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Rapid report

Unmeasured confounding in pharmacoepidemiology

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Results from observational studies using registries of routinely recorded health data are possibly biased because information on potential confounders such as life style factors (e.g., smoking status) may not be available [1]. Rather than measuring such potential confounders for all study participants, it may be more efficient to do so only in a subset of participants and incorporate that information in the analysis using, for example, two-stage analysis, propensity score calibration, or multiple imputation [2–6]. We aimed (1) to assess the impact of potential confounders that are not routinely recorded in health care databases, and (2) to compare different methods (notably two-stage analysis, propensity score calibration, and multiple imputation) on their ability to control for confounding using additional confounder information from a subset of the study population.

We performed two case-control studies within the Utrecht Cardiovascular Pharmacogenetic (UCP) study: [7] a study of long-acting beta2-agonist (LABA) use and myocardial infarction (MI), and another study of calcium channel blocker (CCB) use and MI. For the study of LABA use and MI, we selected 826 MI cases and 6451 controls from the UCP subset of users of any inhaled adrenoceptor or muscarinic agonist (i.e., long-acting and short-acting beta2-agonist and long-acting and short-acting muscarinic antagonist). For the study of CCB use and MI, we selected 3635 MI cases and 33,264 controls from the UCP subset of antihypertensive medication (CCBs, beta-blockers, diuretics, or agents acting on the renin-angiotensin system) users. In both studies, the outcome status (MI) was based on hospital discharge files. Exposure to the medication of interest and concomitant medication was based on dispensings issued during the 3 months before the index date. In a subset of these populations, additional information on potential confounders (i.e., body mass index, smoking status, level of physical exercise, and family history of MI) was collected through questionnaires. Questionnaires were available for 1110 (15%) and 1111 (3%) subjects in the LABA and the CCB studies, respectively, and were filled in as early as possible after the index date. Although information of confounders ideally reflects the condition of study participants at the time of initiation of treatment, such information could not be collected through questionnaires in this case-control study. Hence, the confounder information collected through questionnaires is considered as proxy information for actual confounding variables at initiation of treatment.

Adjustment for routinely recorded confounders (i.e., age, sex, and comedication use) resulted in a reduction of the odds ratio (OR) in the study of CCB use and MI but did not importantly change the OR of LABA use and MI (Table 1). Additional adjustment for nonroutinely recorded confounders, of which, information was obtained through questionnaires, increased the ORs in both studies (in the study of LABA use from 1.00 to 1.25 and in the study of CCB from 1.18 to 1.42). However, a similar change was observed when restricting the analysis to those subjects who returned the questionnaire and only adjusting for the routinely recorded confounders. Hence, the differences in ORs observed on additional adjustment for nonroutinely recorded confounders are due to a

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Table 1
Impact of nonroutinely recorded confounders on the relation between LABA use or calcium channel blockers and risk of MI in the Utrecht Cardiovascular Pharmacogenetic study

Model	OR (95% CI) of exposure to LABAs and risk of MI	OR (95% CI) of exposure to calcium channel blockers and risk of MI
Crude	1.02 (0.85–1.23)	1.41 (1.31–1.52)
Adjusted for routinely recorded confounders*	1.00 (0.82–1.21)	1.18 (1.09–1.27)
Adjusted for routinely recorded confounders*, restriction to subset of those who returned the questionnaire	1.27 (0.85–1.91)	1.43 (0.99–2.06)
Adjusted for routinely recorded confounders and questionnaire confounders†, restriction to subset of those who returned the questionnaire	1.25 (0.83–1.88)	1.42 (0.98–2.06)
Two-stage analysis‡	0.98 (0.80–1.20)	1.17 (1.06–1.29)
Propensity score calibration‡	0.99 (0.81–1.19)	1.07 (0.90–1.14)
Multiple imputation	0.97 (0.73–1.29)	1.19 (0.89–1.58)

OR = odds ratio, obtained through unconditional logistic regression; CI = confidence interval.
* Routinely recorded confounders are sex, acetylsalicylic acid, antithrombotic agents, beta-blocking agents, vasodilators, drugs used in diabetes, lipid-modifying agents, diuretics, agents acting on the renin–angiotensin system, oral corticosteroid, and CCBs (in the study of LABA) or LABA (in the study of CCB [all measured at or up to 1.5 years before index date], and age [at index date]).
† Questionnaire confounders are body mass index, smoking status, level of physical exercise, and family history of MI (all measured at the index date).
‡ Confidence intervals obtained through bootstrapping.

selection of those subjects who returned the questionnaire rather than the effect of confounding adjustment. Selective response may induce a selection bias of the drug-outcome association, or the effect of the drugs may be different among those who returned the questionnaire. For example, in the study of LABA use, those who returned the questionnaire were younger (mean age = 66.2 years, SD = 10.2) than those who did not return the questionnaire (mean = 68.3 years, SD = 11.3) and modification of the effect of LABA by age may explain these findings (although in our study, the interaction was nonsignificant, $P > 0.05$).

The three methods to incorporate the confounder information that is available for a subset of the study population (two-stage analysis, propensity score calibration, and multiple imputation) yielded similar results, although confidence intervals were noticeably wider for multiple imputation (Table 1). This may not come as a surprise because the power to detect any differences between methods is likely small in this study, given that the potential for confounding due to the nonroutinely recorded patient characteristics appeared to be low.

There is always the threat of unmeasured confounding in observational studies performed in (large) electronic health care records databases and irrespective of the number of records. Possible sources of unmeasured confounding include life style factors, such as smoking and exercise levels. However, adjustment for these variables had little impact in the studies that we conducted. Possible explanations for this are the granularity by which life style factors are measured (which may be too coarse), or that the confounding by, for example, life style factors is already captured to a large extent by routinely recorded confounders ("adjustment by proxy"). This finding cannot be generalized to other studies, because whether, for example, life style factors have a confounding effect in addition to routinely recorded confounding variables depends on the amount and structure of confounding, which may differ between studies.

What our studies illustrate is that differences in effects observed on adjustment for nonroutinely recorded potential confounders may be due to a restriction to those subjects for whom additional information is actually available, rather than a reflection of (unmeasured) confounding. Possibly a selective nonresponse to the questionnaires induced a selection bias; a risk that is not specific for our studies, but more generally related to collecting information about nonroutinely recorded confounders through questionnaires. It seems preferable to incorporate the additional information of nonroutinely recorded confounders by means of two-stage analysis, propensity score calibration, or multiple imputation instead of including those confounders as covariates in an ordinary regression analysis, which by default will result in an analysis of those who returned the questionnaire (i.e., complete case analysis).

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