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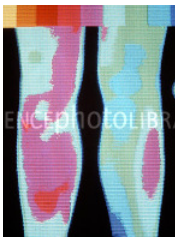

Thrombophilias increase the risk for pregnancy associated VTE, but absolute risk varies by type of thrombophilia
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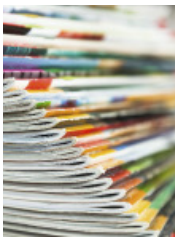

Industry payments to US medical journal editors are not rare and can be substantial
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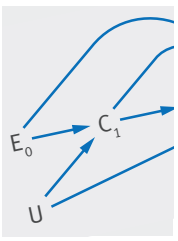

How to handle time-varying confounding in observational research
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ORIGINAL RESEARCH Systematic review and bayesian meta-analysis

Pregnancy, thrombophilia, and the risk of a first venous thrombosis

Croles FN, Nasserinejad K, Duvekot JJ, et al

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Study question What is the risk of a first venous thromboembolism (VTE) in pregnant women with hereditary thrombophilia?

Methods A systematic review and bayesian meta-analysis was performed. Eligible observational studies reported on pregnancies without use of anticoagulants and the outcome first VTE for women with thrombophilia. Bayesian meta-analysis was used to calculate relative and absolute risks of pregnancy associated VTE, and probabilities of increased risk of pregnancy associated VTE. Additionally, the probabilities of absolute risks being above the threshold for thrombosis prophylaxis (considered to be 3% for each antepartum or postpartum period) were calculated.

Study answer and limitations All thrombophilias increase the risk for pregnancy associated VTE (probabilities ≥91%). Regarding absolute risks of pregnancy associated VTE, high risk thrombophilias were antithrombin deficiency (antepartum: 7.3%, 95% credible interval 1.8% to 15.6%; postpartum: 11.1%, 3.7% to 21.0%), protein C deficiency (3.2%, 0.6% to 8.2% and 5.4%, 0.9% to 13.8%), protein S deficiency (0.9%, 0.0% to 3.7% and 4.2%, 0.7% to 9.4%), and homozygous factor V Leiden mutation (2.8%, 0.0% to 8.6% and 2.8%, 0.0% to 8.8%). Absolute antepartum or postpartum VTE risks for women with heterozygous factor V Leiden mutation or heterozygous prothrombin G20210A mutations, and compound heterozygous factor V Leiden and prothrombin G20210A mutations both antepartum and postpartum were far below 3%. This study was limited by the quality of studies as risk estimates were generally lower in high quality studies. Absolute risk estimates of VTE in women with rare thrombophilias were mainly based on family studies.

What this study adds Thrombosis prophylaxis is generally not warranted for heterozygous factor V Leiden mutation, heterozygous prothrombin G20210A mutation, or compound heterozygous factor V Leiden and prothrombin G20210A mutation. Antepartum and postpartum thrombosis prophylaxis is warranted in women with antithrombin deficiency or protein C deficiency and a family history of VTE. Postpartum prophylaxis only is warranted in women with protein S deficiency.

Funding, competing interests, data sharing No external funding. See full paper on bmj.com for competing interests. The dataset and statistical code are available from the corresponding author.

Relative and absolute risks (AR) of pregnancy associated venous thromboembolism (VTE)

Thrombophilic defect	Odds ratio*	AR† of VTE, all studies, % pregnancies			Prophylaxis considered	
		Antepartum	Postpartum	Antepartum and postpartum	Antepartum	Postpartum
Antithrombin deficiency	9.5	7.3	11.1	16.6	Yes	Yes
Protein C deficiency	9.3	3.2	5.4	7.8	Yes	Yes
Protein S deficiency	7.0	0.9	4.2	4.8	No	Yes
Homozygous factor V Leiden mutation	35.8	2.8	2.8	6.2	Yes	Yes
Heterozygous prothrombin G20210A mutation	5.1	0.0	0.9	0.9	No	No

The recommendation for homozygous factor V Leiden mutation carriers to consider thrombosis prophylaxis stems from the closeness of the point estimate to treatment threshold. Additional risk factors for VTE should be taken into account. NA=Data not available.
*Estimates are for pregnancy associated VTE for each thrombophilia compared with controls or non-carriers.
†Numbers are point estimates from meta-analyses of absolute risks of all studies.

Competing interests in journal editors

ORIGINAL RESEARCH Retrospective observational study

Payments by US pharmaceutical and medical device manufacturers to US medical journal editors

Liu JJ, Bell CM, Matelski JJ, Detsky AS, Cram P
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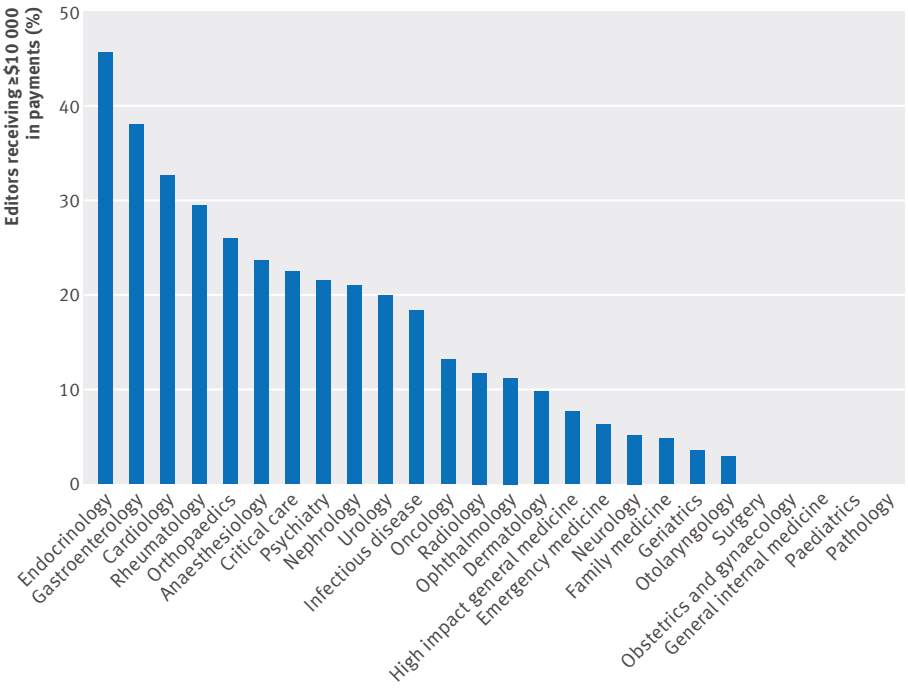
Study question What is the extent of financial payments from industry to editors of US medical journals?

Methods The authors identified editors at the associate level and above at 52 influential (high impact factor for their specialty) US medical journals from 26 specialties using each journal's online masthead. Through the US Open Payments database they identified all general payments and research related payments from pharmaceutical and medical device manufacturers to eligible physicians in 2014. They compared the percentages



Percentage of editors receiving any general payment >$10 000, by journal specialty, 2014

COMMENTARY Financial conflicts are common, and must be declared and managed

Individuals are almost incapable of determining whether their own competing interests might affect their judgment. To mitigate bias or perception of bias in published work, journals are increasingly tightening their requirements for authors and reviewers to declare and publish competing interests. The study by Liu and colleagues opens up a new front in the debate—reporting payments by drug and device companies to US doctors who are also editors of academic journals.

The study mines a relatively new and fascinating initiative: the Open Payments database, set up as a requirement of the US Affordable Care Act. The database is a public record of payments to US doctors and teaching hospitals from drug and device companies operating in the US, who are reimbursed by the three federal healthcare programmes.

Liu and colleagues identified payments made to doctors at or above the associate editor level at 52 journals across 26 specialties. The findings are interesting, of concern in parts, and should probably now set new expectations of disclosures by journals and editors.

> Not every interest is harmful. But consumers of journal content should be able to judge for themselves

Notable outliers

The authors found that in 2014 just over half of 713 journal editors eligible for Open Payments had received payments of some sort from drug or device companies and 19.5% (n=139) had received research funding. The range in magnitude of the payments was huge; whereas the median for general payment was just $11 (£8; €9) (interquartile range $0-2923), two notable outliers received more than $1m each. There were also considerable differences among specialties, with the highest payments going to editors of journals in cardiology, orthopaedics, endocrinology, and rheumatology.

This study cannot determine whether payment influenced journal content—and the authors do not explore the source of payments to individual editors, or any associations between editors and specific products. Furthermore, the authors analysed payments made in 2014, to editors identified in 2016, and this time lag could have affected the findings. Journals were given the opportunity to check the records of who was on their editorial board were correct, but the response to this survey was regrettably low (28.8%).

What do these findings mean for journals, editors, readers, and patients who rely on impartial research to inform their healthcare decisions? First and foremost it seems clear that information about editors' interests must be declared and made public. The Committee on Publication Ethics (COPE) has long had an expectation that editors have procedures to manage their own competing interests.

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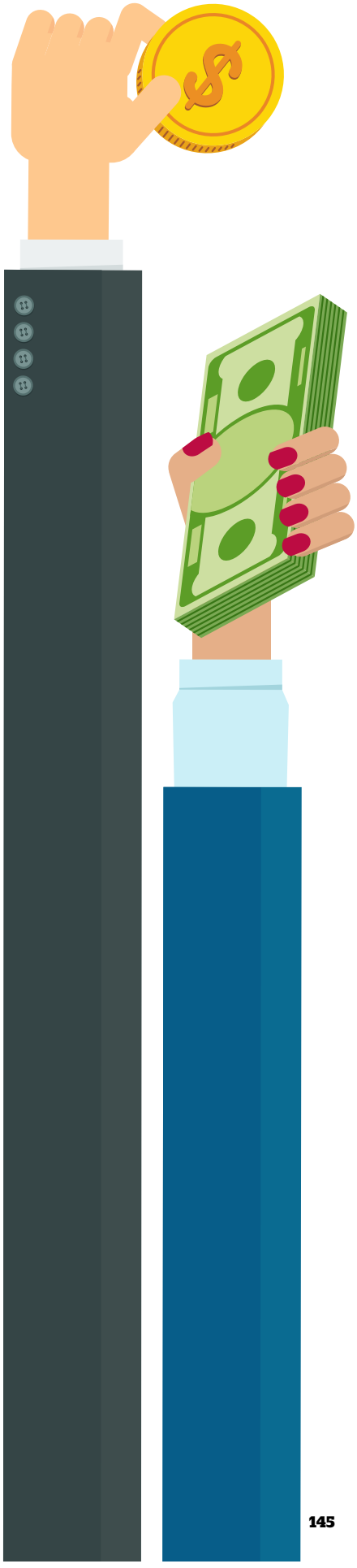
Of 713 eligible editors, 363 received some general payments in 2014

of editors receiving payments and the magnitude of such payments across journals and by specialty. To determine if conflict of interest policies for editors were readily accessible (ie, within five minutes), they also reviewed the websites of each journal.

Study answer Of 713 eligible editors, 363 (50.9%) received some (>$0) general payments in 2014 and 139 (19.5%) received payments for research. The median general payment was $11 (interquartile range $0-2923) and the median research payment was $0 ($0-0). The mean general payment was $28 136 (SD $415 045), whereas the mean research payment was $37 963 (SD $175 239). The highest median general payments were received by journal editors from endocrinology ($7207, interquartile range $0-85 816), cardiology ($2664, $0-12 912), gastroenterology ($696, $0-20 002), rheumatology ($515, $ 0-14 280), and urology ($480, $90-669). For high impact general medicine journals (journals with a global impact and that encompass topics from across all specialties and disciplines), median payments were $0 ($0-14). Editor conflicts of interest policies were readily accessible online for 32.7% (17/52) of the journals.

What this study adds Industry payments to journal editors are not rare, can be of substantial monetary value, and vary considerably among journals and by specialty. Journals should consider the potential impact of such payments on public trust in published research.

Funding, competing interests, data sharing PC is supported by a K24 award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (AR062133). The authors have no competing interests. No additional data available.



Some journals, including *The BMJ* and *PLoS Medicine* have required editors to disclose competing interests for many years, but their policies seem to be far from the norm; Liu and colleagues found easily accessible (that is, within five minutes) editorial competing interest policies in only one third of the 52 journals.

Are editors falling prey to the fallacy that they can judge their own competing interests? Or equally erroneous, that a journal's content is somehow immune from the influence of editors' interests? We know that journals are not just machine sorted collections of objects, and they are of course shaped by the experiences and biases of their editors. Like it or not, these influences can be part of a journal's appeal to audiences. *PLoS Medicine*, for example, was once described to me as the "journal of left wing epidemiology." As an editor, I took it as an unintended compliment.

Not every interest is harmful. But consumers of journal content should be able to judge for themselves. Non-disclosure is no longer acceptable. In the same way that it seems right (although not the norm) for patients to be informed when clinicians are paid by drug and device manufacturers,[4 5] it seems right that journals have a clear policy on editors' competing interests that includes public declaration of all relevant interests coupled with publicly described and diligently enforced policies to manage competing interests when they arise. Journals should also be open about their own sources of funding; another potential source of bias in journal content.

Openness and transparency are increasingly important in medical science and publishing. If medical journals want to remain a trusted source of evidence, then editors need to step up and apply to themselves the same standards of transparency that they expect of others.

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Handling time-varying confounding in observational research

Mansournia MA, Etminan M, Danaei G, Kaufman JS, Collins G

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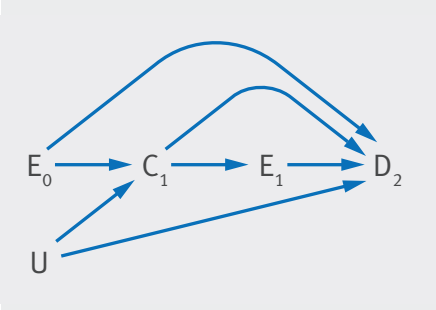
Many exposures of epidemiological interest are time-varying, and the values of potential confounders may change over time leading to time-varying confounding. The aim of many longitudinal studies is to estimate the causal effect of a time-varying exposure on an outcome that requires adjusting for time-varying confounding. Time-varying confounding affected by previous exposure often occurs in practice, but it is usually adjusted for by using conventional analytical methods such as time dependent Cox regression, random effects models, or generalised estimating equations, which are known to provide biased effect estimates in this setting. The resolution for the dilemma of time-varying confounding affected by past exposure requires the longitudinal data on both the exposure and the confounders affected by the previous exposure. It also requires use of a statistical method that adjusts for the confounding effect of the covariate, but not for the effect of exposure on the confounder. Three causal methods were proposed to adjust appropriately for this potential bias: inverse-probability-of-treatment weighting, the parametric G formula, and G estimation. The success of G methods for appropriately adjusting time-varying confounders affected by past exposure is because, unlike conventional methods such as stratification or regression modelling, they do not fix the value of confounders to adjust for them so they do not introduce over-adjustment or selection bias.



Causal diagram showing time-varying confounding affected by past exposure

Advantages and disadvantages of three G methods

G method	Advantages	Disadvantages
Inverse-probability-of-treatment weighting	They resemble standard statistical procedures and are simple to understand; available in almost all statistical software; useful when the reasons for exposure assignment are known (eg, in the presence of confounding by indication)	Cannot be used if there is a confounder level for which all participants are exposed or not exposed (eg, those who leave their occupation cannot be exposed to occupational exposures); unstable in the presence of extreme weights; less useful for studying the interaction between exposure and time-varying confounders
Parametric G formula	Ideal for studies that examine interventions on multiple risk factors (joint interventions) and interventions dependent on evolving risk factor values (dynamic interventions); computes causal measures of interest such as risk ratios and risk differences	Computationally intensive, requires extra programming, and can lead to fitting problems; requires models for confounders as well as outcomes; subject to the "G null paradox": the method rejects the causal null hypothesis, even when true, in sufficiently large samples, so it can only be used for interventions when the null is believed to be untrue
G estimation	Can be used even if there is a confounder level for which all participants are exposed or not exposed; useful for studying the interaction between exposure and time-varying confounders	Computationally intensive, requires extra programming, and can lead to fitting problems; the methodology and resulting effect variable are somewhat difficult to understand

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