ORIGINAL REPORT

Instrumental variable analysis as a complementary analysis in studies of adverse effects: venous thromboembolism and second-generation versus third-generation oral contraceptives

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ABSTRACT

Purpose   A potentially useful role for instrumental variable (IV) analysis may be as a complementary analysis to assess the presence of confounding when studying adverse drug effects. There has been discussion on whether the observed increased risk of venous thromboembolism (VTE) for third-generation oral contraceptives versus second-generation oral contraceptives could be (partially) attributed to confounding. We investigated how prescribing preference IV estimates compare with conventional estimates.
Methods   Women in the Clinical Practice Research Database who started a second-generation or third-generation oral contraceptive from 1989 to 2013 were included. Ordinary least squares and two-stage least squares regression were used to estimate risk differences in VTE. Cox regression and IV for Cox proportional hazards regression were used to calculate hazard ratios (HR). The instrument used was the proportion of prescriptions for third-generation oral contraceptives by the general practitioner in the year preceding the current prescription.
Results   All analyses pointed in the direction of an increased VTE risk for third-generation oral contraceptives. The adjusted HR from the conventional Cox regression was 1.62 (95% confidence interval 1.16–2.27) and the fully adjusted HR from the IV Cox regression was 3.45 (95% confidence interval; 0.97–11.7), showing a larger risk and wider confidence intervals in the IV analysis.
Conclusions   The similarity in direction of results from the IV analyses and conventional analyses suggests that major confounding is unlikely. IV analysis can be a useful complementary analysis to assess the presence of confounding in studies of adverse drug effects in very large databases. Copyright © 2016 John Wiley & Sons, Ltd.

KEY WORDS—instrumental variable; adverse effects; confounding; pharmacoepidemiology

INTRODUCTION

Observational data analyses of intended effects of drug therapy are always suspected to be strongly confounded by factors that determine prognosis. This has been termed 'confounding by indication'.[1] However, this is often not the case for adverse effects.[2–4] Although confounding by contraindication[5] can exist, for many adverse effects of treatments, little confounding is expected because these adverse effects are difficult to predict.[2–6] Still, controversies can emerge

due to different views about the potential for confounding when studying adverse effects. Performing an instrumental variable (IV) analysis may then be a consideration, because this method rests upon different assumptions. It requires identification of a variable that determines treatment but is not otherwise associated with the outcome — thereby mimicking randomisation. We explore the value of IV analysis as a 'complementary analysis' to assess the presence of confounding when studying adverse effects.

As an example, we use the controversy about the risk of venous thromboembolism (VTE) of third-generation versus second-generation combined hormonal oral contraceptives (OCs). In general, it can be expected that prescribers did not take a patient's thrombosis risk

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into account when choosing between different OCs before 1995, when evidence of an increased risk of VTE in third-generation in comparison with second-generation OCs was published.[2,7–9] Users of different classes of OCs before 1995, included in the studies published in 1995 and major studies based on data from before 1995,[7–11] can therefore be expected to have had a comparable background risk of VTE. However, there was an extensive debate on (the direction of) the relation between thrombosis risk and OC choice in these studies and the resulting confounding.[12–14] After 1995, general practitioners (GPs) will have become aware of the increased VTE risk for third-generation OCs and may have started taking patients' thrombosis risk into account when choosing between OCs.[7–9] Yet this risk is difficult to predict in young women, and we therefore expect confounding by contraindication to have remained limited.

If the observed difference in risk of VTE between second-generation and third-generation OCs was only based on confounding, in principle, an IV analysis (e. g. using GP's preference as an instrument) should show no difference in VTE incidence. On the other hand, if there is indeed little confounding by contraindication for the association between third-generation versus second-generation OCs and VTE, effect estimates from conventional analyses and IV analyses should yield similar results. Therefore, we investigated how GP's preference IV estimates of the effect of third-generation versus second-generation OCs on occurrence of VTE compare with conventional estimates from observational data.

METHODS

Study population

The study population comprised all women aged 15–44 years with a first prescription for a combined hormonal OC between 1987 and 2013 included in the Clinical Practice Research Datalink (http://www.cprd.com), a UK primary care database. Those with a first prescription within 6 months of their registration date or date on which practice data were up to standard were excluded ($n = 366\,354$) as this may be a repeat prescription. Further reasons for exclusion were a prescription for emergency contraceptives only ($n = 11\,575$), a first prescription with a repeat prescription code ($n = 29$), occurrence of VTE before the first prescription ($n = 509$) or an unknown prescriber for the first prescription ($n = 11\,561$). Of the 502 163 remaining women, 444 542 were first prescribed a second-generation or third-generation combined hormonal OC (as defined subsequently) and were included in the study population.

Exposure

Second-generation OCs were defined as OCs containing levonorgestrel, lynestrenol or norethisterone as a progestagen and $<50\,\mu g$ of oestrogen. Third-generation OCs were defined as OCs containing desogestrel, gestodene or norgestimate progestagen and $<50\,\mu g$ of oestrogen. Supporting Information Codelist 1 lists the codes used. Users of contraceptives containing other progestagens, such as drospirenone, were not included.

Outcomes

Outcomes were defined based on records of Read codes for deep-vein thrombosis or pulmonary embolism (Supporting Information Codelist 2). Codes for deep-vein phlebitis or thrombophlebitis were also included, as these may contain misclassified VTE events. An additional requirement was prescription of anticoagulant treatment in the period from 1 month before until 6 months after the diagnosis code date. For the analyses estimating risk differences, we included events that occurred within 1 or 3 years after the first OC prescription. Patients who started OCs after 31 December 2012 (1 year) or after 31 December 2010 (3 years) were excluded from these analyses. For the Cox regression analyses, only events occurring during the continuous period of use of the same OC since the first prescription were included.

Other patient characteristics

Information on smoking and body mass index (BMI) were obtained if available. The most recent information before the first prescription for OCs was used, with a minimum age of 12 years for smoking behaviour and 14 years for BMI. BMI values >14 or <60 were excluded.

Instrument definition

We used previous prescriptions of the patient's GP as a proxy for GP's preference for second-generation or third-generation OCs at the time of that patient's first OC prescription. We considered the following instruments:

1 The previous first-time OC prescription of the same GP.
2 The proportion of third-generation OCs among the previous five first-time prescriptions of the same GP.
3 The proportion of third-generation OCs among all first-time prescriptions of the same GP in the year preceding the current treatment decision.

The strength of all three instruments (first-stage risk difference for third-generation OC prescription, partial

r^2 and partial F-statistic (1 numerator degree of freedom)) was determined (Supporting Information Table S1). Instrument 3 (unadjusted: partial $r^2 = 0.191$, $F(99\,357)$; adjusted for calendar time: partial $r^2 = 0.085$, $F(38\,881)$) was selected for use in the IV analyses. We preferred this instrument over instrument 2 because of the fixed time interval in which preference was determined. All further analyses were performed in the 420 152 subjects with a value for this instrument (excluding subjects whose GP had not prescribed any combined hormonal OC in the year preceding their prescription date).

Instrumental variable assumptions

Figure 1 depicts the assumed causal relations in this study. For previous prescription(s) of the GP to be a valid instrument, the following assumptions must hold:

(1) Previous first-time prescriptions of the same GP for second-generation or third-generation OCs must be associated with the type of OC prescribed to the current patient.

(2) The prescriptions of previous patients may not affect the VTE risk of the current patient other than through the type of OC the current patient receives (i.e. in Figure 1, there may not be an arrow from 'previous prescriptions: 2nd or 3rd generation oral contraceptives' to 'venous thromboembolism', either directly or through another factor such as co-medication).

(3) The prescriptions of previous patients and the baseline VTE risk of the current patient do not have a common cause (i.e. in Figure 1, there may not be a factor such as case-mix of a general practitioner with an arrow to both 'previous prescriptions: 2nd or 3rd generation oral contraceptives' and 'patient characteristics').

In order to obtain a point estimate, we further assume stochastic monotonicity: that the prescriptions of previous patients are associated with the type of oral contraceptive prescribed in the same direction for all relevant subgroups of patients.[15] These subgroups are strata of a sufficient set of common causes of the type of oral contraceptive prescribed and the risk of VTE (i.e. a sufficient set of confounders). Under this assumption, a strength-of-IV weighted average treatment effect is estimated (i.e. a weighted average of the effects of type of oral contraceptive on risk of venous thromboembolism in these relevant subgroups, where the weights are the strength of the instrumental variable within these subgroups).[15] The interpretation of the estimate (but not the analysis or estimate itself) differs from the interpretation under a different point-identifying
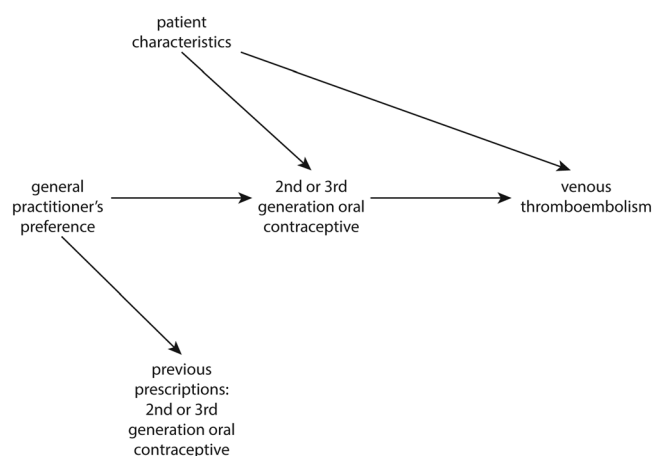

Figure 1. Directed acyclic graph of the assumed causal relations in this study

assumption, such as deterministic or global monotonicity (that if physician A would prescribe a third-generation OC to a certain patient, then all physicians with a preference for third-generation OCs greater than or equal to the preference of physician A should also prescribe a third-generation oral contraceptive to that patient).[15–17] For an explanation of the interpretation of the estimates under these different assumptions and for a discussion of the plausibility of these different assumptions, we refer to the literature.[15,16]

Statistical analyses

All statistical analyses were performed using Stata 10.1.

(1) Ordinary least squares analysis (OLS)

First, OLS regression was used to estimate the difference in risk of VTE between users of third-generation OCs and users of second-generation OCs 1 and 3 years after first prescription. We performed these analyses: (i) unadjusted and (ii) adjusted for calendar year (using year continuously, ≤1995 versus ≥1996, and their interaction term), age, BMI and smoking (non-smoker/smoker/ ex-smoker).

(2) Two-stage least squares analysis (2-SLS)

Next, 2-SLS regression was performed, using the instrument selected previously. The estimates obtained are risk differences of VTE for third-generation versus second-generation OCs. Heteroscedasticity-robust standard errors were used. We performed these analyses: (i) unadjusted; (ii) adjusted for calendar year; and (iii) adjusted for calendar year, age, BMI and smoking.

(3) Cox proportional hazards regression

Next, Cox proportional hazards regression was performed to estimate the hazard ratio (HR) for venous thrombolism for users of third-generation OCs versus

users of second-generation OCs. We used the full period of uninterrupted use of the first prescribed OC as the observation period (ending if OC use was stopped, if a switch to another class of OC was made (e.g. from a second-generation to a third-generation OC), if the patient was no longer registered in the practice, if the patient developed a VTE or if the patient died). We performed these analyses: (i) unadjusted and (ii) adjusted for calendar year, age, BMI and smoking.

(4) IV for Cox proportional hazards regression

We used an adapted version of IV regression to take into account the length of follow-up. The model used was IV for Cox proportional hazards model, the use of which has been shown to be appropriate in case of a rare outcome.[18] The first stage of this model is linear regression of the treatment on the instrument (and, for the adjusted analysis, the covariates). The second stage is Cox regression, with the fitted probability of a third-generation OC from the first stage as the independent variable (and, for the adjusted analysis, including the same covariates as in the first stage). To obtain a confidence interval (confidence interval), we used non-parametric bootstrap (1000 runs). We performed the following analyses: (i) unadjusted; (ii) adjusted for calendar year; and (iii) adjusted for calendar year, age, BMI and smoking. For the fully adjusted analysis, the average of the 2.5th and 97.5th bootstrap percentile across the 10 imputations was used as an approximation, which gives a slightly too narrow CI.

Initially, we planned to perform all analyses in two time periods, namely, the time periods before and after publication of evidence of an increased risk of VTE for third-generation OCs in 1995; that is, 1987–1994 and 1996–2011. Unfortunately, because of the low number of patients newly starting a second-generation or third-generation OC before 1995 ($n = 46\,747$, $n = 45\,354$ with a value of the instrument), this was not feasible.

Missing values

Missing values for BMI and smoking were imputed using multiple imputation using chained equations, using linear regression for BMI and multinomial logistic regression for smoking. All versions of the outcome from the different analyses, log-transformed follow-up time, the exposure (second-generation or third-generation OCs), the instrument and all covariates were included in the imputation model.

Sensitivity analyses

The exclusion of women with a first prescription within 6 months of the entry date may not be sufficient to exclude all patients for whom the first prescription recorded is a repeat prescription. We therefore performed sensitivity analyses in which we excluded all patients with a first prescription within a year of the entry date.

The requirement of a record of a prescription for anticoagulation by the GP within 6 months after the potential thromboembolic event may be too strict, as some patient may have received all prescriptions for anticoagulants via the hospital. We therefore performed sensitivity analyses without this requirement.

RESULTS

Patient characteristics

Characteristics of the study subjects are shown in Table 1, both by actual treatment and by value of the instrument. Patients who received a third-generation OC were older (median age 24.3 versus 20.3 years) and smoked slightly more (26.5% versus 25.0%) than patients who received a second-generation OC. As the percentage of third-generation prescriptions in the preceding year by the same GP increased, the age of the patients increased (median of 23.2 years in the highest group versus 20.0 years in the lowest group) and the percentage of smokers also increased (highest group: 27.3%; lowest group: 23.8%).

Changes in prescription behaviour over time

A reason why the instrument was related to age and smoking is that the instrument was strongly related to calendar time. In Figure 2, we show the proportion of prescriptions for third-generation and second-generation OCs (and drospirenone-containing contraceptives) per calendar year. From 1989 (40%) to 1994 (78%), the proportion of prescriptions for third-generation OCs increased. During 1995 (68%), this trend stopped, leading into a drop in third-generation OC prescriptions in 1996 (21%). After 1996, the proportion of second-generation OCs remained relatively constant between 75% and 80%, with the proportion of third-generation OCs gradually decreasing as the proportion of drospirenone-containing OCs increased. Supporting Information Table S7 shows that the age at first prescription and the proportion of smokers decreased over time.

Ordinary least squares and two-stage least squares regression

Differences in 1-year and 3-year risk of VTE between third-generation and second-generation OCs obtained using OLS regression and 2-SLS IV regression are displayed in Table 2. All OLS results

Table 1. Patient characteristics by actual type of oral contraceptive and by quintiles of prescriptions for third-generation oral contraceptives by their GP in the past year

	Actual prescription		Prescriptions of the same GP in past year (%, third-generation)			
	second-generation	third-generation	0	Q1 (1.6–20.0)	Q2 (20.2–44.4)	Q3 (44.6–100)
N	309 508	110 644	133 349	98 423	94 119	94 261
Actual prescription third-generation	N/A	N/A	16 121 (12.1)	15 068 (15.3)	23 967 (25.5)	54 796 (58.7)
Age (y), median (IQR)	20.3 (17.0–28.1)	24.3 (18.5–30.6)	20.0 (17.0–27.7)	21.0 (17.2–28.7)	22.1 (17.6–29.4)	23.2 (17.9–29.9)
BMI (kg/m^2), median (IQR)[†]	22.9 (20.6–26.2)	22.8 (20.7–25.8)	23.0 (20.5–26.3)	23.0 (20.7–26.4)	22.9 (20.6–26.0)	22.7 (20.6–25.7)
Smoking[‡]						
Yes	62 515 (25.0)	22 612 (26.5)	26 356 (23.8)	20 408 (25.4)	19 414 (25.9)	18 949 (27.3)
Ex	20 304 (8.1)	7800 (9.2)	9349 (8.4)	6997 (8.7)	6470 (8.6)	5288 (7.6)
Venous thromboembolism (years)*						
1	91 (0.03)	45 (0.04)	48 (0.04)	27 (0.03)	26 (0.03)	35 (0.04)
3	180 (0.07)	101 (0.10)	81 (0.08)	55 (0.06)	64 (0.08)	81 (0.09)

BMI, body mass index; GP, general practitioner; IQR, interquartile range.
[†]Data available for 239 593 patients.
[‡]Data available for 335 553 patients.
*Available for 403 864 (1 year) and 364 211 patients (3 years).
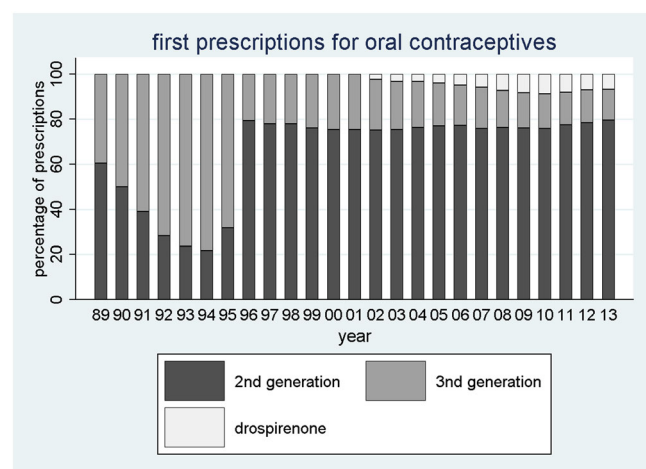Data are presented as n (%) unless stated otherwise.

Figure 2. Proportion of prescriptions for third-generation and second-generation oral contraceptives (and drospirenone-containing contraceptives) per calendar year

show an increased risk for VTE for third-generation OCs in comparison with second-generation OCs: the adjusted 1-year risk difference was 1.2 events per 10 000 patients (95%CI −0.2;2.6) and the adjusted 3-year risk difference was 2.0 events per 10 000 patients (−0.2;4.2). All point estimates from the 2-SLS regression were also in the direction of an increased risk for VTE for third-generation OCs but with much wider CIs. The fully adjusted 2-SLS analyses gave a 1-year risk difference of 3.5 events per 10 000 patients (−1.2;8.3) and a 3-year risk difference of 3.0 events per 10 000 patients (−4.5;10.4).

Cox proportional hazards and instrumental variable for Cox proportional hazards regression

Median follow-up time was 234 days, 38% had at least 1 year, and 11% had at least 3 years of continuous use of the same OC. There were 179 events during a continuous period of use of the same OC. HRs for VTE of third-generation OCs compared with second-generation OCs obtained using conventional Cox proportional hazards regression and IV for Cox proportional hazards regression are displayed in Table 3. Both the conventional Cox regression estimate (adjusted HR 1.62; 95%CI 1.16–2.27) and the IV Cox regression estimate (fully adjusted HR 3.45; 95%CI 0.97–11.7) were in the direction of an increased VTE risk for third-generation OCs (although with very wide CIs for the IV Cox regression).

Sensitivity analyses

The sensitivity analysis requiring a minimal registration time of 1 year gave slightly larger 1-year risk difference estimates in both the OLS analysis (adjusted RD 1.7; 95%CI 0.2;3.3) and the 2-SLS analysis (fully adjusted RD 5.7; 95%CI 0.0;11.4). Other results did not change materially (Supporting Information Tables S2–S4).

The sensitivity analysis without requirement of a record of anticoagulant treatment in the event definition resulted in a larger absolute number of events and somewhat larger risk differences in the OLS analyses (Supporting Information Table S5). All other results

Table 2. Conventional and instrumental variable estimates of the risk differences of venous thromboembolism per 10 000 patients for third-generation versus second-eneration oral contraceptives within 1 year and within 3 years of first prescription

		Ordinary least squares (risk difference per 10 000)		Two-stage least squares (risk difference per 10 000)		
Time (years)	no. events	Unadjusted	Adjusted for calendar year, age, BMI and smoking	Unadjusted	Adjusted for calendar year	Adjusted for calendar year, age, BMI and smoking
1	136	1.1 (−0.2;2.4)	1.2 (−0.2;2.6)	0.8 (−2.4;4.0)	4.0 (−1.1;9.1)	3.5 (−1.7;8.7)
3	281	3.0 (1.0;5.0)	2.0 (−0.2;4.2)	4.1 (−0.8;9.0)	3.8 (−3.7,11.4)	3.0 (−4.7;10.6)

Table 3. Conventional and instrumental variable estimates of the hazard ratio of venous thromboembolism for third-generation versus second-generation oral contraceptives

Conventional Cox proportional hazards regression		IV for Cox proportional hazards regression*		
Unadjusted	Adjusted for calendar year, age, BMI and smoking	Unadjusted	Adjusted for calendar year	Adjusted for calendar year, age, BMI and smoking
1.78 (1.30–2.44)	1.62 (1.16–2.27)	2.05 (0.96–4.39)	4.16 (1.22–13.0)	3.45 (0.97–11.7)

*Instrumental variable (IV) regression with a linear regression first stage and a Cox regression second stage, confidence intervals derived using bootstrapping (see Methods for details).

(Supporting Information Tables S5 and S6) were very similar to those from the main analyses.

DISCUSSION

The results of the IV analyses showed a similar picture to results from the conventional analyses. All estimates were consistently in the direction of an increased risk of VTE for third-generation OCs in comparison with second-generation OCs. The point estimates from the IV analysis were generally higher than those from the conventional analyses, albeit with wide CIs. The results of the IV analyses do not indicate that unknown confounding could explain the higher VTE incidence with third-generation OCs.

To our knowledge, no previous studies have used IV analysis to investigate the effect of third-generation versus second-generation OCs on the risk of VTE. Previous studies include both case–control studies[7,8,14,19–21] and cohort studies.[9,14,19,22] Many of these studies compared levonorgestrel-containing contraceptives with gestodene-containing or desogestrel-containing contraceptives,[7,9,19,22] whereas we included a broader range of second-generation and third-generation OCs (although there has been discussion whether norgestimate-containing OCs should be grouped with third-generation OCs)[12]. To mimic the randomised trial situation, we only used 'incident users' of OCs in our analysis.[23–25] For the Cox proportional hazards regression analyses, we only included the period of use of the class of OC a patient was first prescribed. This highlights a limitation of the least squares analyses: these

included women who started using a certain OC but switched, stopped or were lost to follow-up.

A limitation of IV analysis in general is the larger variance in comparison with conventional analyses. Although our study population was very large, the number of events was small, resulting in large CIs for the IV estimates in particular. Unfortunately, this limits the informativity of the IV analyses regarding the effect size. In our study, the IV analyses do provide a reasonably strong indication of the direction of the effect. A further limitation is the difficulty of identifying all true VTE events. We used an extensive list of diagnosis codes and required a record of an anticoagulant prescription for the events in our main analyses as an additional safeguard against misclassification (as in previous studies). However, this may have resulted in exclusion of some true events. Sensitivity analyses without the anticoagulant requirement did not yield substantially different results.

The analysis across the 25-year time period and the changes in prescribing preferences over time posed some problems. Because both prescribing preference and the age and smoking behaviour of patients who were first prescribed an OC changed substantially over time, prescribing preference was related to age and smoking behaviour. This violates the independence assumption (the instrument may not be related to other factors which affect the outcome). Restricting the data to a shorter time period across which prescribing preference was more or less stable was not possible due to the low incidence of VTE, which would result in a study with a very low power.

Adjusting the IV analyses for calendar year was considered the best alternative.

As explained in the methods, in order to obtain a point estimate in the instrumental variable analyses, we assume that the stochastic monotonicity assumption holds. For our study, it is plausible that the direction in which GP's preference affects the type of OC prescribed is the same for all relevant subgroups, because it is unlikely that GPs with a general preference for third-generation OCs would be less likely to prescribe third-generation OCs to a specific subgroup of patients than GPs with a general preference for second-generation OCs. The strength-of-IV weighted average treatment effect (SIVWATE) estimated by the instrumental variable analyses has a slightly different interpretation than the average treatment effect in the population estimated by the conventional analyses. As mentioned previously, it is a weighted average of the effects of type of OC on risk of venous thromboembolism in these relevant subgroups (weighted by the strength of the instrument in these subgroups). This makes the interpretation difficult, because these subgroups cannot be readily identified and the variation in the strength of the instrument within these subgroups is not known. However, within our study, we do not expect the strength of the instrument to vary widely between subgroups, and hence, we do not expect the SIVWATE to be vastly different from the average treatment effect.

In conclusion, we found an increased risk of VTE for third-generation OCs in comparison with second-generation OCs using both conventional analyses and IV analyses. The consistent direction of these results, obtained under different sets of assumptions, suggests that major confounding is unlikely in this study of a minimally predictable side-effect. The IV analysis results therefore do not support the objection by some researchers in the late 1990s that the higher VTE incidence for third-generation contraceptives was due to selective prescribing of third-generation OCs to women at an increased risk of VTE. IV analysis can be a useful complementary analysis under an alternative set of assumptions in studies of adverse effects in very large databases, where there is discussion regarding the presence of confounding in the conventional analyses.

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ETHICS APPROVAL

The protocol for this study was approved by the Independent Scientific Advisory Committee (ISAC) for CPRD research on 28 April 2014 (Reference number 14_082) and has been made available to reviewers.

CONFLICT OF INTEREST

The authors report no conflict of interest.

Key points
- In observational studies of adverse effects of drug therapy, discussion can arise regarding the presence of confounding by (contra)indication.
- In a population of women who started second-generation or third-generation oral contraceptive, results from instrumental variable analyses and conventional analyses were consistently in the direction of an increased risk of venous thromboembolism for third-generation oral contraceptives in comparison with second-generation oral contraceptives.
- Instrumental variable analysis can be a useful complementary analysis to assess the presence of confounding in studies of adverse effects in very large databases.

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