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SUMMARY

Multi-centre, multi-database studies with common protocols: lessons learnt from the IMI PROTECT project

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ABSTRACT

Purpose To assess the impact of a variety of methodological parameters on the association between six drug classes and five key adverse events in multiple databases.

Methods The selection of Drug–Adverse Event pairs was based on public health impact, regulatory relevance, and the possibility to study a broad range of methodological issues. Common protocols and data analytical specifications were jointly developed and independently and blindly executed in different databases in Europe with replications in the same and different databases.

Results The association between antibiotics and acute liver injury, benzodiazepines and hip fracture, antidepressants and hip fracture, inhaled long-acting beta2-agonists and acute myocardial infarction was consistent in direction across multiple designs, databases and methods to control for confounding. Some variation in magnitude of the associations was observed depending on design, exposure and outcome definitions, but none of the differences were statistically significant. The association between anti-epileptics and suicidality was inconsistent across the UK CPRD, Danish National registries and the French PGRx system. Calcium channel blockers were not associated with the risk of cancer in the UK CPRD, and this was consistent across different classes of calcium channel blockers, cumulative durations of use up to >10 years and different types of cancer.

Conclusions A network for observational drug effect studies allowing the execution of common protocols in multiple databases was created. Increased consistency of findings across multiple designs and databases in different countries will increase confidence in findings from observational drug research and benefit/risk assessment of medicines. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—pharmacoepidemiology (PE); Innovative Medicines Initiative; PROTECT; observational studies; methodology; electronic healthcare databases; European Medicines Agency; pharmacoepidemiology

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As part of its work program, the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium (PROTECT) project investigated the association between six drug classes and five key adverse events (AEs) in several European or US electronic health record (EHR) databases. The purpose of this investigation was to assess the impact of a variety of methodological parameters such as study design, definition of study population, exposure and outcome definitions and methods to control for confounding on the associations of interest. The aim of this discussion paper is to summarize the main lessons learned from the PROTECT project with regard to practical, operational and scientific issues. The selection of Drug–Adverse Event pairs was based on public health impact, regulatory relevance and the possibility to study a broad range of methodological issues.[1] Important features of the approach included the joint development of common study protocols and data specifications (including statistical analysis plans), the independent conduct of the study in the individual databases by different research teams and the independent replication of the initial studies in the same databases as well as in different databases. After agreement of a common protocol for each Drug–AE pair, research teams were blinded as to each other's results.

The common study protocols and data specifications were implemented locally by each database partner, unlike similar initiatives (e.g. OMOP, Sentinel, EU-ADR) which developed Common Data Models.[2–4] Operational definitions of exposures, outcomes and confounders were harmonized and only varied if an available database had additional variables (e.g. socioeconomic or lifestyle factors). This approach provided insight to the optimal methodology and data source(s) for particular safety issues. It showed that multinational database studies for various safety issues as performed by the PROTECT network, including the investigation of rare, serious AEs, are possible without using common data models

Study protocols and their amendments were registered and documented in the EU PAS Register (http://www.encepp.eu/encepp_studies/indexRegister.shtml).

We considered the cohort and nested case–control designs appropriate for all Drug–AE pairs. The cohort design was applied to all Drug–AE pairs, and was the only design that was used to study inhaled long-acting beta2-agonists and the risk of acute myocardial infarction, and calcium channel blockers and the risk of cancer. The focus in these two case studies was on methods to control for confounding and the handling of a long induction period for the outcome of cancer. Given the acute and transient nature of hip fracture and acute liver injury we also evaluated case crossover and self-controlled case-series designs for these events.

In addition we investigated the validity and use of national drug utilization data to facilitate estimation of the public health impact adverse drug reactions. To this aim an inventory of nationwide drug consumption databases was established.

METHODOLOGICAL ISSUES EXAMINED IN PROTECT: SUMMARY OF FINDINGS AND LESSONS LEARNED

Consistency of findings across study designs and databases

With the exception of anti-epileptics and suicide most associations were consistent in the direction of the effect estimate on either side of the null value across the different designs and different databases, but varied somewhat in terms of magnitude of the effect estimate (Figures 1–5, Table 1).

For associations investigated with multiple study designs (antibiotics and acute liver injury, benzodiazepines/antidepressants and hip fracture) we found that the case-only studies tended to result in larger effect estimates compared to cohort and (nested) case control designs[5–9] (Figures 1–4). One possible explanation includes violations of underlying assumptions of case-only designs. For instance, in the case-cross over study on antidepressants and hip fracture in the Dutch Mondriaan database, control periods were likely not exchangeable because of a fixed (median duration of chronic prescriptions in the Netherlands) duration of prescription that coincided with control moments close (−90 and −180 days) to the case mo-

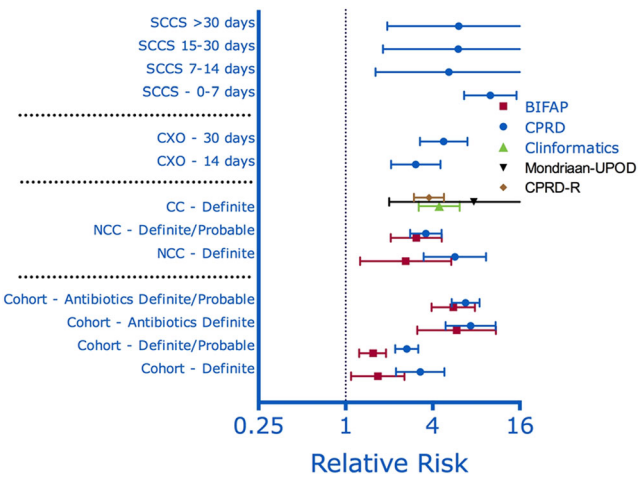

Figure 1. Antibiotics and the risk of acute liver injury. Impact of study design, database, exposure and outcome definitions. SCCS: self-controlled case series, CXO: case cross-over, CC: case–control, NCC: nested case–control

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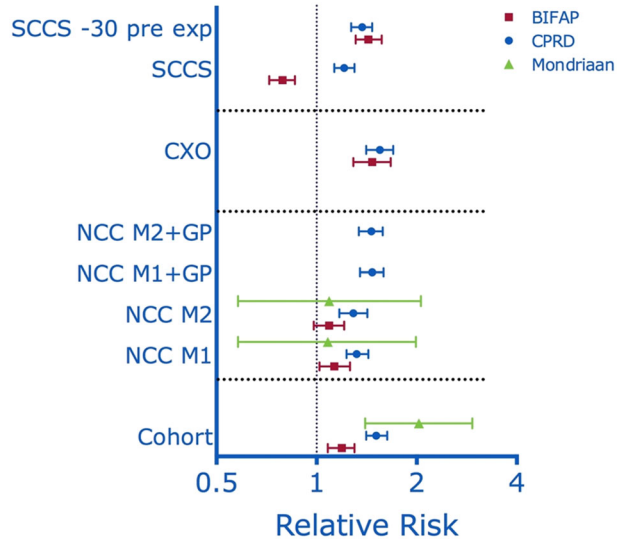

Figure 2. Benzodiazepines and the risk of hip fracture. Impact of study design, database and control for confounding (different matching strategies in case–control study). SCCS: Self-controlled case series, CXO: Case cross-over, NCC: nested case–control, M1: simple matching algorithm including sex, age (+/−2 years) and follow-up time, M2: Euclidean distance matching algorithm including sex, age (+/−2 years) and follow-up time, GP: general practice included as matching factor

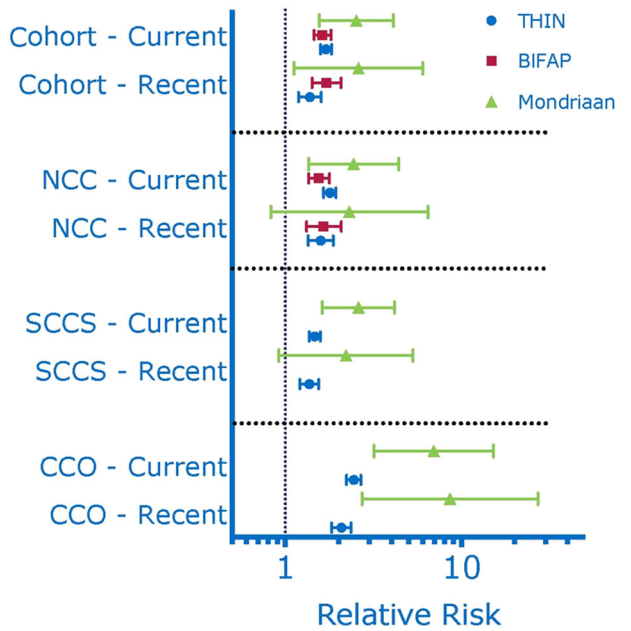

Figure 3. Antidepressants and the risk of hip fracture. Impact of study design and database. SCCS: self-controlled case series, CXO: case cross-over, NCC: nested case–control

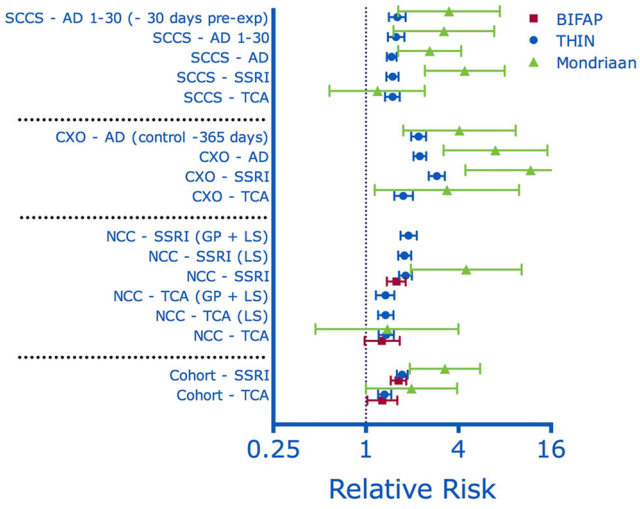

Figure 4. Antidepressants and risk of hip fracture. Impact of exposure definitions and methods to control for confounding. SCCS: self-controlled case series, CXO: case cross-over, NCC: nested case–control, AD: antidepressant, SSRI: Selective Serotonin Uptake Inhibitor, TCA: tricyclic antidepressant, GP: general practitioner included in matching algorithm, LS: additional adjustment for lifestyle factors

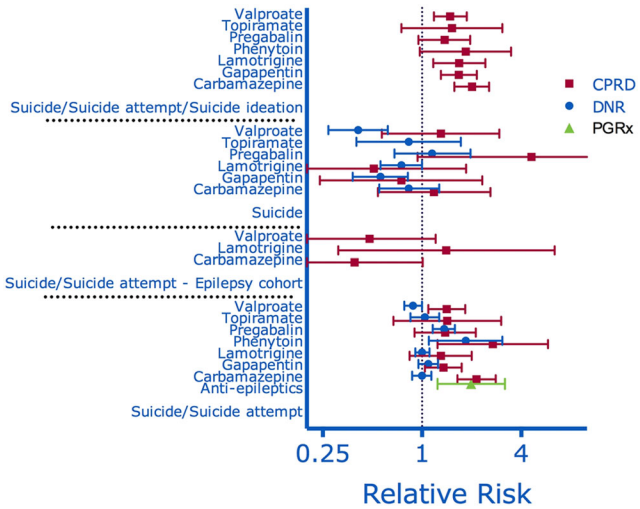

Figure 5. Antiepileptic drugs and the risk of suicide. Impact of database, exposure and outcome definitions

ment. Furthermore, in the self-controlled case series analysis of antibiotics and acute liver injury in CPRD one key assumption, namely that of events not influencing future exposure (e.g. stopping of antibiotics after acute liver injury), may not have been fulfilled. Second, higher relative risk estimates in case only designs may suggest a better control for confounding by between-subject differences, which do not affect the within-subject comparisons made in these designs. Third, subjects that are chronic users of medications (e.g. antidepressants, benzodiazepines) with no unexposed observation time are excluded from the estimated relative risk in case-only designs, but can contribute in cohort and nested case–control studies. Finally, the statistical models used for the analyses provide different relative effect estimates according to the underlying design (e.g. hazard ratios, odds

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Table 1. Key findings of impact of methodological determinants on Drug–Adverse Event associations

Drug–AE pair	Design	Database/Study population	Outcome ascertainment	Exposure ascertainment	Confounding control	Replication
Antibiotics–acute liver injury	All designs consistent in direction, Case-only slightly stronger associations than cohort/case–control	Population-based versus antibiotic users	Strict versus broad definition resulted in slightly stronger associations with less precision	Broader exposure time window of 30 days versus 14 days decreased the association		In same databases consistent In different database consistent
Benzodiazepines–hip fracture	All designs consistent in direction, Case-only slightly stronger associations than cohort/case–control	n.a.	n.a.	Greater risk associated with concomitant use of anxiolytics and hypnotic drugs versus single use Greater risk associated with short-term use (only in Mondriaan)	Control for lifestyle factors little impact Matching strategy little impact	n.a.
Antidepressants–hip fracture	All designs consistent in direction, Case-only slightly stronger associations than cohort/case–control	n.a.	n.a.	Selective serotonin uptake inhibitors versus tricyclic antidepressants stronger association, except for SCCS design in THIN	Control for lifestyle factors little impact Matching strategy little impact Multivariable Cox regression versus IPTW of MSM little difference IV analysis inconsistent	n.a.
Antiepileptic drugs–suicidality	n.a.	Antiepileptic drug users versus depression versus epilepsia inconsistent CPRD versus Danish registries inconsistent	Strong impact of definition of suicidality based on different data sources, large variability in size and direction of association	Individual antiepileptic drugs varied in relative risk		Not consistent in different databases
Inhaled long-acting beta2-agonists–acute myocardial infarction	n.a.	Asthma versus COPD versus Asthma and COPD provided consistently no association	n.a.	Current versus recent (reference) lower RR compared to current versus past (reference)	Control for lifestyle factors little impact Differences between multivariable Cox regression and IPTW of MSM IV analysis inconsistent	In different database consistent

IPTW: inverse probability of treatment weighting, MSM: Marginal Structural Model, IV: instrumental variable.

ratios, incidence rate ratios) that may slightly differ in magnitude.

With regard to benzodiazepines and risk of hip fracture we initially observed a decreased risk of hip fracture associated with benzodiazepine use in the Spanish BIFAP database, whereas in CPRD an increased risk was found (Figure 2). However, after conducting a sensitivity analysis excluding a 30-day pre-exposure period to test the key event-exposure independence assumption of the self-controlled case-series design, we also found an increased risk of hip fracture in the Spanish BIFAP database which suggests an increased prescribing of benzodiazepines after a hip fracture in Spain.

Outcome definition

Associations between antibiotics and acute liver injury were slightly impacted by the definition of acute liver injury[6] (Figure 1). A more stringent definition using all available information on laboratory measurements of liver enzyme elevation, diagnostic codes and hospitalization resulted in a slightly stronger association, compared to a less stringent definition, whereas precision was greater for the latter definition.[6] The less stringent definition results in more false positive diagnoses of acute liver injury which is unlikely to be associated with antibiotic exposure. This non-differential misclassification is probably causing some bias toward the null and slightly weaker associations between acute liver injury and antibiotic exposure. Associations between antiepileptic drugs and suicidality were strongly affected by the type of outcome (e.g. completed suicide, suicide attempt using different sources of information such as mortality, hospitalization, and general practitioner (GP) diagnoses[10]) (Figure 5). Suicide rates in CPRD including Hospital Episode Statistics, and the Danish National Registries were largely consistent with estimates from national statistics and therefore considered the most reliable measure for suicidality in pharmacoepidemiological studies.

Exposure definition

Important exposure aspects that had an impact on the associations of interest were time window of exposure for antibiotics and acute liver injury.[11] Time windows of 30 days at risk were associated with lower relative risks compared to time windows of 14 days at risk. These findings illustrate the importance of considering biological mechanisms when defining time windows at risk which for acute events such as acute liver injury should be relatively short (14 days) to accurately measure the associations of interest. Classification of individual compounds or classes of drugs (benzodiazepines/antidepressants and hip fracture, antiepileptic drugs and suicide) had an impact on the associations.[7,10] These findings indicate the importance of considering individual compounds or classes of drugs which may have a different risk associated with outcomes of interest. Important class differences were observed between tricyclic antidepressants and serotonin reuptake inhibitors and the risk of hip fracture. In conventional cohort and case–control designs we observed larger relative risks associated with hip fracture for tricyclic antidepressants compared to selective serotonin reuptake inhibitors. However in the self-controlled case series design in THIN tricyclic antidepressants and selective serotonin reuptake inhibitors were associated with a similar risk of hip fracture suggesting that unmeasured confounding through preferential prescribing of selective serotonin reuptake inhibitors to avoid adverse drug reactions caused by tricyclic antidepressants might be prevented by this case-only design.[9] Defining calcium channel blocker use according to type of calcium channel blocker, or duration of use did not have an impact on the association with cancer.[12] See Figures 1–5 and Table 1 for further details. These findings suggest that the association between calcium channel blocker use and the risk of cancer is not likely to be present.

Control of confounding

After control for age and gender, additional control for comorbidity, co-medication and lifestyle factors (only in THIN and CPRD) had little effect on the adjusted relative risk.[8,13] Also, in Mondriaan it was observed that the confounding effect of non-routinely recorded lifestyle factors was small.[14] This finding may suggest that lifestyle factors were not major confounding factors in the studies on antidepressants, benzodiazepines and risk of hip fracture or alternatively that these factors were not measured accurately enough to warrant adequate control for confounding. Whatever the reason for this finding, it indicates that findings between the databases that we investigated were not impacted by controlling for these factors. Our finding differ from the results found by Schneeweiss *et al.* in a study on selective serotonin reuptake inhibitor use and risk of hip fracture in Medicare which did find an impact of ignoring lifestyle factors for confounding adjustment.[15] However, databases vary in the lifestyle factors recorded and the quality of their measurement making comparisons difficult. Different matching strategies (algorithm, in-/exclusion of GP practice) also had little impact on the relative risks[8,13] (Figures 2 and 4). In particular the matching on GP practice which is commonly applied in THIN and CPRD in

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an effort to control for socioeconomic factors apparently does not have a major impact.

The direction of the change in effect estimates observed upon confounding adjustment differed across databases (e.g. the direction of age/sex adjustment in the antidepressant-hip fracture study differed across databases[8]). This is likely because of different prescribing practices across countries, and illustrates that confounding structures may differ across databases (and Drug–AE pairs).

Relative risks of hip fracture associated with antidepressant use were similar for inverse probability of treatment weighting (IPTW) of Marginal Structural Models (MSM) and conventional Cox proportional hazards models.[16] However, in the study of long-acting beta2-agonists and acute myocardial infarction these methods led to different conclusions,[17] which shows that the impact of time-varying confounding that is affected by previous treatment differs (and thus, the necessity to adequately model differs) across Drug–AE pairs.

Control for confounding using instrumental variable (IV) approaches based on physician prescribing preference were generally not valid given the violation of at least one of the main assumptions underlying IV analysis.[18,19] Pooled IV analysis across multiple databases increases the strength of IV because of larger variation in prescribing and increased sample size. Importantly, the likely extent to which these IV assumptions were violated differed across databases. This suggests that generic claims about the (confounding) structure of a particular Drug–AE relation or the validity of a particular method to control for (unmeasured) confounding are not possible. Rather, it underscores the importance of checking the assumptions underlying the methods to control for confounding whenever possible[20], a check that should be made in every dataset and for every Drug–AE pair that is studied.

Choice of study population

Different study populations were investigated for the association between antiepileptic drugs and suicide (depression, epilepsy), for inhaled long-acting beta2-agonists and acute myocardial infarction (asthma, Chronic Obstructive Pulmonary Disease (COPD), asthma + COPD) and for calcium-channel blockers and cancer (population based versus antihypertensive drug users). The investigation of the association between Inhaled long-acting beta2-agonists and acute myocardial infarction is under review elsewhere (see summary results in Figure 6).[21] Stratification for a diagnosis of depression had no impact on the association between antiepileptic drugs and suicide, whereas in a UK population

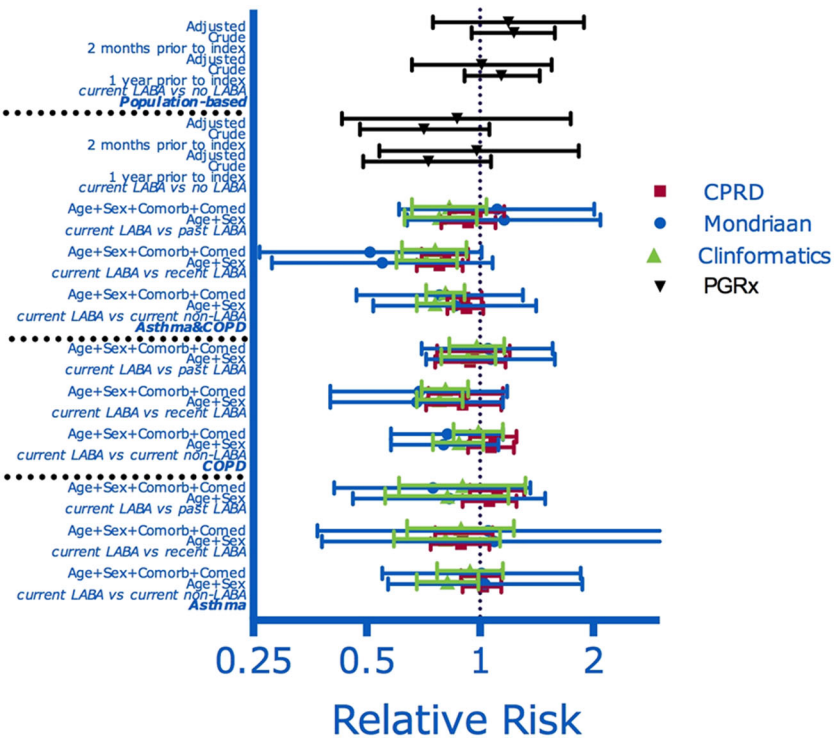

Figure 6. Long-acting beta2-agonist and the risk of acute myocardial infarction. Impact of database, study population and exposure definition

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of people with epilepsy the risk of suicide was decreased in antiepileptic drug users compared to non-use.[10] This finding of an increased risk during periods of non-use among epilepsia patients has been observed by others as well suggesting that individuals go through periods of lower and higher risk of suicidality in their lives.[11,22] This stresses the importance to evaluate different observation periods to help assess the influence of drug exposure compared to other factors. Calcium-channel blockers were associated with a reduced risk of cancer in the general population, whereas among antihypertensive drug users calcium-channel blocker use was not associated with risk of cancer[12] (Figure 7). Inhaled long-acting beta2-agonists were not associated with risk of acute myocardial infarction, and this was consistent across asthma and COPD populations.[21]

Replication studies WP6

The association between antibiotics and acute liver injury was initially investigated in CPRD and BIFAP, and independently and consistently replicated (in magnitude and direction) in CPRD (same database, different team) and in UPOD (hospital pharmacy/clinical laboratory database) and Clinformatics (US claims database)[21,23] (Figure 1). The association between inhaled long-acting beta2-agonists and acute myocardial infarction, initially investigated in the Dutch Mondriaan database and in CPRD, was independently and consistently replicated (no association present) in Clinformatics and the French PGRx case-referent system[21,24] (Figure 6). The association between antiepileptic drugs and suicidality was not replicated (not in direction or magnitude) in the Danish registries and the French PGRx case-referent system[10,25] (Figure 5).

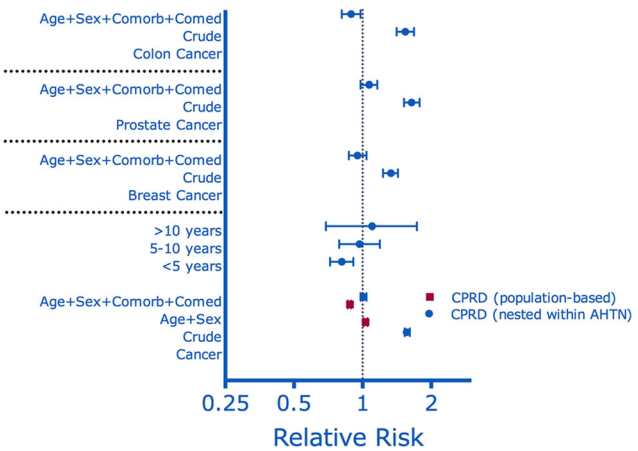

Figure 7. Calcium-channel blockers and the risk of cancer. Impact of study population, exposure and outcome definitions and confounding control

Sources of drug utilization data and drug utilization studies:

An inventory of national drug consumption data sources in the out- and inpatient health care sectors was developed to be comprehensive, and incorporates findings from previous European initiatives (http://www.imi-protect.eu/drugConsumption.shtml). The inventory provides a systematic description of the availability of data in 27 countries as well as characteristics of 31 nationwide administrative databases (health care utilization databases) that monitor drug consumption in Europe. Particular emphasis is placed on the accessibility, validity and reliability of medicine consumption data for research purposes.[26,27] The inventory notes a remarkable scarcity of inpatient databases at the national level. Most in-hospital nationwide administrative databases register sales from wholesalers only, rather than patient level data. Some countries health authorities (i.e. Sweden, Scotland, Catalonia and Norway) are currently implementing programs with the aim of coordinating a patient's pharmacotherapy between the out- and in-patient healthcare system.[28]

DISCUSSION

The PROTECT project has provided important insights into the operational and methodological challenges of conducting multi-database studies based on a common protocol. Consistency in findings across multiple designs, databases and various sensitivity analyses increases confidence in results from observational studies on drug effects which in turn increases their value for the assessment of the benefits and risks of medicines.

The impact of study design and choice of database has been extensively investigated within the OMOP project on a battery of 53 Drug–AE pairs.[29] For the new user cohort design 23 Drug–AE pair associations were consistent in direction, whereas for the self-controlled case series 18 Drug–AE pairs were consistent in direction. An important difference between the OMOP approach and the PROTECT approach is that for each Drug–AE pair we developed a protocol that was tailored to each specific Drug–AE pair and database. OMOP, for instance, implemented a fixed exposure time-window of 30 days since start of exposure, whereas in PROTECT this was defined based on clinically informed assumptions regarding the hazard function of the outcome in relation to the exposure of interest. Furthermore, in each of the databases we calculated the duration of exposure based on the

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prescribed quantity and dosage instructions as registered in each of them. As hypothesized by Madigan *et al.* this customized approach has produced largely consistent results for all Drug–AE pairs that we investigated except for the association between antiepileptic drugs and suicidality.[29] The reasons for inconsistency for the latter association are not clear, but may relate to the difficulty of ascertaining suicidality in electronic health care database and the possibility of uncontrolled and/or unmeasurable confounding by indication (and thereby the possibility that the associations are not causal). The finding that the decreased risk of hip fracture associated with benzodiazepines using a SCCS design in the Spanish BIFAP database was increased after exclusion of a 30-day pre-exposure period (consistent with the finding in CPRD) in particular underlines the importance of planning extensive sensitivity analyses and separate evaluation of individual databases prior to pooling them. Post-hoc sensitivity analyses in order to explain unexpected findings should be documented as amendments to the original protocol. The approach of implementing a common protocol across different databases has also been applied by the CNODES network in Canada and demonstrated more consistency in Drug–AE associations (both in direction and size) as compared to the OMOP "one-size-fits-all" approach.[30–33]

Strengths and limitations

The strengths of our procedures include the development of a common protocol resulting in transparency and increased consistency in design, the conduct of the studies across different databases and the independent replication of study findings. Our selection of Drug–AE pairs and the different types of databases (GP, claims and registries) within the PROTECT network allowed the investigation of a variety of common drug safety issues presenting different methodological challenges. Nonetheless, our findings may not be extendable to other safety issues or other databases that we did not study. Compared to the US Mini-sentinel initiative PROTECT was less extensive with regard to validation of outcomes, development of common data models and size of the databases.[3] Nonetheless, the heterogeneity of the European databases allows evaluation of drug safety issues in different contexts.

Among the main strengths of the inventory of drug consumption databases is the compilation of the high number of nationwide health care utilization databases in the in- and outpatient health care setting that monitor drug consumption in Europe and its systematic description of their characteristics.

With respect to drug utilization studies, one of the main problems pointed out when studying the patterns of drug use globally in a country or in different regions within a country or in cross-national comparisons is the lack of information on indication for use.[34,35] Indication for use has been studied through the diagnoses codes assigned in ambulatory care or at hospital discharge close to the time of the prescription of a medicine. These diagnostic codes can only be considered as proxy markers of indication for a drug therapy.

Implications for scientific and operational practice

Initially, the process of reaching a final common protocol and detailed data specification involving multiple private and public partners was time consuming (6–12 months). Nonetheless, reaching agreement on all details of the protocol created support for a common approach that will be useful for future studies within and potentially outside the PROTECT network. Despite the joint development of a detailed common protocol, we experienced during the analysis phase of the project that interpretation of certain aspects such as definition of in- and exclusion criteria, exposure, outcome and confounder definitions was sometimes different between centers. This made amendments to the protocol necessary in order to harmonize our approach. Programming of the analytical datasets was performed locally in each research center. We shared program codes to check consistency and compared results of time-varying analyses in different statistical packages.

We observed a learning curve in the development and implementation of a common protocol. An increasing knowledge of the databases, including their population characteristics and coding system for exposure, outcomes and confounders, led to more efficient design of studies, protocol development and planning of statistical analyses.

Recommendations

Conducting multi-centre database studies requires very detailed common protocols and data specifications that reduce variability in interpretation by researchers as much as possible. Ongoing communication without sharing results during the conduct of the study is important to harmonize analyses as much as possible. When studies are conducted in parallel in different databases the replication has already been built-in. Pooling databases "a priori" may disguise heterogeneity and should be avoided. Rather, we advocate to analyze databases in parallel and explore reasons for heterogeneity through extensive sensitivity analyses that are documented as pre-specified or post hoc analyses as amendments to

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the original study protocol. This approach will eventually increase consistency in findings from observational drug effect studies, or reveal causes of differential drug effects.

Choosing from multiple possible designs should be a deliberate process, instead of simply repeating a study design with similar underlying assumptions, e.g. case–control versus cohort. Case-only designs are truly alternative and can add additional insight into associations because of the different assumptions of these approaches. Furthermore, which method to control for confounding works best for a Drug–AE pair, given a particular database, needs to be assessed on a case-by-case basis; no universal recommendations can be made based on our findings. The PROTECT project did not examine summary scores such as disease risk scores and automated propensity score methods, and therefore we cannot make general statements about these methodologies.

The inventory of national consumption databases should be kept updated, and we recommend free accessibility to these data for researchers in different institutions (academia, regulatory agencies, health policy organizations, pharma industry). It would be useful to organize a permanent contact and communication between the major providers of drug utilization data, to exchange insights and compare disparities between data. It can also be useful to produce a complete picture of all aspects of drug utilization in the country, if possible in a longitudinal way over extended periods of time.[36]

In conclusion, the PROTECT project has delivered a network for observational drug effect studies allowing the execution of common protocols in multiple databases. Increased consistency of findings across multiple designs and databases in different countries will increase confidence in findings from observational drug research and benefit/risk assessments on medicines. The current PROTECT network can easily be expanded with additional databases and partners to provide a platform for testing new safety signals and development and testing of new methodologies. Further development of the network infrastructure includes automation of the library of codes and programs, governance, structure for collaboration and communication, and the potential for collaboration with other networks in North America, Europe or Asia.

DISCLAIMER

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KEY POINTS

- Consistency in findings from Drug–Adverse Event studies across multiple designs, analyses and databases increases usefulness for benefit /risk assessment of medicines
- A European research network was created for future safety signal assessment and method development
- Multi-database pharmacoepidemiological studies should be analyzed in parallel to explore heterogeneity before meta-analytically pooling results.
- Design and analysis of multi-database pharmacoepidemiological studies should be tailored to the specific Drug–Adverse Event association of interest to enhance consistency in findings
- Registration of study protocols of Drug–Adverse Event studies is recommended to improve transparency

ETHICS STATEMENT

Study protocols were approved by institutional review boards responsible for each individual database.

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