External adjustment of unmeasured confounders in a case-control study of benzodiazepine use and cancer risk

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Running head: External adjustment of unmeasured confounders

Keywords: benzodiazepines; neoplasms; pharmacoepidemiology; population-based; bias (epidemiology); confounding factors (epidemiology); propensity score; propensity score calibration.

Word count: 3255

Number of tables and figures: 4 tables, 2 online tables, and 0 figures.\

Abbreviations:

ATC, Anatomical Therapeutic Chemical; BZRD, benzodiazepines; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; DDD, defined daily doses; ICD, International Classification of Diseases; IQR, interquartile range; OR, odds ratio; PS, propensity score

Summary

Introduction: Previous studies have reported diverging results on the association between benzodiazepine use and cancer risk.

Methods: We investigated this association in a matched case–control study including incident cancer cases during 2002-2009 in the Danish Cancer Registry (n=94,923) and age and sex-matched (1:8) population controls (n=759,334). Long-term benzodiazepine use was defined as ≥500 defined daily doses 1-5 years prior to the index date. We implemented propensity score (PS) calibration using external information on confounders available from a survey of the Danish population. Two PSs were used: The error-prone PS using register-based confounders and the calibrated PS based on both register- and survey-based confounders, retrieved from the Health Interview Survey.

Results: Register-based data showed that cancer cases had more diagnoses, higher comorbidity score and more co-medication then population controls. Survey-based data

showed lower self-rated health, more self-reported diseases, and more smokers as well as subjects with sedentary lifestyle among benzodiazepine users. By PS calibration, the odds ratio for cancer overall associated with benzodiazepine use decreased from 1.16 to 1.09 (1.00, 1.19) and for smoking-related cancers from 1.20 to 1.10 (1.00, 1.21).

Conclusion: We conclude that the increased risk observed in the solely register-based study could partly be attributed to unmeasured confounding.

What is known about this subject

- Previous studies have reported diverging results of the association between benzodiazepines and cancer risk.
- It has been suggested that unmeasured confounding may explain these differences.

What this study adds

- When including detailed information on confounders from a survey of the Danish population, the association with an all cancer composite outcome and for smoking-related cancers decreased.
- Based on the direction of confounding by life-style factors and the possibility for residual confounding, our findings support that BZRDs are not carcinogenic.

Introduction

Post-licensing studies evaluating effectiveness and safety of drugs are typically nonexperimental and based on existing administrative databases or registers [1, 2]. Register-based studies have several strengths including the possibility to give timely answers to important questions, complete follow-up and absence of recall bias. However, they also have several limitations. One such common and important limitation is the lack of detailed information on confounders including life-style factors, over-the-counter medications, clinical characteristics, comorbidity, treatments, and self-rated health [3], which may bias the estimation of drug effects. It has been suggested that qualitative evaluation of unmeasured confounding should be replaced by quantification of the influence of unmeasured confounding [4-7].

In 2013, we published a register-based study of the association between use of benzodiazepines or benzodiazepine-related drugs (BZRDs) and cancer risk [8]. BZRDs are widely used in Western countries, mainly to treat anxiety and insomnia. Previous epidemiological studies have reported equivocal results on the association between BZRD use and cancer risk [9-14]. In our previous study, we found a marginally increased risk of cancer overall associated with BZRD use and a slightly higher risk of smoking-related cancers [8]. We interpreted that the slightly increased ORs with BZRD use resulted from residual confounding by smoking habits and other lifestyle factors, however, this spurred a discussion which has not been resolved [15-17].

In the present study, we implemented a method using external information on confounders available from a survey of the Danish population (validation study) with the aim of achieving a more comprehensive confounder adjustment than performed in the original main study.

Methods

First, we analysed the association between BZRD use and risk of cancer overall, and of smoking- and alcohol-related cancers, using the register-based confounder data available in our previous study [8]. In addition to cancer overall, we focused on smoking- and alcohol-related cancers and specific cancers (lung, breast and head and neck cancers), because these cancer types are likely prone to unmeasured confounding by smoking or alcohol consumption. Next, we supplemented the original data material with information from the Danish Health Interview Surveys [18, 19]; a detailed general survey among a sample of the Danish population, to perform propensity score (PS) calibration and thereby reduce unmeasured confounding in the solely register-based analysis [4, 6].

The original study of BZRD use and cancer risk (main study) was designed as a nationwide nested case-control study using risk-set sampling [8]. The study base consisted of all Danish residents aged 18-85 years and alive on 1 January 2002 who were followed until 31 December 2009. We required cases and controls to have lived in Denmark continuously from 1995 to the index date and to have no history of cancer (except non-melanoma skin cancer) prior to the index date, i.e., date of diagnosis of the cases and their corresponding controls.

Using the detailed survey data (described below) [18, 19], we sampled participants aged 18-85 years and related their use of BZRD to self-reported information on potential confounders, including self-reported health, comorbidities and drug use, smoking habits, alcohol consumption, physical activity and obesity.

Data sources

The Danish Cancer Registry has recorded incident cases of cancer on a nationwide basis since 1943 and has accurate and almost complete registration of incident cancer in Denmark [20]. Cancer diagnoses are recorded according to the *International Classification of Diseases*, version 10 (ICD-10), and the *ICD for Oncology* (ICD-O-1-3) for details of topography and morphology.

The Danish National Prescription Registry [21] contains data on all prescription drugs filled by Danish citizens since 1995. The prescription data include the type of drug, date of dispensing, and quantity. The dosing schedule and indication(s) are not available, and no information is available on drug use in the hospital setting. Drugs are categorised according to the Anatomical Therapeutic Chemical (ATC) index, a hierarchical classification system developed by the WHO [22], and the quantity dispensed for each prescription is expressed by the number of defined daily doses (DDD).

The Danish Civil Registration System [23] contains data on date of death and migration to and from Denmark, allowing unambiguous sampling of population controls and follow-up of all study subjects.

The Danish National Patient Register [24] holds nationwide data on all somatic hospital admissions since 1977 and on all outpatient hospital contacts and psychiatric admissions since 1995. Discharge diagnoses are coded according to ICD-8 (1977-1993) and ICD-10 (1994-current).

The national representative Danish Health Interview Surveys were conducted in 2000, 2005 and 2010 among Danish residents above 15 years of age [18, 19]. The number of respondents was 16,688 in 2000 (response rate 74.2%), 14,566 in 2005 (66.7%) and 15,165 in 2010 (60.7%). The surveys included questions on self-reported health, comorbidities, drug use, and life-style factors, including, e.g., smoking habits and alcohol consumption.

The data sources were linked by the personal identification number, a unique identifier assigned to all Danish residents [25]. We were not able to merge data for participations of the validation study to those also in the case-control study, which means that the survey should be considered an external validation study. All linkages and analyses were performed at servers of Statistics Denmark.

Survey participants

Initially, we identified all subjects participating in one or more of the three health surveys (n=36,701). For persons who participated in more than one survey, we included information only from their first survey. Among persons aged 18-85 years with complete information on all confounders (n=35,291), we randomly selected a sample (n=6,804) frequency matched to the age and sex distribution of the cases and controls included in the main study.

Case-control population

Cases were all Danish residents with a histologically verified first time cancer diagnosis (except non-melanoma skin cancer) between January 1, 2002 and December 31, 2009. The

date of cancer diagnosis was defined as the index date. Further, we defined five cancer categories: i) smoking-related cancers [26](oral cavity and pharynx, oesophagus, stomach, colorectal, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, cervix, ovary, kidney, renal pelvis and ureter, urinary bladder or myeloid leukaemia), ii) alcohol-related cancers [27](oral cavity, pharynx, oesophagus, colorectal, liver, larynx and breast); iii) lung cancer (smoking-related cancer), iv) breast cancer (alcohol-related cancer), and v) head and neck cancer (oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses, nose and para-nasal sinuses, (upper) oesophagus, and salivary glands) (smoking- and alcohol-related cancers).

Controls were selected by use of a risk set sampling strategy, applying the same in- and exclusion criteria as for cases. For each case, we selected eight controls among all Danish residents matched by sex and birth year and month. Subjects were eligible for sampling as controls before they became cases. Thereby, the calculated ORs provide unbiased estimates of the incidence rate ratios (IRRs) that would have emerged from a cohort study in the source population.

Exposure definition

BZRD use was defined as prescription of any drug within the ATC groups N05BA or N05CD (benzodiazepine derivates) or N05CF (benzodiazepine-related drugs) (see online supplementary table 1 for list of drugs).

As in the original case-control study, we disregarded prescriptions filled within the last year prior to the index date in order to reduce the possibility for reverse causation [28]. Long-

term use of BZRD was defined as filling of a cumulative amount of ≥500 DDD BZRD within 1-5 years prior to the index date. BZRD use five or more years before the index date was not considered.

In the survey sample, we included register-based prescription data five years prior to participation in the survey, using the above definition of long-term BZRD use prior to the participation date.

Confounder information

For all subjects in the case-control study, we obtained register-based information on the following potential confounders: a) dispensed prescriptions of drugs known or suspected to modify the cancer risk, including aspirin, non-aspirin NSAIDs, 5-α-reductase inhibitors, statins, angiotensin-II receptor antagonists, antidepressants, antipsychotics, oral contraceptives and menopausal hormone therapy [29]; b) diagnosis of diseases known to modify the risk of some cancers, including inflammatory bowel disease, chronic obstructive pulmonary disease (COPD), alcohol abuse and diabetes; and c) Charlson Comorbidity Index (CCI) [30, 31] defined as none (CCI: 0), low (CCI: 1), or medium/high (CCI: ≥2). For all register-based confounders, we disregarded the year before the index date.

In the survey sample, we included the above mentioned register-based information and in addition register-based information on highest achieved education, categorised as 1) basic school, 2) high school, 3) short/medium-term education (11-12 years), 4) long education (≥13 years), or 5) missing or unknown [32]. We also retrieved the following self-reported information on potential confounding factors: a) self-rated health dichotomised as

excellent/very good versus good/medium/bad; b) self-reported comorbidities including diabetes, hypertension, myocardial infarction, stroke and COPD; c) self-reported drug use for treatment of hypertension, heart disease or pain, d) smoking habits classified as never, former and current smokers (categorised into 1-4, 5-14, 15-24 and 25+ cigarettes/day); e) alcohol intake categorised as abstainers, 1-14 and 15+ drinks/week for women and abstainers, 1-21 and 22+ drinks/week for men; f) physical activity categorised as sedentary, medium (low intensive physical activity >4 hours per week), high (hard physical activity >4 hours per week) and intensive (vigorous competitive activity several times each week); and g) body mass index categorised as <18.5, 18.5-24.9, 25-29.9 and ≥30 kg/m^2.

Statistical analyses

We estimated the association between BZRD use and cancer risk in the case-control study using multivariable logistic regression models. We estimated an age- and sex adjusted model and a model adjusted for register-based confounders (prescription use of drugs known or suspected to modify cancer risk, diagnosis of diseases known to modify the risk of some cancers, and Charlson Comorbidity Index, as proxy for concomitant diseases).

We performed PS calibration to adjust risk estimates of the solely register-based case-control study for unmeasured confounding by including survey data [6]. We calculated two PS in the survey data. The first was the error-prone PS (X_{EP}), where we estimated the probability of exposure conditional on confounders measured in the original register-based study. The second was the "gold"-standard PS (X_{GS}), where we estimated the probability of BZRD use conditional on all relevant confounders measured in both the case-control study

and in the survey sample. Both PS models were estimated using multivariable logistic regression.

We then estimated a linear measurement error model by regressing the "gold"-standard PS on the error-prone PS and BZRD use (E):

$$E(X_{GS} \mid E, X_{EP}) = \lambda_0 + \lambda_E E + \lambda_X X_{EP} ,$$

where λ_0, λ_E and λ_X are regression estimates. From the estimated coefficient for BZRD use (β_E) and cancer from the case-control study adjusted for the error-prone PS, we subsequently subtracted the estimated coefficient for the error-prone PS (β_X) multiplied by the ratio of the parameter for BZRD use and the error-prone PS estimated in the measurement model [6, 33, 34]:

$$\beta^*_E = \beta_E - \beta_X \lambda_E / \lambda_X ,$$

where β^*_E was the calibrated coefficient estimate for BZRD use and cancer.

We computed the variances of the adjusted estimates to include the uncertainty of estimating the measurement model in the survey sample [33, 35]. We used the *%blinplus* macro [36] to include information on parameter estimates, error-prone and "gold"-standard PS models to correct the estimates from the case-control study. The *%blinplus* macro provided the adjusted OR estimates, including 95% confidence intervals (CI) adjusted for additional uncertainty from the estimation of the measurement error model in the survey study. By estimating the error prone PS in the case-control study, we took account of the sampling strategy of the case-control study by giving controls weights that were inversely proportional to the sampling fraction of the general population for each age and sex

category [37]. By reweighting, the controls would mimic the general population with same age and sex distribution.

The analyses were performed using SAS version 9.3 (SAS Institute, Cary, North Carolina, USA) and Stata Release 14.0 (StataCorp, College Station, TX, USA).

Results

We identified 94,923 eligible cancers cases matched to 759,334 controls (Table 1). Cases were more likely than controls to have used oral contraceptives and menopausal hormone therapy, and had a higher prevalence of COPD, diabetes and alcohol abuse (Table 1). The remaining characteristics were similar in prevalence among cases and controls.

Among subjects who had participated in the survey, 1,854 reported use of BZRD and 4,950 were non-users (Table 1). BZRD users were more likely than non-users to use other drugs and had higher prevalence of COPD, diabetes, and alcohol abuse, and exhibited higher comorbidity scores (Table 2). The self-reported data revealed lower self-rated health among BZRD users with more self-reported diseases and more frequent use of drugs for hypertension, heart disease and pain compared with non-users. A higher proportion of BZRD users were smokers, non-drinkers and had a sedentary life-style. This pattern was more apparent among long-term users (≥500 DDD) compared to short-term users. There were no consistent differences between users of benzodiazepine derivates and benzodiazepine-related drugs (available as online supplementary table 2).

The OR for BZRD use in the case-control study showed that use of antidepressants or antipsychotics, and diagnosis of alcohol abuse, had the strongest associations with BZRD use (Table 3). The ORs for various independent predictors of BZRD use of the error-prone model were quite similar in the case-control study and survey sample, e.g., 6.79 in the case-control study versus 7.44 in the survey sample for antidepressants (Table 3). The largest difference was seen for the influence of inflammatory bowel disease. Among the self-reported survey confounders, smoking or any reduction of self-rated health showed the strongest associations with increased probability of BZRD use.

The analyses of associations between BZRD use and cancer overall and the cancer subgroups showed increased ORs for all cancer groups, except breast cancer, in the age- and sex- adjusted model. BZRD use was, however, not associated with alcohol-related cancers, breast or head and neck cancer in the fully adjusted model (Table 4). Similar results emerged in the PS adjusted models in the case-control study. In the PS calibrated model, the increased OR for BZRD use and cancer overall decreased from 1.16 to 1.09 (95% CI: 1.00, 1.19). For smoking-related cancers and lung cancer separately, the corresponding OR reductions were from 1.20 to 1.10 (95%CI: 1.00, 1.21) and 1.48 to 1.23 (95%CI: 1.03, 1.46), respectively (Table 4).

Discussion

In this study, we investigated the influence of unmeasured confounding in a large register-based study of BZRD use and cancer risk by including detailed survey data on life-style related confounders. We found that especially low self-reported health and smoking were associated with increased use of BZRD. This finding supports the notion that our previous purely register-based analysis of BZRD use and smoking-related cancers suffered from unmeasured confounding, whereas alcohol-related cancers appeared less influenced by unmeasured confounding. We showed that by using data from an external validation study and PS calibration, the slightly increased risk of cancer overall and, notably, of smoking-related cancers with BZRD use was decreased. The risk of lung cancer with BZRD use was also attenuated substantially, but remained elevated after including the survey data, which may mirror residual confounding by smoking in the survey data. The associations with alcohol-related cancers were not influenced materially by adjusting for additional confounders.

Previous epidemiological studies have reported mixed results of the association between BZRD use and cancer risk [8-14], but it has been suggested that use of hypnotics is associated with cancer risk as well as all-cause mortality, depression and suicide [38, 39]. Our study documented that users of BZRD or hypnotics have a confounder profile compatible with a higher cancer risk as reported in some studies [11-14]. Our results thus emphasize that unmeasured confounding from e.g. life-style factors can, if left unmeasured, infer confounding of some studies based on registers and administrative databases.

We used PS calibration to include survey information on lifestyle factors available from a survey of the Danish population to account for unmeasured confounding. As we were

unable to directly merge data for participants of our validation study to those also in the main study, the information from the survey should therefore be considered an external validation study. Other approaches have been proposed to evaluate the magnitude of the influence of unmeasured confounding, e.g. evaluation of how strongly associated a potential confounding factor has to be with both exposure and outcome in order to explain increases (or decreases) in cancer risk in a register-based setting [4]. Other methods include instrumental variable analysis [40-44] and the 'missing cause approach', proposed by Abrahamowicz et al. (42), which in brief estimates the discrepancy between the effects of observed treatment compared to expected treatment based on observed data and use this treatment-by-discrepancy interaction to test for the presence of unmeasured confounding.

The main advantage of PS calibration is the inclusion of numerous confounders in the analysis based on external data. The main disadvantage of PS calibration is the underlying surrogacy assumption. Surrogacy means that the error-prone variable contains no additional information on the outcome above and beyond the gold-standard (calibrated) variable. For PSC this essentially means that the error-prone PS is independent of the outcome given the gold-standard PS [45] which requires, at a very minimum, that the direction of confounding of the observed and unmeasured confounders is the same. Same direction of confounding is plausible in our study study since most of the register-based confounders are used as proxies for unmeasured confounders, e.g. diagnosis of COPD as a proxy for smoking. Lunt et al. have shown that, in addition to direction of confounding, surrogacy requires a certain balance of measured and unmeasured confounding; a strong and often implausible assumption [46]. Thus, some violation of the surrogacy assumption is likely biasing the PSC

results to some extent. Since we are unable to estimate the effect of unmeasured covariates on the outcome of interest in our validation study, we cannot address this "balance" of measured and unmeasured confounding and the direction of magnitude of PSC bias in our setting. Another element is that the confidence intervals of PS calibration do not take the uncertainty of model misspecification into account and, therefore, confidence intervals should be interpreted as a minimum estimate of the inherent uncertainty [6].

PS calibration relies on the use of PS for confounding control and regression calibration, both developed and theoretically derived primarily for cohort studies. In our case-control approach, we thus took precautions to minimize collider bias due to conditioning on the outcome. We weighted the controls to mimic the age- and sex-distribution of the general population. Still, weighted case-control PS may produce artefactual effect modification of the OR across the estimated PS [37]. The magnitude of this spurious effect measure modification decreases with increasing sample size (34), whereby this effect seems negligible in our large study. To our knowledge, regression calibration has never been implemented in case-control studies.

Our study had several strengths including large sample sizes of both the register-based and the survey-based studies. We had information on virtually all Danish residents with incident cancer and almost complete follow-up of subjects during the study period from 1995 (start of the Prescription Registry) until cancer diagnosis or corresponding date for controls thereby minimizing selection bias. The health care services in Denmark are in general publicly funded and the included information therefore has universal coverage. A high validity has been shown for several of the used registers [20, 21, 23, 24]. The survey data were based on a large national representative health survey among the adult population in

Denmark and included self-reported variables, including life-style variables, which were not available in the solely register-based study [18, 19].

The study also had limitations. The use of prescription data may result in exposure misclassification due to non-compliance, although we probably minimised this bias by using cumulative long-term BZRD use as main exposure measure. Furthermore, we evaluated BZRD use more than one year before index date thereby minimizing the influence of reverse causality due to drug use just before cancer diagnosis, but we may have underestimated the influence of BZRD use by only including exposure information up to five years before index date. Another important limitation was that survey data may have been influenced by non-response and validity issues regarding the questionnaire. It has been shown that non-responders of the survey have higher morbidity and mortality than responders, especially for alcohol-, drugs- and smoking-related outcomes [47]. Consequently, health survey information may be influenced by non-participation bias if individuals with unfavourable health status are underrepresented in the survey. The validity of regression calibration depends on the transportability of the measurement error model from the survey to the main study [33]. However, as the Danish Health Interview Survey is a national representative study among adults in Denmark with fairly good response rates, this assumption seems plausible.

In conclusion, we have demonstrated that PS calibration improve the adjustment of main study estimates for unmeasured confounding by life-style factors. Based on the direction of confounding by these life-style factors and the possibility for residual confounding, our findings bring further support to the evidence that BZRDs are not carcinogenic.

Approvals

The study was approved by the Danish Data Protection Agency. Approval from the Ethics Committee was not required.

Conflict of interest

All authors do not have any competing interests. Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Servier and Leo Pharma, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. Jesper Hallas has participated in research projects funded by Novartis, Pfizer, Menarini, MSD, Nycomed, Astellas and Alkabello with grants paid to the institution where he was employed. He has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers and from Pfizer and Menarini.

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