cancer), chronic kidney disease stages 3-5, chronic

obstructive pulmonary disease, coronary heart disease, dementia, depression, diabetes, epilepsy, heart failure, hypertension, hypothyroidism, psychosis, schizophrenia, bipolar disorders and stroke/transient ischaemic attack (**Appendix Table A1**). These diseases were identified in THIN using Read codes and their prevalence at baseline was calculated.

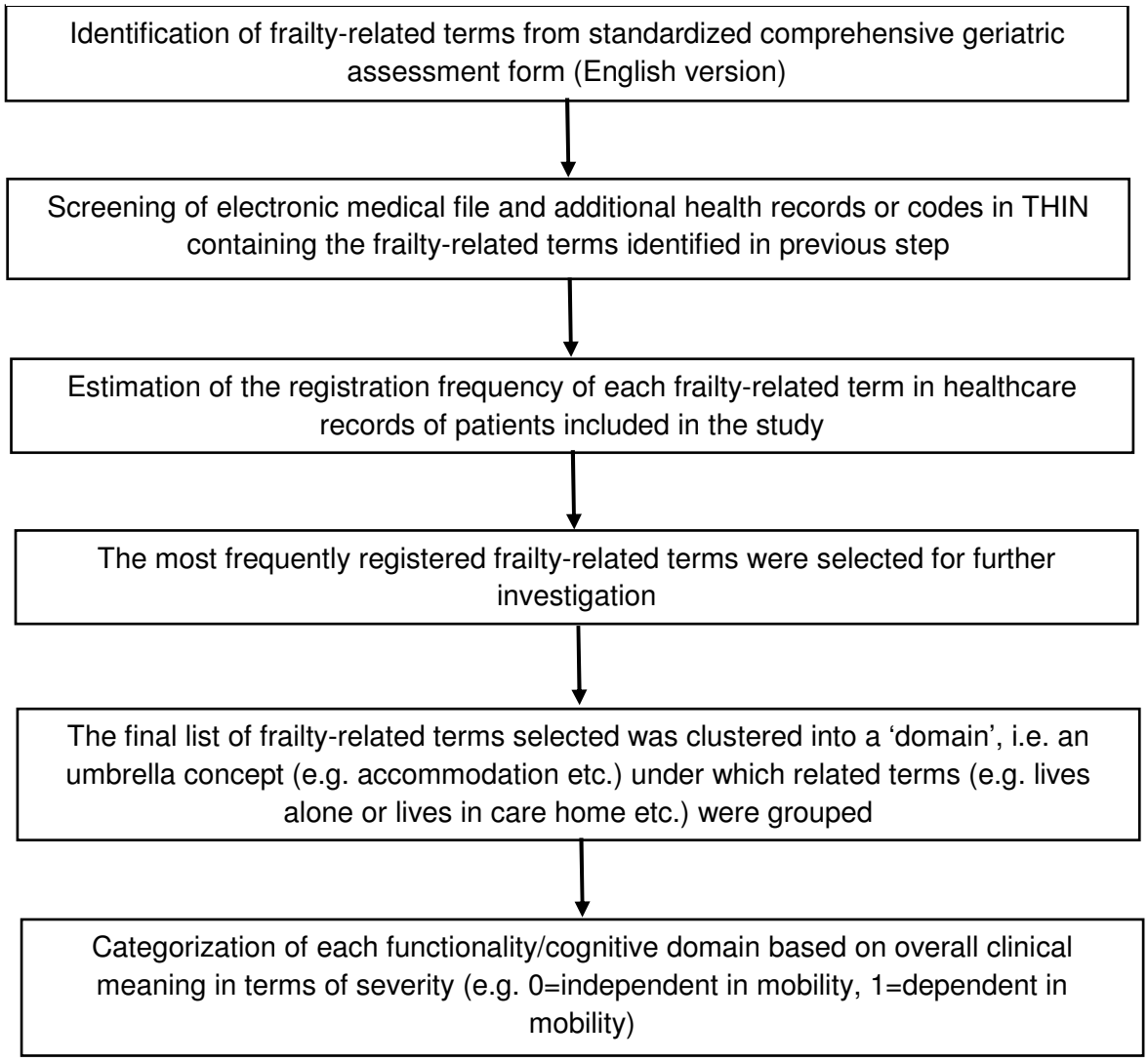
A primary care morbidity score using QOF diseases was constructed based on a previously developed QOF score using THIN data for persons aged 65 and over [23]. The score consists of nine out of the fifteen QOF diseases that were found to be predictive of mortality with a hazard ratio of 1.2 or higher (i.e., the standard QOF score) according to the original paper by Carey et al. The following weights were applied to each included QOF disease based on the size of the hazard ratio quantifying the association between that disease and mortality in elderly persons [23]: atrial fibrillation assigned one point; cancer assigned three points; chronic obstructive pulmonary disease assigned two points; dementia assigned three points; diabetes assigned one point; epilepsy assigned two points; heart failure assigned two points; psychosis, schizophrenia and bipolar disease assigned two points; stroke or transient ischaemic attack assigned one point.

Functional and cognitive domains

THIN was mined for keywords related to the following functional/cognitive domains as identified in a comprehensive geriatric assessment chart previously used in geriatric epidemiological research [25,26]: nursing home resident or otherwise, activities of daily living (bathing, cooking, dressing, feeding, house-cleaning, money management, personal hygiene and toileting), nursing needs (bladder or bowel incontinence, nasogastric tube or other feeding tube, nephrostomy, long-term oxygen treatment, tracheostomy and urinary catheter), the presence of pressure sores, independence in mobility and cognitive decline. The proportion of functional and cognitive domains identified in THIN was calculated by dividing the number of patients with at least one relevant code registered in the medical file from 2000 to 2012 by the number of eligible patients during the study period. This was done in order to identify which functional and cognitive domains were registered frequently enough to be included in the mortality prediction (arbitrarily defined as a threshold of at least 5,000 persons based on preliminary patient frequencies). Once the most frequently registered functional and cognitive domains were identified, these were grouped into functional/cognitive domains, i.e., umbrella terms for a particular aspect of functional/cognitive ability such as mobility. Within a domain, functional and cognitive domains were categorised into two or more levels to allow the identification of patients who are frailer than others (**Figure 1**), thus accounting for severity. For example, a functional/cognitive domain level would be given a value of 0 if it indicated good mobility and 1 if it indicated poor mobility.

For the cohort of elderly persons as well as persons with dementia having a registered functional and cognitive domain, the index date was assigned as the date when subjects had a first registration of a functional/cognitive domain; age and co-morbidities were re-evaluated at this date.

Figure 1: Algorithm of cognitive/functional "domain" construction in THIN.



Statistical analysis

Demographic and clinical characteristics were reported as mean ± standard deviation or median (first-third quartiles range) and frequency (percentage) for continuous and categorical variables, respectively.

The crude mortality rates within one year (per 1,000 person-months) and within one month (per 1,000 person-weeks) after the functional/cognitive domain registration were calculated for all persons ≥65 and those with dementia separately, dividing the number of deaths by the number of person-months or person-weeks at risk respectively, and were multiplied by 1,000.

Multivariable logistic models were fitted to predict one year and one month mortality risk and were applied to: 1) all patients and 2) patient subgroups within each functional/cognitive domain. When considering all patients, the predictive value achieved by a model, which included patient's age and sex only (model 1) was evaluated and compared to the predictive power achieved by a new model additionally including the QOF score (model 2). When considering patients' subgroup, the predictive power of the model which included patient's age, sex and QOF score was compared to that achieved by a new model which further included the functional and cognitive domains (model 3).

The predictive value (i.e. the prognostic ability to distinguish subjects who will develop the death from those who will not) achieved by each model was assessed by computing the area under the Receiver Operating Characteristics (ROC) curve (AUC) (also known as the "c-statistic") along with their 95% confidence interval (95%CI) [27]. Comparisons between the c-statistics estimated from different models were performed following DeLong method[28]. Moreover, improvement in discriminatory ability was further evaluated by the Integrated Discrimination Improvement (IDI) [29]. In comparing the models, the IDI measures the increment in the predicted probabilities for the subset experiencing the event and the decrement for the subset not experiencing the event. It can also be interpreted as the change in R-squared achieved by adding the new covariate to the model (the magnitude of this change depends on the discriminatory ability provided by the model without the covariate). A two-sided p-value <0.05 was considered for statistical significance.

All data management and statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC).

Subgroup and sensitivity analysis

The multivariable logistic models were stratified by gender in order to see whether mortality prediction was differential between males and females. Moreover, in order to evaluate the presence of a potential selective registration of the functional/cognitive domains, mortality rates and Kaplan-Meier curves were estimated within one year of follow-up among persons ≥65 in THIN with and without a functional/cognitive domain registration, irrespective of functional/cognitive domain severity (*post hoc* analyses).

Results

Cohort characteristics

From 2000 to 2012, 1,193,268 subjects aged ≥65 years were identified in THIN. The mean age of this study population was 70.7±6.8 years and 55% were males (**Table 1**). The cohort of elderly people with dementia included 15,300 persons of whom 65% were males, with a mean age of 79.3±6.2 years. The distribution of the QOF co-morbidities was broadly comparable to previously published work (Carey et al., 2013).Within the cohort of persons aged ≥65, the most frequent QOF score (i.e. the mode) was 0 (73%), followed by a QOF score of 1 (10%). Among dementia patients, the QOF score's mode was 3 (62%) followed by a score of 4 (14%). The overall median survival time of the cohort (survival from the cohort entry date until their date of death) was 5.5 years (first-third quartile range: 2.5-9.9), while this was lower in dementia patients, at1.8 years (first-third quartile range: 0.8-3.5)). Among all patients ≥65 years, the crude mortality rate estimated within one year of follow-up was 2.5 per 1,000 person-months (34,337 deaths in 13,657,531 person-months), while the crude mortality rate estimated within one month of follow-up was 0.7 per 1,000 person-weeks (3,166 deaths per 4,757,259 person-weeks). Among dementia patients ≥65, the crude mortality rate within one year was 10.8 per 1,000 person-months (1,656 deaths per 153,340 person-months) while the crude mortality rate within one month was 2.8 per 1000 person-weeks (171 deaths per 60,333 person-weeks).

Table 5: Distribution of co-morbidities among all patients ≥65 and those with dementia specifically in THIN (UK).

	All patients ≥65 years N=1,193,268	Dementia patients ≥65* years N=15,300
	N (%)	N (%)
Age (mean ± standard deviation) (range)	70.7 ± 6.8 (65.0-75.5)	79.3 ± 6.2 (75.3-84.3)
Males	654,388 (54.8)	9,970 (65.2)
Atrial fibrillation	48,068 (4.0)	1,110 (7.3)
Asthma	104,069 (8.7)	1,249 (8.2)
Cancer	72,594 (6.1)	1,352 (8.8)
Congestive heart disease	160,766 (13.5)	2,490 (16.3)
Chronic kidney disease	23,718 (2.0)	1,529 (10.0)
Chronic obstructive pulmonary disease	54,039 (4.5)	825 (5.4)
Dementia	13,906 (1.2)	15,300 (100)
Depression	155,350 (13.0)	3,391 (22.2)
Diabetes mellitus	72,025 (6.0)	1,209 (7.9)
Epilepsy	16,123 (1.4)	425 (2.8)
Heart failure	44,542 (3.7)	832 (5.4)
Hypertension	394,028 (33.0)	5,817 (38.0)
Hypothyroidism	69,542 (5.8)	1,447 (9.5)
Psychosis, schizophrenia, bipolar-affective disorders	12,614 (1.1)	348 (2.3)
Stroke	69,748 (5.8)	1,601 (10.5)
QOF score: 0	875,377 (73.4)	-
QOF score: 1	114,581 (9.6)	-
QOF score: 2	83,390 (7.0)	-
QOF score: 3	83,185 (7.0)	9,525 (62.3)
QOF score: 4	19,775 (1.7)	2,142 (14.0)
QOF score: 5	10,919 (0.9)	1,479 (9.7)
QOF score: 6	3,930 (0.3)	1,404 (9.2)
QOF score: 7	1,379 (0.1)	412 (2.7)
QOF score: ≥8	732 (0.1)	338 (2.2)

*The dementia cohort is composed of the 13,906 subjects (those with a diagnosis of dementia any time prior to the index date of the cohort aged ≥65), in addition to 1,394 subjects with a dementia diagnosis that were not captured in the cohort ≥65 because the dementia diagnosis was registered after their index date.

Functional and cognitive domains

After the functional and cognitive domains found in THIN were defined (**Appendix Table A2**), it was found that mobility (4.6%), accommodation (2.0%) and dressing ability (0.4%) were the most commonly registered, each exceeding a threshold of 5,000 persons with a registration (**Table 2**); therefore only these domains were used to evaluate improvement in model's prognostic ability. The mobility domain was a two-level variable (i.e. 0=good mobility, 1=poor mobility), accommodation was a three-level variable (i.e. 0=lives with relatives or not alone, 1=lives alone in non-institutional accommodation, 2=lives in nursing home or other institutional accommodation), and dressing ability was a two-level variable (i.e. 0=independent, 1=dependent).As shown in **Appendix Table A3**, all of three domains were registered for 217 (0.02%) persons.

Table 6: Most commonly registered functional/cognitive domains in THIN among all patients ≥65.

Domains N (%)	Category	N (%)
Mobility N=55,597 (4.7%)	0=good mobility	3,540 (6.37%)
	1=poor mobility	52,057 (93.63%)
Accommodation N=23,684 (2.0%)	0=lives with relatives or not alone	6,485 (27.38%)
	1=lives alone in non-institutional accommodation	5,714 (24.13%)
	2=lives in nursing home or other institutional accommodation	11,485 (48.49%)
Dressing ability N=5,197 (0.4%)	0=independent	4,747 (91.34%)
	1=dependent	450 (8.66%)

Prediction of one year and one month mortality

Compared to the model based on age and sex only, the inclusion also of the QOF score significantly improved the model's prediction accuracy of 1-year mortality in patients ≥65 with the c-statistic increasing from 0.78 (95%CI: 0.78-0.79) to 0.82 (95%CI: 0.81-0.82) (p-value <0.001) (**Table 3)**. All functional/cognitive domain-related domains statistically improved the discriminatory power of the models in patients >65. Compared to age, sex and QOF score, the greatest improvement in prediction accuracy (in terms of effect size) was found for accommodation, as shown by an increase in c-statistic from 0.71 (95%CI: 0.70-0.72) to 0.76 (95%CI: 0.75-0.77) (p-value <0.001)as well as by a highest IDI, at 0.036 (95%CI: 0.033; 0.039) (p-value <0.001). Among elderly people with dementia, only accommodation statistically improved the model's prediction accuracy of one year mortality albeit modestly, with the c-statistic increasing from 0.63 (95%CI: 0.59-0.67) to 0.64 (95%CI: 0.61-0.68) (p-value= 0.015) and an IDI value of 0.0098 (95%CI: 0.005-0.015) (p-value <0.001). Furthermore, even dressing ability was found to improve prediction accuracy in dementia patients, as highlighted by the relatively high IDI of 0.033 (95%CI: 0.005-0.061) (p-value 0.011), even though this finding was not supported by the improvement in c-statistic, probably due to the low number of patients with a registration for this domain (i.e. 143 patients), the low number of death events (i.e. 28 events) and the subsequent loss of statistical power, as reflected by the wide confidence intervals. Overall, the functional/cognitive domains predicted one month mortality to a lesser extent than one year mortality in the cohort of all persons aged ≥65 (**Table 4**). Only accommodation and mobility improved model's discrimination, increasing

the c-statistic from 0.73 (95%CI: 0.71-0.75) to 0.79 (95%CI: 0.77-0.80) and from 0.65 (95%CI: 0.63-0.66) to 0.66 (95%CI: 0.65-0.67) (p-value <0.001 for both).

The model's prediction accuracy among dementia patients was relatively poor for one month mortality, as suggested by the lack of improvement in model discrimination when the QOF score was added to age and sex as predictors. Accommodation and mobility improved the one month mortality modestly among dementia patients with c-statistics increasing from 0.67 (95%CI: 0.58-0.76) to 0.71 (95%CI: 0.63-0.79) and 0.67 (95%CI: 0.60-0.75) to 0.69 (95%CI: 0.61-0.76) respectively (p-value <0.001 for both). The effect of dressing on the logistic models predicting one month mortality in dementia patients could not be evaluated as there were too few patients with a registration for this domain (i.e., 143 patients) and very low number of events (i.e., 2 events).

There was no major difference between mortality prediction at one year and one month for females and males separately, whether for all persons aged ≥65 or only those with dementia (**Appendix Tables A4 and A5**).

Post hoc analyses aiming to shed light on potential selective registration of functional domains identified showed that having a functional/cognitive domains (irrespective of severity) was associated with higher mortality rates as well as steeper survival plots than not having a functional/cognitive domain at all (**Appendix Table A6 and Appendix Figure A1**). This difference was most pronounced for mobility and accommodation and much less so for dressing.

Table 3: One year mortality risk prediction in a cohort of patients ≥65 in THIN and those with dementia.

Sample	Patient subgroups	Events/ N° subjects (%)	Logistic model	C-statistic (95%CI)	p-value*	IDI (95%CI)	p-value†
≥65 years	All patients	34,337/1,193,268 (2.9)	Age + Sex	0.78 (0.78-0.79)	---	[reference]	---
			Age + Sex + QOF	0.82 (0.81-0.82)	<0.001	0.0151 (0.0145; 0.0158)	<0.001
	Patients with accommodation registration	3,764/23,684 (15.9)	Age + Sex + QOF	0.71 (0.70-0.72)	---	[reference]	---
			Age + Sex + QOF + Accommodation	0.76 (0.75-0.77)	<0.001	0.0360 (0.0333; 0.0387)	<0.001
	Patients with mobility registration	11,069/55,597 (19.9)	Age + Sex + QOF	0.66 (0.65-0.66)	---	[reference]	---
			Age + Sex + QOF + Mobility	0.66 (0.66-0.67)	<0.001	0.0034 (0.0030; 0.0039)	<0.001
	Patients with dressing registration	379/5,197 (7.3)	Age + Sex + QOF	0.70 (0.67-0.72)	---	[reference]	---
			Age + Sex + QOF + Dressing	0.72 (0.70-0.75)	<0.001	0.0207 (0.0138; 0.0276)	<0.001
≥65 years with dementia	All patients	1,656/15,300 (10.8)	Age + Sex	0.66 (0.64-0.67)	---	[reference]	---
			Age + Sex + QOF	0.66 (0.65-0.69)	<0.001	0.0052 (0.0037; 0.0068)	<0.001
	Patients with accommodation registration	286/1,174 (24.4)	Age + Sex + QOF	0.63 (0.59-0.67)	---	[reference]	---
			Age + Sex + QOF + Accommodation	0.64 (0.61-0.68)	0.015	0.0098 (0.0051; 0.0146)	<0.001
	Patients with mobility registration	348/1,497 (23.2)	Age + Sex + QOF	0.59 (0.55-0.62)	---	[reference]	---
			Age + Sex + QOF + Mobility	0.59 (0.55-0.62)	0.592	0.0015 (-.00003; 0.0033)	0.051
	Patients with dressing registration	28/143 (19.6)	Age + Sex + QOF	0.62 (0.51-0.73)	---	[reference]	---
			Age + Sex + QOF + Dressing	0.69 (0.58-0.80)	0.134	0.0333 (0.0047; 0.0618)	0.011

*p-value from DeLong test for difference between the two c-statistics; † p-value from test that IDI is not significantly different than zero.

Abbreviations: CI: confidence interval; IDI: Integrated Discrimination Improvement; QOF- quality outcomes framework score

Table 4: One month mortality prediction in a cohort of patients ≥65 in THIN and those with dementia.

Sample	Patient subgroups	Events/ N° subjects (%)	Logistic model	C-statistic (95%CI)	p-value*	IDI (95%CI)	p-value†
≥65 years	All patients	3,166/1,193,268 (0.3)	Age + Sex	0.78 (0.78-0.79)	---	[reference]	---
			Age + Sex + QOF	0.83 (0.82-0.83)	<0.001	0.0028 (0.0025; 0.0031)	<0.001
	Patients with accommodation registration	503/23,684 (2.1)	Age + Sex + QOF	0.73 (0.71-0.75)	---	[reference]	---
			Age + Sex + QOF + Accommodation	0.79 (0.77-0.80)	<0.001	0.0091 (0.0078; 0.0103)	<0.001
	Patients with mobility registration	1,903/55,597 (3.4)	Age + Sex + QOF	0.65 (0.63-0.66)	---	[reference]	---
			Age + Sex + QOF + Mobility	0.66 (0.65-0.67)	<0.001	0.0015 (0.0013; 0.0017)	<0.001
	Patients with dressing registration	20/5,197(0.4)	Age + Sex + QOF	0.77 (0.65-0.89)	---	[reference]	---
			Age + Sex + QOF + Dressing	0.80 (0.68-0.92)	0.368	0.0139 (0.0005; 0.0273)	0.021
≥65 years with dementia	All patients	171/15,300 (1.1)	Age + Sex	0.65 (0.60-0.69)	---	[reference]	---
			Age + Sex + QOF	0.67 (0.63-0.72)	0.027	0.0015 (0.0004; 0.0027)	0.004
	Patients with accommodation registration	36/1,174(3.1)	Age + Sex + QOF	0.67 (0.58-0.76)	---	[reference]	---
			Age + Sex + QOF + Accommodation	0.71 (0.63-0.79)	<0.001	0.0052 (0.0037; 0.0066)	<0.001
	Patients with mobility registration	50/1,497(3.3)	Age + Sex + QOF	0.67 (0.60-0.75)	---	[reference]	---
			Age + Sex + QOF + Mobility	0.69 (0.61-0.76)	<0.001	0.0021 (0.0015; 0.0027)	<0.001

*p-value from DeLong test for difference between the two c-statistics; †p-value from test that IDI is not significantly different than zero.

Abbreviations: CI: confidence interval; IDI: Integrated Discrimination Improvement; QOF- quality outcomes framework score

Discussion

Clinical implications

The main finding from this study is that information on functional domains found in a large primary care database improves the prediction of one year, and to a lesser extent one month, mortality in elderly patients, when included in a model in addition to age, sex and co-morbidity (QOF) score. This finding suggests that electronic healthcare databases such as THIN have currently unused potential to provide a more global assessment of geriatric health status compared to the standard diagnostic and prescription data that is usually used in pharmacoepidemiology studies as well as addressing residual confounding especially when exploring the risk of death in older persons.

Accommodation was the best predictor of one year mortality among elderly persons and those with dementia. This is because persons who live relatively independently or have social support are likely to be healthier overall than those who are institutionalised [30]. Cognition, a domain with great potential for the identification of frailty, in particular in persons with dementia, was very poorly registered and as a result could not be used to predict mortality. Overall among elderly persons with dementia, the functional domains were much less powerful in predicting mortality compared to elderly persons irrespective of dementia. This is because a population with heterogeneous traits is a pre-requisite for the prediction analysis requires, whereas the presence of dementia diagnosis could inadvertently lead to the selection of a population with similarly high health risks. As a result, future pharmacoepidemiologic research restricting similar analyses solely to persons with dementia may be counter-productive.

As expected, the number of deaths was substantially reduced when considering a time window of one month. As a result, no reliable conclusions can be drawn regarding one-month mortality due to the significant loss of statistical power. One-month mortality could only have been estimated if functional/cognitive domains had been systematically registered. Nevertheless, accommodation and mobility were found to be positively predictive of one-month mortality in older persons, suggesting that some functional domains may be used to predict mortality in older persons even at one month. Educational interventions to promote the systematic assessment and registration of functional variables for elderly persons by GPs could improve the identification of the frail patients. This in turn could inform clinicians on which category of patients requires more cautious pharmacological management, thus optimizing the quality of care in clinical practice on a large scale. There are currently existing databases that contain systematically registered frailty data. An example is the Arianna database, a GP database in Caserta (Campagna region, Italy) where data on functional status (using the Barthel scale or Barthel index), mobility, accommodation, comprehension of language, hearing and visual impairment and mental health (using the Short Portable Mental Status Questionnaire- SPMSQ) is registered systematically for roughly 75% of persons aged 65 and over under the care of GPs [31]. Another example is the systematic registration of results of the SPMSQ, the Barthel index and the Exton-Smith pressure sore scale, as well as nursing care requirements and social network support for all older persons requesting nursing home admission or home care from the national health system in Padova (Veneto region, Italy). This data is available in the Administrative Repository Database of the ULSS 16 in Padova [26].

Implications for future research

The operational definition of frailty in pharmacoepidemiologic studies poses a challenge: on one hand the comprehensive evaluation of several functional and cognitive domains using healthcare databases and their compilation into a frailty index may be a holy grail in observational research. It would provide valuable information on an important source of unmeasured confounding [20]. The present study however, shows that despite extensive data mining in one of the largest and most widely used European healthcare databases, there was a low number of registered functional and cognitive items which could be further explored. This may be an important caveat for the feasibility of future research aiming to build a frailty index using electronic healthcare record databases. Nevertheless, the association between mortality and the functional domains identified, in particular accommodation, mobility and dressing, suggests that these domains may be used to partly account for some unmeasured confounding in pharmacoepidemiologic studies carried out in THIN. Where such functional domains are not available, age, sex and the QOF score also predicted one month and one year mortality, although often to a lesser degree than when functional domains were included.

The inclusion of functional domains in epidemiologic analysis using healthcare databases may prompt concern on the potential selective registration of data for persons at greater risk of death compared to persons with no such registration. Indeed, the selective registration of such data was confirmed by *post hoc* analyses investigating the mortality rate per 1,000 person months as well as the survival curves over 12 months in persons $\geq$65. This difference was most pronounced for mobility and accommodation and much less so for dressing and may limit the generalizability of these results in particular. These *post hoc* analyses in the general population along with the main findings on the predictive value of the functional domains, accounting for severity, among persons having a functional domain provide suggestions on the role that functional domains may have in pharmacoepidemiologic studies using THIN. In the general population, the benefit of accounting for the severity of functional status must be weighed against the probable selective registration of functional domains: there is a higher risk of death for persons with a functional domain registered, irrespective of the *severity* of functional/cognitive status, as compared to persons without a functional domain. In the general population, the presence of a functional domain itself may be informative as a risk factor for death, irrespective of severity (e.g., person with a registered domain indicating independence in mobility has a higher risk of death than a person without such a domain registered). On the other hand, the value of the functional domains, in particular the value of data on the severity of functional status, has been shown in the present study despite their probable selective registration. Persons with a better functional status are indeed at a higher risk of death compared to those with a worse functional status. Future work aiming to account for severity of functional status as defined in the present study may have to restrict their study population to persons with a functional domain to avoid introducing bias due to selective registration. Where functional domains such as those identified in the present study are not available, proxies might include healthcare claims for medical apparatus (e.g. wheelchairs or other mobility-related apparatus, stoma apparatus etc.) or frequency of hospitalisation.

Strengths and limitations

A primary strength of this study is its novelty in mining a large primary care database containing 11 million persons for functional and cognitive domains and the evaluation of these indicators as predictors of mortality. The use of co-morbidities and functional domains that relate to impaired

functionality such as accommodation and independence/independence in dressing/mobility (both considered activities of daily living indicative of disability) is consistent with the cumulative deficit model of frailty [22]. Given the close link between accommodation status (e.g., a nursing home resident), disability (based on independence or otherwise in the two activities of daily living evaluated) and frailty, we consider the choice of these functional domains to be justified as proxies of frailty. Indeed, these domains were shown to be clinically meaningful as components of a frailty score in predicting mortality in previous work from which the functional domains in the present study were derived [25,26,32].The results of the present study provide valuable information on a potential point of improvement in GP practice, that is, the evaluation and registration of functional domains in the elderly. An additional strength is the use of the QOF score as a reference model when comparing the performance of the functional and cognitive domains, since the QOF score has been recently used and validated in a cohort of elderly persons identified in THIN, and found to predict mortality better than the Charlson co-morbidity score. The gender-stratified sensitivity analyses added a further detail on the value of functional and cognitive domains in THIN, showing that there is no major difference between mortality prediction between male and female patients. The present study also investigated the value of data on the severity of functional status in view of potential selective registration in the prediction of mortality.

However, this study also has some limitations. The predictive accuracy of the logistic models used was contingent on the frequency of functional domain codes registered in the database, which was found to be generally low. While a higher registration would have improved the discrimination of the models, the present study highlights that mortality can be better predicted in the elderly even using limited data on functional domains, in addition to models based on age, sex and QOF score. The QOF score did not improve mortality prediction as significantly in elderly persons with dementia, suggesting that health-related factors other than the QOF co-morbidities played a role in the mortality risk among these patients. In fact, the inclusion of accommodation in the logistic models predicting one year and one month mortality in persons with dementia improved the prediction of mortality (compared to the model including age, sex and QOF score) more than the inclusion of the QOF score (compared to the model including only age and sex).

Conclusion

Despite the low registration of functionality domains in THIN, their inclusion in logistic models along with age, sex and co-morbidities improved the prediction of mortality in elderly patients, and to a lesser degree, persons with dementia. Such indicators may be of value in accounting for some unmeasured confounding in pharmacoepidemiologic analysis, particularly in safety studies in the elderly.

Compliance with ethical standards

Conflict of Interest: The authors declare that they have no conflict of interest.

Research involving Human Participants and/or Animals: The present study did not involve direct contact with human participants since all the data analysed was collected retrospectively during routine clinical practice. All patient-level data used was anonymized.

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Appendix

Table A1: Read codes used in the identification of QOF co-morbidities.

Disease	Read code
Asthma	H33..% (excluding H333., H33z1)
Atrial fibrillation	G573.% (excluding G5731)
Cancer(excluding non-melanotic skin cancers)	B0... - B32z., B34.. -B6z0., Byu.. - Byu41,Byu5. - ByuE0
Chronic kidney disease(stages 3-5)	1Z12. – 1Z16., 1Z1B. – 1Z1L.
Chronic obstructive pulmonary disease	H3..., H31..% (excluding H3101, H31y0, H3122), H32..%, H36.. - H3z..
Coronary heart disease	G3... - G330z, G33z. - G3401, G342. - G366., G38.. – G3z.., Gyu3.%
Dementia	Eu02.%, E00..%, Eu01.%, E02y1, E012.%, Eu00.%, E041., Eu041, F110. – F112., F116.
Depression	E0013, E0021, E112.%, E113.%, E118., E11y2. E11z2, E130., E135. E2003, E291., E2B.., E2B1., Eu204, Eu251, Eu32.%, Eu33.%, Eu341, Eu412
Diabetes	C10E.%, C10F.% (excluding C10F8)
Epilepsy	F1321, F25..% (excluding F2504, F2511, F2516, F256.%, F258. – F25A.), SC200
Heart failure	585f., 585g., 662f. – 662i., G58..%, G581.%,G1yz1, G5yy9, G5yyA
Hypertension	G2..., G20..%, G24.. - G2z.. (excludingG24z1)
Hypothyroidism	C03..%, C04..%
Psychosis, schizophrenia, bipolar disorders	E10..%, E110.%,E111.%, E1124, E1134,E114. – E117z, E11y.% (excluding E11y2), E11z., E11z0, E11zz, E12..%, E13..% (excluding E135.), E2122, Eu2..%, Eu30.%, Eu31.%, Eu323, Eu328, Eu333
Stroke or transient ischaemic attack	F4236, G61..% (excluding G617.), G63y0 - G63y1, G64..%, G65..- G654., G656.- G65zz, G66..%, G6760, G6W.., G6X.., Gyu62 – Gyu66, Gyu6F, Gyu6G

Table A2: Functional/cognitive domain with score assigned with the individual Read codes used.

Domain	Score	Score meaning	Read Code	Read Code description
Accommodation	0	Lives with relatives or not alone	13F1.00	Independent housing, not alone
			13FH.00	Lives with relatives
	1	Lives alone in non-institutional accommodation	13FJ.00	Independent housing, lives alone
			13F3.00	Lives alone -no help available
			13F3100	Lives alone needs housekeeper
			13FC.11	Lives in a bedsit
			13F9.11	Living in sheltered accommodation
			13Fa.00	Lives in non-institutional accommodation
			13F2.00	Lives alone - help available
	2	Lives in nursing home or other institutional accommodation	13F7100	Lives in a welfare home
			13FV.00	Lives in a welfare home
			13F4.11	Lives in warden controlled accommodation
			13F6100	Lives in a nursing home
			13FK.00	Lives in a residential home
			13F7200	Lives in an old people's home
			13FT.00	Lives in an old people's home
			13FX.00	Lives in care home
			13F6.00	Nursing/other home
			13F7.00	Residential institution
Dressing ability	0	Independent	Z8A6.00	Ability to dress
			Z8A..00	Ability to perform dressing activity
			ZM51.00	Ability to take care of clothes
			Z8A6100	Able to dress
			Z8A1.00	Able to perform dressing activity
			Z8A7100	Able to undress
			Z8A8311	Adjusts clothing
			Z8A6300	Does dress
			395..00	Dressing ability
			3952.00	Independent with dressing

	1	Dependent	3950.00	Dependent for dressing
			Z8A8500	Difficulty adjusting clothing
			Z8A6500	Difficulty dressing
			Z8A5.00	Difficulty performing dressing activity
			Z8A6400	Does not dress
			Z8A4.00	Does not perform dressing activity
			3951.00	Needs help with dressing
			173F.00	Short of breath dressing/undressing
			Z8A6200	Unable to dress
			Z8A2.00	Unable to perform dressing activity
Mobility	0	Independent	ZO9..00	Ability to mobilise using mobility aids
			ZO96.00	Ability to mobilise using wheelchair
			ZO91.00	Able to mobilise using mobility aids
			ZO96100	Able to mobilise using wheelchair
			ZO96300	Does mobilise using wheelchair
			3981.00	Independent in wheelchair
			3992.00	Independent on stairs
			3983.00	Independent walking
			3963.00	Independent: chair/bed transf.
			3982.00	Minimal help in wheelchair
			ZO93.11	Mobilises using mobility aids
			ZO96311	Mobilises using wheelchair
			13CZ.00	Mobility NOS
			13CG.00	Mobility fair
			8F75.00	Use of indoor mobility aids
			Z6R3.00	Wheelchair dancing therapy
			ZO96.11	Wheelchair mobility
			Z6R8100	Wheelchair sport
			398E.00	Does walk
			39B1.00	Stick only for walking
			ZOA6.00	Ability to manage stairs

			ZOA..00	Ability to manage steps and stairs
			ZOB2.00	Ability to use stair lift
			ZOA6611	Able to climb stairs
			ZOA6100	Able to manage stairs
			ZOA1.00	Able to manage steps and stairs
			ZOB2100	Able to use stair lift
			ZOA7B00	Able to walk down step
			ZOA6600	Able to walk up stairs
			ZOA7600	Able to walk up step
			ZOA6300	Does manage stairs
			ZOA6R00	Does manage stairs backwards
			ZOA6M00	Does manage stairs on bottom
			ZOA3.00	Does manage steps and stairs
			ZOB2300	Does use stair lift
			ZOA6C00	Does walk down stairs
			ZOA7D00	Does walk down step
			ZOA6700	Does walk up stairs
			ZOA7800	Does walk up step
			ZOA6311	Manages stairs
			ZOA3.11	Manages steps and stairs
			399..00	Stairs - ability
			ZOB2311	Uses stair lift
			ZOA6712	Walks up stairs
			ZOA7811	Walks up step
	1	Dependent	398A.00	Dependent on helper pushing wheelchair
			16ZB300	Dependent on others
			3960.00	Dependent: chair/bed transfer
			ZO95.00	Difficulty mobilising using mobility aids
			ZO96500	Difficulty mobilising using wheelchair
			3993.00	Difficulty walking up stairs
			ZO94.00	Does not mobilise using mobility aids

			ZO96400	Does not mobilise using wheelchair
			13CC.00	Immobile
			3980.00	Immobile
			N233100	Immobility syndrome
			13CP.00	Impaired mobility
			ZO51.00	Impaired mobility
			13CE.00	Mobility poor
			13CD.00	Mobility very poor
			ZO7T.11	Moves around supporting self on furniture
			ZO92.00	Unable to mobilise using mobility aids
			ZO96200	Unable to mobilise using wheelchair
			R00A.00	[D] Poor mobility
			R00C.00	[D]Immobility
			ZV4L011	[V] Poor mobility
			ZV4L300	[V]Need for assistance due to reduced mobility
			ZV4L000	[V]Reduced mobility
			Ryu3200	[X]Other and unspecified abnormalities of gait and mobility
			13C6.00	Bed-ridden
			13C6.11	Bedbound
			398D.00	Transfers using hoist
			13CA.00	Housebound
			663x.00	Asthma limits walking on the flat
			398B.00	Deterioration in ability to walk
			N097.00	Difficulty in walking
			N097z00	Difficulty in walking NOS
			N097300	Walking difficulty due to ankle and foot
			N097200	Walking difficulty due to lower leg
			N097400	Walking difficulty due to other specified site
			N097100	Walking difficulty due to pelvic region and thigh
			N097000	Walking difficulty due to unspecified site
			185..11	Walking distance reduced

			Z6A2.00	Walking with patient - mobilisation
			Ryu3100	[X]Difficulty in walking, not elsewhere classified
			663w.00	Asthma limits walking up hills or stairs
			ZOA6911	Difficulty climbing stairs
			ZOA6500	Difficulty managing stairs
			ZOA6J00	Difficulty managing stairs on all fours
			ZOA7500	Difficulty managing steps
			ZOA5.00	Difficulty managing steps and stairs
			ZOB2500	Difficulty using stair lift
			ZOA6E00	Difficulty walking down stairs
			ZOA7F00	Difficulty walking down step
			ZOA6900	Difficulty walking up stairs
			ZOA7A00	Difficulty walking up step
			ZOA6400	Does not manage stairs
			ZOA4.00	Does not manage steps and stairs
			ZOB2400	Does not use stair lift
			ZOA6D00	Does not walk down stairs
			ZOA6800	Does not walk up stairs
			3991.00	Needs help on stairs
			3990.00	Unable to climb stairs
			ZOA6200	Unable to manage stairs
			ZOA7200	Unable to manage steps
			ZOA2.00	Unable to manage steps and stairs
			ZOB2200	Unable to use stair lift
			ZOA6B00	Unable to walk down stairs
			ZOA7C00	Unable to walk down step
			ZOA7700	Unable to walk up step

Table A3: Number of patients ≥65 with codes for more than one functional/cognitive domain registered and the number of deaths observed at one year and one month.

Functional/cognitive domain	**N** (%)	**N. deaths at one year (%)**	**N. deaths at one month (%)**
Accommodation and mobility	4,891 (0.41)	1,264 (25.8%)	206 (4.2%)
Accommodation and dressing	547 (0.05)	87 (15.9%)	4 (0.7%)
Mobility and dressing	1,139 (0.10)	160 (14.1%)	20 (1.8%)
Accommodation, mobility and dressing	217 (0.02)	40 (18.4%)	5 (2.3%)

Table A4: One year mortality risk prediction in a cohort of male patients ≥65 in THIN and those with dementia.

Sample	Patient subgroups	Events/ N° subjects (%)	Logistic model	C-statistic (95%CI)	p-value*	IDI (95%CI)	p-value#
≥65 years	All patients	18608/654388 (2.8)	Age	0.80 (0.80-0.81)	---	[reference]	---
			Age + QOF	0.83 (0.82-0.83)	<0.001	0.0129 (0.0121; 0.0138)	<0.001
	Patients with accommodation registration	2341/15284 (15.3)	Age + QOF	0.71 (0.70-0.72)	---	[reference]	---
			Age + QOF + Accommodation	0.75 (0.74-0.76)	<0.001	0.0268 (0.0240; 0.0297)	<0.001
	Patients with mobility registration	6129/35353 (17.3)	Age + QOF	0.65 (0.64-0.65)	---	[reference]	---
			Age + QOF + Mobility	0.65 (0.65-0.66)	<0.001	0.0032 (0.0027; 0.0037)	<0.001
	Patients with dressing registration	194/3053 (6.4)	Age + QOF	0.70 (0.67-0.74)	---	[reference]	---
			Age + QOF + Dressing	0.74 (0.70-0.77)	0.003	0.0269 (0.0164; 0.0373)	<0.001
≥65 years with dementia	All patients	1003/9970 (10.1)	Age	0.67 (0.65-0.69)	---	[reference]	---
			Age + QOF	0.68 (0.66-0.69)	0.327	0.0044 (0.0026 ; 0.0063)	<0.001
	Patients with accommodation registration	189/852 (22.2)	Age + QOF	0.62 (0.57-0.66)	---	[reference]	---
			Age + QOF + Accommodation	0.63 (0.59-0.67)	0.051	0.0063 (0.0022; 0.0104)	0.001
	Patients with mobility registration	216/1008 (21.4)	Age + QOF	0.58 (0.53-0.62)	---	[reference]	---
			Age + QOF + Mobility	0.59 (0.54-0.63)	0.116	0.0036 (0.0008; 0.0064)	0.006
	Patients with dressing registration	21/96 (21.9)	Age + QOF	0.58 (0.44-0.71)	---	[reference]	---
			Age + QOF + Dressing	0.63 (0.49-0.77)	0.414	0.0254 (-0.0067; 0.0576)	0.061

*p-value from DeLong test for difference between the two c-statistics; #p-value from test that IDI is not significantly different than zero.

Abbreviations: CI: confidence interval; IDI: Integrated Discrimination Improvement; QOF- quality outcomes framework score

Table A5: One year mortality risk prediction in a cohort of female patients ≥65 in THIN and those with dementia

Sample	Patient subgroups	Events/ N° subjects (%)	Logistic model	C-statistic (95%CI)	p-value*	IDI (95%CI)	p-value#
≥65 years	All patients	15,729/538,880 (2.9)	Age	0.76 (0.75-0.76)	---	[reference]	---
			Age + QOF	0.80 (0.80-0.81)	<0.001	0.0181 (0.0171; 0.0192)	<0.001
	Patients with accommodation registration	1,423/8,400 (16.9)	Age + QOF	0.72 (0.70-0.73)	---	[reference]	---
			Age + QOF + Accommodation	0.77 (0.76-0.79)	<0.001	0.0503 (0.0450; 0.0556)	<0.001
	Patients with mobility registration	4,940/20,244 (24.4)	Age + QOF	0.65 (0.64-0.66)	---	[reference]	---
			Age + QOF + Mobility	0.65 (0.65-0.66)	<0.001	0.0038 (0.0030; 0.0045)	<0.001
	Patients with dressing registration	185/2,144 (8.6)	Age + QOF	0.69 (0.65-0.73)	---	[reference]	---
			Age + QOF + Dressing	0.71 (0.67-0.75)	0.022	0.0155 (0.0065; 0.0245)	<0.001
≥65 years with dementia	All patients	653/5,300(12.3)	Age	0.63 (0.61-0.65)	---	[reference]	---
			Age + QOF	0.65 (0.63-0.67)	0.002	0.0078 (0.0048; 0.0109)	<0.001
	Patients with accommodation registration	97/322 (30.1)	Age + QOF	0.64 (0.58-0.71)	---	[reference]	---
			Age + QOF + Accommodation	0.66 (0.60-0.73)	0.219	0.0212 (0.0070; 0.0353)	0.002
	Patients with mobility registration	132/489 (27.0)	Age + QOF	0.57 (0.51-0.63)	---	[reference]	---
			Age + QOF + Mobility	0.57 (0.51-0.63)	0.593	0.0000 (-0.0002; 0.0001)	0.512
	Patients with dressing registration	7/47 (14.9)	Age + QOF	0.76 (0.58-0.94)	---	[reference]	---
			Age + QOF + Dressing	0.79 (0.59-0.98)	0.677	0.0353 (-0.0177; 0.0882)	0.096

*p-value from DeLong test for difference between the two c-statistics; #p-value from test that IDI is not significantly different than zero.

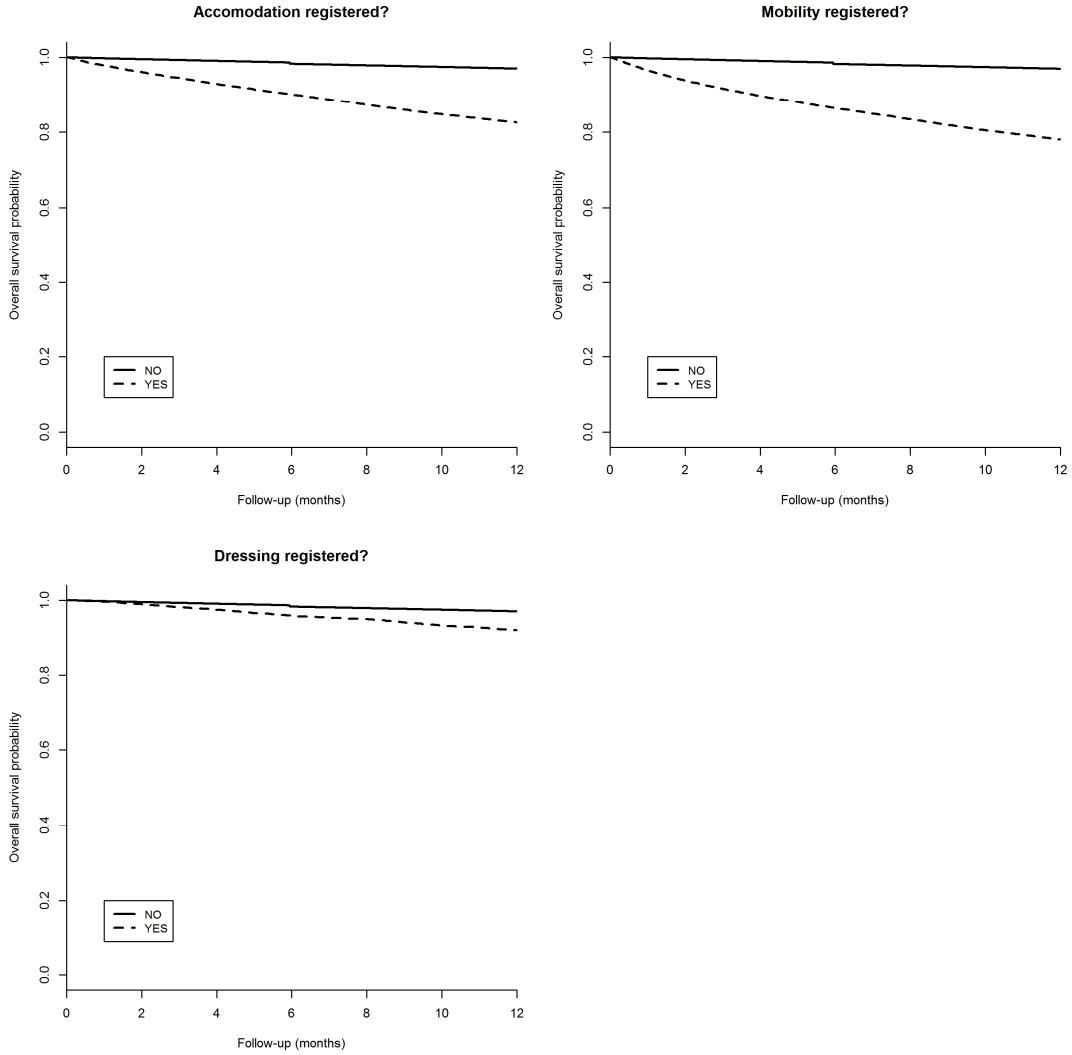
Abbreviations: CI: confidence interval; IDI: Integrated Discrimination Improvement; QOF- quality outcomes framework score

Table A6: Mortality rates within one year of follow-up among persons ≥65 in THIN with and without a functional/cognitive domain registration, irrespective of severity

		Events	Subjects	Person-months	Mortality rate*
Accommodation registered?	No	34,021	1,169,584	13,376,051	2.5
	Yes	3,764	23,684	232,880	16.2
Dressing registered?	No	34,325	1,188,071	13,595,304	2.5
	Yes	379	5,197	54,623	6.9
Mobility registered?	No	33,621	1,137,671	12,995,576	2.6
	Yes	11,069	55,597	517,486	21.4

*Events per 1,000 person-months

Figure A1: Kaplan Meier curves plotting survival in persons aged ≥ 65 who had a functional/cognitive domain and those who did not have a functional/cognitive domain registered, irrespective of severity.



4.2. Drug safety warnings: a message in a bottle? Janet Sultana[1], Gianluca Trifirò[1]. J Drug Des Res 1(1): 1004.

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Introduction

Before being launched on the market, the randomised clinical trials (RCTs) that investigate drug efficacy also investigate the safety profile of therapeutic drugs. Since RCTs are often conducted in populations which are not strictly representative of the population which will actually use them and because the study population size and the follow-upin an RCT is usually limited, the spectrum and frequency of adverse drug reactions (ADRs) detected is however very limited. As a result, it is possible that the true nature and frequency of potential ADRs may only emerge after large numbers of people are exposed to drugs in the real world of clinical practice. After being identified, any new findings on drug safety must be effectively communicated to prescribers and patients with the aim of minimising the risk associated with drug use. Often this is done through black-box warnings or “Dear Doctor” letters.

The impact of safety warnings on antipsychotic use in dementia

The complexity of risk communication in the context of drug safety is illustrated by the case of antipsychotic drug use in elderly persons with dementia. As early as October 2002, Jannsen-Ortho advised Canadian prescribers that the use of risperidone was associated with an increased risk of stroke in dementia patients. A few years later, in March 2004, the European Medicines Agency (EMA) warned prescribers about the risk of cerebrovascular events with olanzapine use in dementia and in the same month, the UK Committee on Safety of Medicines (CSM) issued a similar warning related to risperidone and olanzapine use in elderly patients with dementia. These warnings triggered a series of observational safety studies and other warnings around the world. Attention was later shifted from olanzapine and risperidone to all atypical antipsychotics, and finally, to any antipsychotic, including conventional antipsychotic use in dementia patients.

Evaluating the impact of safety warnings on drug prescribing pattern is of great importance because it is the most basic measure of whether a warning has been successful in reaching a target population and of modifying prescribers’ behaviors. Such investigations have been carried out in the context of the antipsychotic warnings and these highlight the different ways in which safety warnings change prescribing practices or otherwise. As one would expect, a common finding among these studies is that warnings targeting the use of specific antipsychotics, such as those related to olanzapine and risperidone, reduced the prescription of specific target drugs but much less the overall prescribing of antipsychotics in dementia patients. However, the findings reported in these studies suggest that targeting the use of specific drugs in safety warnings comes with a caveat. The initial warnings concerning olanzapine and risperidone use in dementia specifically and successfully having an impact on these two antipsychotics resulted in a paradoxical and significant increase of a similar drug that had been recently marketed, quetiapine, to fill a void in the prescribing inventory. Similarly, several observational studies have reported a general increase in the prescription of conventional antipsychotic drugs in dementia patients that coincided with the warnings on the use of atypical antipsychotics in this population. This is significant because later safety warnings about the risk of stroke and all-cause mortality were extended to all atypical antipsychotic use, including quetiapine as

well as the entire class of conventional antipsychotics. It can be argued that the reduction of olanzapine and risperidone use and the ensuing reduction in health risk were at least partly, and possibly significantly, offset by the increased use of conventional antipsychotics, which may be poorly tolerated especially in elderly patients compared to atypical antipsychotics, thus making the initial warnings counterproductive in this sense.

Do safety warnings lead to risk minimisation?

Drug utilization studies aiming to evaluate the impact of drug warnings on antipsychotic prescribing have undoubtedly shed light on how such warnings impact antipsychotic use. However, it is important to note that the final objective of the safety warnings is not directly to reduce the use of a drug but to minimise the *risk* associated with drug use (**Figure 1**). On one hand, it can be argued that a reduction in the use of a drug may be correlated with a reduction in drug-associated risk. On the other hand, it is possible that the prevalence of drug use after a warning does not appear to change significantly in absolute numbers, but that the nature of the population to which the drugs are prescribed as well the daily dosage and treatment duration change in a way which translates into a reduced drug-related risk. For example in the case of antipsychotic prescribing in dementia, it would be possible antipsychotics to be used more selectively in a population with a lower risk of cardio-cerebrovascular adverse events, resulting in an effective risk minimising effect of the warning. This impact of safety warnings is however not quantifiable using drug utilization studies alone. The challenge of the impact of health policy interventions has lead the Food and Drug Administration (FDA) to launch an initiative, in the context of the Mini-Sentinel project, aiming to describe research approaches used to assess outcomes related to FDA regulatory actions and to recommend the most suitable research methods to evaluate such regulatory outcomes.

There is increasing acknowledgement that it is of paramount important to evaluate potential risk minimization after a safety warning is issued. Without such an evaluation of risk reduction, the real and intended impact of the warnings on the safe use of drugs in patients remains unknown. Until such an impact is identified and measured, it is not known whether drug safety warnings are just messages in a bottle.

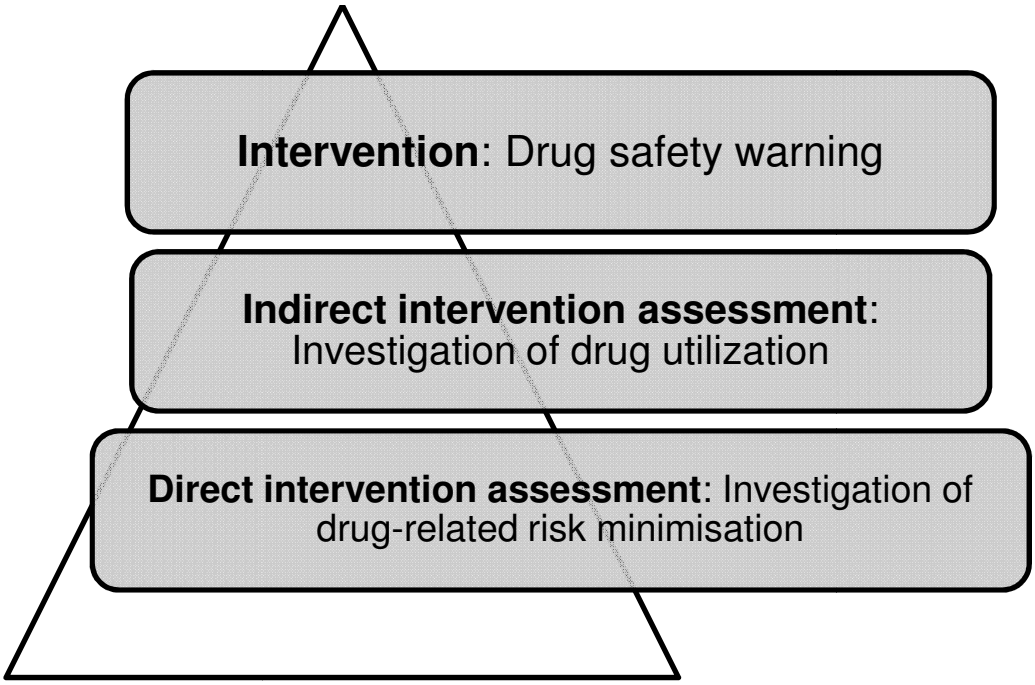

Figure 2: The drug risk minimization process, starting with the issuing of an intervention (drug safety warning) followed by the assessment of the warning effect indirectly (e.g., drug utilisation studies) or directly (e.g., observational studies investigating the risk of an outcome before and after an intervention).

5. Conclusions

The reviews presented herein show that antipsychotic use in dementia is associated with several adverse outcomes such as all-cause mortality, stroke, pneumonia, venous thromboembolism and hip-fracture. The observational studies considered have several advantages such as the large and often nationally representative patient samples available, which reflect clinical practice. On the other hand such studies may be limited by several biases and are subject to confounding if not well-designed, in addition to residual confounding which cannot be accounted for. Findings from each study must be evaluated based on the merits of the methods employed.

Antipsychotic use in dementia is on the increase in Europe, in particular in Italy. The warnings in the UK seem to have been effective in particular when several entities including MHRA but also the Alzheimer's Society UK and the All Parliamentary Group on Dementia launched their awareness campaigns. On the other hand, a less intensive and more seemingly bureaucratic approach such as that used in Italy did not appear to lead to a decrease in the use of antipsychotics in dementia. Antipsychotic use in the Netherlands appeared to be relatively lower compared to the UK and Italy as well as being in line with national guidance issued.

It should be noted that the drug utilisation studies in question are limited in the sense that it is the use of antipsychotics in dementia that is being described; it was not possible to evaluate whether such use was specifically for BPSD, as diagnoses of the symptoms for which antipsychotics would be used, such as aggression, are not routinely available. Notwithstanding, the fact that to date, according to the summary of product characteristics only risperidone is licensed for the short-term management of aggression in dementia and the fact that all identified populations in the drug utilization studies had a diagnoses of dementia, suggests that the studies carried out in THIN, HSD and IPCI address an important information gap in the description of potentially inappropriate antipsychotic use in this population.

With regards to future antipsychotic safety studies, these should try to account for frailty as a confounder or effect modifier as well as accounting for public health interventions that may modify the pattern of drug use and the associated drug-related risks, giving risk to a "calendar year effect".