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Instrumental Variables in Influenza Vaccination Studies: Mission Impossible?!

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ABSTRACT

Objectives: Unobserved confounding has been suggested to explain the effect of influenza vaccination on mortality reported in several observational studies. An instrumental variable (IV) is strongly related to the exposure under study, but not directly or indirectly (through other variables) with the outcome. Theoretically, analyses using IVs to control for both observed and unobserved confounding may provide unbiased estimates of influenza vaccine effects. We assessed the usefulness of IV analysis in influenza vaccination studies.

Methods: Information on patients aged 65 years and older from the computerized Utrecht General Practitioner (GP) research database over seven influenza epidemic periods was pooled to estimate the association between influenza vaccination and all-cause mortality among community-dwelling elderly. Potential IVs included in the analysis were a history of gout, a history of orthopaedic morbidity, a history of antacid medication use, and GP-specific vaccination rates.

Results: Using linear regression analyses, all possible IVs were associated with vaccination status: risk difference (RD) 7.8% (95% confidence interval [CI] 3.6%; 12.0%), RD 2.8% (95% CI 1.7%; 3.9%), RD 8.1% (95% CI 6.1%; 10.1%), and RD 100.0% (95% CI 89.0%; 111.0%) for gout, orthopaedic morbidity, antacid medication use, and GP-specific vaccination rates, respectively. Each potential IV, however, also appeared to be related to mortality through other observed confounding variables (notably age, sex, and comorbidity).

Conclusions: The potential IVs studied did not meet the necessary criteria, because they were (indirectly) associated with the outcome. These variables may, therefore, not be suited to assess unconfounded influenza vaccine effects through IV analysis.

Keywords: bias, confounding, influenza vaccines, instrumental variable analysis.

Introduction

Observational studies are prone to confounding bias because treatment allocation is an inherently nonrandom process [1,2]. Typically in studies on presumed beneficial treatments, patients with a poorer prognosis tend to receive the treatment. Hence, treatment effects are biased or confounded by these prognostic patient characteristics, so-called confounders. Methods such as matching, stratification, and multivariable regression analysis have been proposed to control for observed confounders. Unobserved confounders, however, cannot be adjusted for by means of these methods [1].

Instrumental variables (IVs) can be of use to derive estimates of treatment effect that are unbiased by both observed *and* unobserved confounders [3–6]. An IV is a variable that is strongly related to the exposure under study, but not with the outcome, either directly or through an association with confounders. Although observed confounders can be adjusted for in IV analysis [7] ideally, observed as well as unobserved potential confounders should be balanced between groups of subjects with and without the IV. If observed confounders are balanced between groups of subjects with and without the IV, the assumption that unobserved confounders are balanced as well seems more likely. An example of a study in which an IV was used to estimate a treatment effect is an observational study on influenza vaccine effectiveness in which gout was used as an IV [8]. Patients suffering from gout more often visited their physician and, therefore, were more likely to be encouraged (by their physician) to take the influenza vaccine. As a result, gout was associated with influenza vaccination status. Furthermore, it was assumed that gout was neither an independent risk factor for the primary outcome all-cause mortality, nor that it was associated with potential confounders (e.g., age, sex, and pulmonary and cardiovascular diseases) for the association between influenza vaccination and mortality.

Within clinical research areas where unobserved confounders are expected to play a role, IVs may be helpful to produce unbiased effect estimates. Because results from studies on influenza vaccine effectiveness have been heavily debated, because of unobserved confounding (e.g., by unobserved functional health status [9,10]), we planned to study the effectiveness of influenza vaccination on all-cause mortality among community-dwelling elderly using several potential IVs to control for observed and unobserved confounding.

Methods

Instrumental Variables

An IV is a variable that is strongly related to exposure, yet independent of the study outcome, given the exposure and potential confounders [4–6]. This is referred to as the main assumption for a valid IV which states that an IV should neither directly nor indirectly (via other variables) be associated with the outcome. Because observed confounders can be adjusted for in IV analysis, consequently, the IV should be independent of uncontrolled confounding factors. Importantly, if the IV is independent of observed confounders, it is assumed to be independent of unobserved confounders. This is in analogy with the comparability of observed and unobserved prognostic variables between the

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intervention and control group achieved by randomization in a trial. As such, the IV method can result in comparability of these potential confounders between those receiving and those not receiving the intervention. This so-called pseudo-randomization on the basis of levels of the IV may indeed, theoretically, guarantee absence of confounding. The underlying assumptions, however, may be difficult to meet for potential IVs [4].

An expert committee (including medical doctors, pharmacists, and epidemiologists) was set up to identify potential IVs for a study on the association between influenza vaccination and mortality risk. Based on the aforementioned definition of an IV, the proposed variable should be strongly related to vaccination status and at the same time not be a risk factor for mortality as well as independent of potential confounders (e.g., age, sex, pulmonary and cardiovascular diseases, diabetes, etc.). Although observed confounders could be adjusted for, we aimed for IVs that were independent of observed confounders, because the assumption of independence of unobserved confounders would seem more valid. As in the example using gout as an IV, we focused on conditions or situations in which we expected subjects more often to visit their physician (hence, were more likely to be encouraged to take the vaccine). Furthermore, it should be reasonable to expect that this condition or situation would not directly or indirectly affect the risk for mortality.

Three groups of potential IVs were distinguished. First, following the study by Yoo and Frick [8], in which gout was used as an IV, classes of comorbidity were suggested to act as IVs. In particular, gout and orthopedic morbidity were suggested as IVs. Patients suffering from gout or orthopedic morbidity more often visit their physician than patients without this morbidity. Furthermore, it was assumed that both were not a risk factor for mortality and were not associated with important known and strong potential confounders as age, sex, diabetes, cancer, and cardiovascular and pulmonary diseases. A history of gout was defined as registration of ICPC-code T92 in the 12 months preceding influenza vaccination. Registration of an ICPC-code (L-codes) indicating orthopedic morbidity in the 12 months preceding influenza vaccination was defined as presence of the IV orthopedic morbidity. Possibly, osteoarthritis is associated with mortality through age. Therefore, additional analyses were planned in which osteoarthritis was excluded from the definition of orthopedic morbidity.

Second, classes of medication were proposed as IVs. Especially drugs that are prescribed to patients suffering from dyspepsia were thought to be related to influenza vaccination status, yet unrelated to comorbidity or mortality. Thus, filling a prescription for antacid medication (ATC-code A02a) in the 12 months preceding influenza vaccination was defined as presence of the IV.

Finally, physician characteristics were considered as potential IVs [11]. Physicians might have specific preferences with respect to influenza vaccination, resulting in varying efforts in persuading their patients to take the vaccine [12]. Therefore, vaccination rates among general practitioner (GP) group practices might differ although, on average, comorbidity distributions can be assumed to be similar. Furthermore, mortality risk was thought to be more or less similar across different GP group practices as well.

Study Population

Information on the potential IVs gout, orthopedic morbidity, use of antacid medication, and GP group practice specific vaccination rates were obtained from the computerized medical database of The Netherlands University Medical Center Utrecht General Practitioner Research Network. This database includes cumulative information on approximately 60,000 patients and has shown to be valid in influenza vaccine effectiveness studies [13]. The patients are registered with six GP group practices. Until 2007, the Dutch immunization guideline on influenza vaccination recommended vaccination for specific patient groups with high-risk medical conditions and for all persons aged 65 years and older. We obtained clinical information on all elderly aged 65 years and older during seven influenza epidemic periods (1995/1996–1999/2000, 2001/2002, 2002/2003). Influenza epidemic periods were defined as periods of at least two consecutive weeks in which each week accounted for at least 5% of the season's total number of influenza isolates [14,15]. We excluded the 2000/2001 winter period because there was virtually no influenza activity [14]. This resulted in 44,418 periods of observation. We collected extensive information on exposure to seasonal influenza vaccination, and on potential confounders such as age and sex, comorbidity and prior health-care consumption for each observation period. In the University Medical Center Utrecht General Practitioner Research Network. all diagnoses are coded according to the International Classification of Primary Care (ICPC) coding system. Vaccination status was ascertained by registration of the ICPC-code R44.1, which has shown to accurately reflect actual receipt of the vaccine (kappa = 93%) [16]. Comorbidity status was based on registration of ICPC-codes during the 12 months preceding each year's influenza epidemic period: cardiovascular comorbidity (code K74, K75, K76, K77, K78-K80, K82-K84, or K90), pulmonary comorbidity (R84, R85, R91, R95, R96), diabetes (T90), and malignancies (B72, B73, B74, D74-77, S77, T71, U75-77, X75-77, Y77). Furthermore, health-care consumption (number of GP visits) and medication use in the year preceding each influenza epidemic period were recorded.

Statistical Analyses

For all of the studied potential IVs, similar analyses were performed. First, univariate associations between IVs and influenza vaccination status were estimated. Second, univariate associations between IVs and observed confounders were estimated. These were compared with univariate associations between influenza vaccination status and observed confounders. Ideally, distributions of potential confounders are balanced between levels of the IV and, hence, associations between the IV and potential confounders are absent (or at least smaller than the associations between influenza vaccination and potential confounders) [10]. Finally, the effect of influenza vaccination on mortality risk was estimated using the IV. As a first step, the association between the IV and mortality was estimated using linear regression analysis, thus estimating a risk difference. Then, the association between the IV and vaccination status was estimated, again using linear regression analysis. The ratio of these estimates is the risk difference of the association between influenza vaccination and mortality risk [4]. The confidence interval (CI) for this risk difference was estimated by drawing 1000 bootstrap samples of the original data set and calculating the risk difference in each sample [17]. The 2.5% and 97.5% quintiles of this distribution indicated the lower and upper bound, respectively, of the 95% CI of the mortality risk difference between vaccinated and nonvaccinated subjects.

Even though observed confounders can be adjusted for [7], unobserved confounders may still bias the association under study. To quantify the potential impact of unobserved confounding, a sensitivity analysis of unobserved confounding was conducted [18]. First, in the analysis in which gout was used as

potential IV, observed confounders were adjusted for. Secondly, an unobserved confounder was simulated and additionally adjusted for. Smoking status is not routinely reported in the computerized medical GP database. Therefore, we considered smoking status to be a potential unobserved confounder. In the Nurses' Health Study, current smokers had an almost threefold increased risk (odds ratio [OR] 2.8) for all-cause mortality as compared to never-smokers [19]. We considered two scenarios of smoking status among gout and nongout patients. In the first scenario, 20% of gout patients and 30% of the nongout patients smoked, whereas in the second scenario 20% of gout patients and 40% of the nongout patients smoked. Based on these assumptions, smoking status was simulated and on top of the observed confounders (i.e., age, sex, and comorbidity status) included as a confounder in the IV analysis [20]. Analyses were carried out in SPSS for Windows (version 14.0, SPSS Inc., Chicago, IL) and R for Windows (version 2.5.1).

Results

In total, 379 persons died during 44,418 influenza epidemic periods of observation. A history of gout was present in 445 periods of observations (1.0%), and was associated with influenza vaccination (OR 1.56; 95% CI 1.23; 1.97). Overall, the magnitude of the associations between gout and potential confounders and the associations between influenza vaccination and potential confounders were similar (Table 1). Nevertheless, the association between gout and presence cardiovascular disease was stronger than the association between influenza vaccination and cardiovascular disease (Table 1). A history of gout increased the risk for all-cause mortality (risk difference (RD) 0.2%, 95% CI –0.6% to 1.1%) and was associated with influenza vaccination status (RD 7.8%, 95% CI 3.6%; 12.0%). Hence, IV analysis estimated influenza vaccination to increase all-cause mortality: RD = 0.24% / 7.84% = 3.1% (95% CI –8.6% to 17.3%).

The instrumental variable orthopedic morbidity was present in 7970 periods of observations (17.9%), and was associated with influenza vaccination (OR 1.16, 95% CI 1.10; 1.22). Overall, associations between orthopedic morbidity and potential confounders were weaker than the associations between influenza vaccination status and potential confounders (Table 1). Male sex, however, had a stronger association with orthopedic morbidity than with influenza vaccination status. Orthopedic morbidity was negatively associated with all-cause mortality (RD –0.1%, 95% CI –0.3%; 0.1%), although it showed a positive association with vaccination status (RD 2.8%, 95% CI 1.7%; 3.9%). As a result, IV analysis estimated influenza vaccination to reduce all-cause mortality (RD –3.8%, 95% CI –12.5%; 4.0%). In additional analyses, in which osteoarthritis was excluded from the definition of orthopedic morbidity, the association between orthopedic morbidity and age was absent (OR 1.00, 95% CI 0.98; 1.02). Nevertheless, the associations between this potential IV and other potential confounders remained similar (Table 1). Consequently, estimates from IV analysis were similar as well (RD –2.8%, 95% CI –12.1%; 5.5%).

In the 12 months preceding the influenza vaccination period, antacid medication was used in 2013 periods of observations (4.5%). Use of this type of medication was associated with influenza vaccination status (RD 8.1%, 95% CI 6.1%; 10.1%). The associations between antacid use and potential confounders on the one hand and the associations between influenza vaccination status and potential confounders on the other hand, were of the same order. IV analysis estimated influenza vaccination to increase all-cause mortality (RD 15.9%, 95% CI 10.3%; 23.6%).

Vaccination rates among the six GP group practices ranged from 68.1% to 77.9% (mean 72.9%). As shown in Table 2, confounder characteristics were, on average, more balanced among levels of the IV than among vaccinated and unvaccinated subjects (i.e., GP group practices were more similar than groups of vaccinated and unvaccinated subjects). Nevertheless, patients were on average older in the GP practice with the highest vaccination rate. Furthermore, with increasing vaccination rates, prevalence of cancer tended to increase as well. Finally, the proportion of males seemed to decrease with increasing vaccination rate. Trivially, vaccination rate (the IV) was strongly associated with vaccination status (RD 100.0%, 95% CI 89.0%; 111.0%), although it showed a positive association with all-cause mortality (RD 1.9%, 95% CI –0.4%; 4.2%). As a result, IV analysis estimated influenza vaccination to increase all-cause mortality (RD 1.9%, 95% CI –0.6%; –4.5%).

In Table 3, estimates of influenza vaccine effectiveness using IVs are compared with regular analyses (without use of an IV). Routine analysis showed influenza vaccination to re-

Table 1 Associations between observed confounders and influenza vaccination status, and dichotomous potential instrumental variables

		Associations between observed confounders and . . .				
Variable	Prevalence of observed confounders	. . . influenza vaccination	. . . a history of gout	. . . a history of orthopedic morbidity (including osteoarthritis)	. . . a history of orthopedic morbidity (without osteoarthritis)	. . . a history of antacid medication use
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Age*	75 (70; 80)†	1.08 (1.06 to 1.09)	1.02 (0.96 to 1.09)	1.03 (1.01 to 1.05)	1.00 (0.98 to 1.02)	1.33 (1.29 to 1.37)
Male sex	38%	1.20 (1.15 to 1.25)	2.06 (1.71 to 2.48)	0.55 (0.52 to 0.58)	0.62 (0.58 to 0.65)	1.45 (1.32 to 1.60)
Presence of cardiovascular disease	10%	1.44 (1.34 to 1.55)	2.11 (1.66 to 2.67)	1.02 (0.94 to 1.11)	1.02 (0.94 to 1.11)	1.43 (1.26 to 1.63)
Presence of pulmonary disease	12%	2.38 (2.20 to 2.58)	1.80 (1.43 to 2.27)	1.07 (0.99 to 1.15)	1.11 (1.02 to 1.20)	1.90 (1.70 to 2.13)
Presence of diabetes mellitus	6.5%	1.98 (1.79 to 2.19)	1.93 (1.45 to 2.58)	0.90 (0.81 to 0.98)	0.92 (0.82 to 1.03)	1.24 (1.05 to 1.47)
Presence of malignancies	2.2%	1.11 (0.96 to 1.28)	0.60 (0.27 to 1.34)	0.95 (0.80 to 1.12)	1.00 (0.83 to 1.20)	1.47 (1.15 to 1.88)
Cardiovascular drug use	47%	1.83 (1.75 to 1.91)	2.64 (2.16 to 3.23)	1.08 (1.03 to 1.13)	1.04 (0.99 to 1.10)	1.81 (1.65 to 1.98)
Pulmonary drug use	11%	2.44 (2.24 to 2.65)	1.86 (1.47 to 2.35)	1.08 (1.00 to 1.16)	1.13 (1.04 to 1.23)	1.99 (1.77 to 2.23)
Diabetic drug use	7.7%	2.28 (2.07 to 2.51)	1.56 (1.17 to 2.09)	0.86 (0.78 to 0.95)	0.90 (0.81 to 1.00)	1.47 (1.27 to 1.70)
Number of GP visits*†	12 (6; 19)†	1.21 (1.20 to 1.23)	1.17 (1.14 to 1.20)	1.16 (1.15 to 1.17)	1.15 (1.14 to 1.16)	1.33 (1.31 to 1.34)

*Odds ratio for age based on 5-year strata, OR for number of GP visits based on strata of five GP visits.
†Median (interquartile range).
CI, confidence interval to GP, general practitioner to OR, odds ratio.

Table 2 Distribution of confounding characteristics among levels of the instrumental variable GP group practice and among vaccinated and unvaccinated subjects

	Levels of the instrumental variable (GP group practice)						Vaccination status	
	1	2	3	4	5	6	Vaccinated	Unvaccinated
Number of subjects	5,156	12,656	3,086	7,494	6,349	9,677	32,388	12,030
Vaccination rate	68.1	69.2	73.0	73.5	76.0	77.9	100	0
Median age (year)	75	74	75	75	73	77	75	74
Proportion (%) male	39.4	41.5	35.8	36.9	40.7	33.5	39.4	35.2
Proportion (%) with cardiovascular disease	7.9	11	9.1	11.8	8.6	10.5	11	7.9
Proportion (%) with pulmonary disease	10	14.8	9.5	11	13.8	10.7	14.3	6.5
Proportion (%) with diabetes	5.2	8	5.2	7.3	7.9	3.8	7.4	3.9
Proportion (%) with cancer	1.8	2.1	2.8	2.8	2.5	3	2.6	2.2
Proportion (%) using cardiovascular drugs	47.4	45.7	46.2	45.9	56	43.6	51	36.2
Proportion (%) using pulmonary drugs	8.9	13.6	8.6	10.3	13.4	9.6	13.2	5.9
Proportion (%) using diabetic drugs	5.9	8.8	6.9	7.1	10	6.4	9	4.2
Median number of GP visits	12	12	10	12	13	11	13	8

GP, general practitioner.

duce all-cause mortality risk: unadjusted RD –0.12% (95% CI –0.31%; 0.07%), and after adjustment for age, sex, comorbidity, medication use and health-care consumption RD –0.57% (95% CI –0.77%; –0.38%).

When gout was the IV under study and observed confounders (i.e., age, sex, and comorbidity status) were adjusted for, IV analysis estimated influenza vaccination to reduce all-cause mortality: RD = –0.5% (95% CI: –16.7%; 15.8%). When 20% and 30% of the gout and nongout patients were considered to be a current smoker, IV analysis estimated influenza vaccination to increase all-cause mortality: RD = 1.3% (95% CI: –14.3%; 16.9%). When 20% and 40% of the gout and nongout patients were considered to be a current smoker, these numbers were: RD = 2.5% (95% CI: –11.8%; 16.8%).

Discussion

All of the assessed potential IVs to study influenza vaccine effectiveness did not meet the assumptions of IV analysis. A history of gout was associated with influenza vaccination status, as well as with observed risk factors for mortality. Therefore, gout was probably not only associated with mortality risk through influenza vaccination, but also through other variables. Hence, it did not meet the main assumption of IV analysis.

Influenza vaccination was associated with a reduction in all-cause mortality risk during influenza epidemic periods in our analysis, using orthopedic morbidity as IV. The estimated association, however, was very imprecise, as indicated by the wide CIs (especially as compared to the CI of the estimate that was adjusted for observed confounders). Technical reasons for these wide CIs are the weak association between the IV and vaccination status and the fact that the CI of a ratio will always be larger than the CIs of the components of the ratio. Although the associations between the IV and most of the observed confounders were weaker than the associations between vaccination status and the observed confounders, sex showed a stronger association with the IV than with vaccination status. Assuming that unobserved confounders are balanced is, therefore, not self-evident. Consequently, orthopedic morbidity did not meet the main assumption of IV analysis, that is independence between the IV and risk factors for the outcome, and therefore estimates cannot be considered unbiased. Exclusion of osteoarthritis from the definition of orthopedic morbidity did not materially affect these results.

A history of antacid medication use was associated with observed confounders and, therefore, it seemed unlikely that antacid use was not related to the outcome through other variables (i.e., it did not meet the main assumption of IV analysis).

Finally, GP group practice specific vaccination rate appeared also invalid as an IV. Although, confounders were more balanced among levels of the IV than among vaccinated and unvaccinated subjects, some confounders still were related to the IV (e.g., age, sex, and a history of cancer). Thus, the assumption that vaccination rates were not directly related to mortality seems unlikely. This could also be derived from the observation that the GP-specific vaccination rate and vaccination status were nearly identical, as indicated by the risk difference of 100%. Furthermore, although vaccination rates among the six GP group practices differed, their range was small (68–78%) and extrapolating a regression line through these points to the full range of possible vaccination rates (i.e., 0–100%) results in inaccurate estimates. This partly explains the wide CI of the IV estimate using GP-specific vaccination rate as IV.

To quantify the potential for observed and unobserved confounding, the IV analysis using gout as IV was first adjusted for observed confounders and, subsequently, adjusted for a simulated unobserved confounder as well. The direction of the association between influenza vaccination and mortality risk changed from positive (crude IV analysis) to negative (adjusted for observed confounders) and back to a positive association again (after additional adjustment for a potential unobserved confounder). Because the assumptions of the characteristics of the

Table 3 Comparison of estimates of the association between influenza vaccination and mortality risk adjusted for observed confounders and instrumental variable (IV) estimates

	Risk difference (95% CI)
Regular estimates	
Crude association	–0.12% (–0.31%; 0.07%)
Adjusted for observed confounders (age, sex, comorbidity status, medication use, prior GP visits)	–0.57% (–0.77%; –0.38%)
Instrumental variable estimates	
History of gout as IV	3.1% (–8.6%; 17.3%)
History of orthopedic morbidity (including osteoarthritis) as IV	–3.8% (–12.5%; 4.0%)
History of orthopedic morbidity (without osteoarthritis) as IV	–2.8% (–12.1%; 5.5%)
History of antacid medication use as IV	15.9% (10.3%; 23.6%)
GP specific vaccination rate as IV	1.9% (–0.60%; 4.5%)

CI, confidence interval; GP, general practitioner.

unobserved confounder seem very realistic, the potential for unobserved confounding appears to be large.

Analyses using IVs seem powerful solutions in observational studies on the effects of interventions. Nevertheless, in situations with considerable confounding, the associations between the exposure under study and potential confounders are strong. As a result, the association between the exposure and a variable (i.e., an IV) that is unrelated to those potential confounders will diminish [4]. Thus, in situations with considerable confounding, the association between the IV and the exposure under study will be weak and the IV cannot be a strong instrument. In The Netherlands, confounding is known to be an important threat to the validity of influenza vaccination studies, indicated by significant imbalance of prognostic characteristics among vaccinated and nonvaccinated subjects and a substantial change in estimate after adjustment for observed confounders [2,13]. Therefore, valid IVs to estimate influenza vaccine effectiveness in The Netherlands seem difficult to obtain.

Still, Yoo and Frick concluded that IV analysis using gout as an IV is a valid method to control for confounding in studies on influenza vaccine effectiveness [8]. They assumed that gout was only related to mortality through influenza vaccine effectiveness. As we previously described, this assumption cannot be tested. Nevertheless, the strengths of the associations between an IV and other risk factors for mortality may indicate whether this assumption seems valid. Unfortunately, Yoo and Frick did not report these associations. Our data indicated that the potential IV gout is strongly associated with important risk factors for mortality such as age, cardiovascular and pulmonary comorbidity. Hence, the conclusion that gout is a valid IV seems incorrect. Nevertheless, a recently published cohort study on influenza vaccine effectiveness among US elderly showed less imbalance of prognostic characteristics among vaccinated and nonvaccinated subjects than we found in our data [21]. Therefore, in the United States, confounding might have less impact on influenza vaccination studies and valid IVs might be available to estimate influenza vaccine effectiveness.

Nevertheless, in research areas with important confounding, IVs could still be of use. In such situations, the researcher might be able to create an IV. For example, to study the effects of maternal smoking on birth weight, Sexton and Hebel randomly allocated pregnant women to either an encouragement program to stop smoking or routine care [22,23]. Because allocation to the program was a random process, it was unrelated to potential confounders of the association between maternal smoking and birth weight. Furthermore, participation in the encouragement program was associated with a higher degree of smoking cessation than the routine care group. Under the assumption that the encouragement program will only affect birth weight through maternal smoking (and not, for instance, also result in a change of dietary habits), the encouragement program could act as an IV to study the association between maternal smoking and birth weight. Likewise, to study influenza vaccine effectiveness, patients could be randomly allocated to either an encouragement program to take the vaccine or to routine care [24]. As in randomized trials, confounders will be balanced between those following the program and those receiving routine care. To act as an IV, the encouragement program should then be associated with higher vaccination rates than in the routine care group (again, under the assumption that the encouragement program will only have an effect on the outcome through influenza vaccination). In The Netherlands, however, vaccination rates among elderly (receiving routine care) are already more than 80%, which leaves little room for improvement [14]. In countries with lower vaccination rates, however, encouragement programs could result in a considerable increase of vaccination rates and allocation to the encouragement program could be a valid IV to study influenza vaccine effectiveness.

In conclusion, observational intervention studies, such as studies on influenza vaccine effectiveness, are prone to confounding bias. IVs are a potential solution for confounding, because IV analyses control for both observed and unobserved confounders. The studied IVs, however, did not meet the assumptions of IV analysis and were therefore inappropriate to study the effects of influenza vaccination. In real life, valid IVs to study the effects of influenza vaccination may be hard to find.

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