In a meta-analysis in this issue, Chandra and colleagues (1) conclude that the best estimate of the effect of travel on venous thrombosis (VT) is a close to 3-fold increase in risk. To arrive at that conclusion, they exclude the case–control studies in which the controls were referred with the suspicion of VT, like the case patients, but tested negative for VT. These studies found no excess risk. Their exclusion from the analysis might surprise readers; controls with the same reasons for referral who came from the same population would seem ideal. Our purpose is to discuss the selection of controls for case–control studies, using Chandra and colleagues’ article as an example. Our principal conclusion is that Chandra and colleagues’ explanation of their results goes in the right direction but is incomplete.

Chandra and colleagues removed case–control studies that used referred controls from their final analysis because, they argue, investigators make a mistake when they think that controls in a case–control study should resemble case patients as closely as possible (1). Making groups as equal as possible is the usual reasoning in follow-up studies or randomized trials. However, as Chandra and colleagues point out, this reasoning is wrong in case–control studies. Case patients will always have more risk factors for disease than controls, whose sole purpose in the study is to yield an estimate of the frequency of the exposure of interest in the population. Matching controls too closely creates the danger that they will have the same level of exposure as the case patients, which would result in a null finding (the key calculation in a case–control study is the ratio of the odds of exposure in the case patients relative to the odds of exposure in the controls). Indeed, Figure 2 of Chandra and colleagues’ article (1) shows that travel is not associated with VT in the studies that used referred controls. We agree with the authors’ reasoning as far as it goes, but we think their reasoning for excluding case–control studies with referred controls is incomplete.

Using referred controls—persons who were initially suspected of having the same disease as the case patients—in a case–control study is not always a mistake; it can be a good strategy for ruling out diagnostic suspicion or referral bias, as exemplified by the association between oral contraceptives and VT. Suppose that oral contraceptives would not cause VT, contrary to physicians’ beliefs. If a young woman presented with signs and symptoms of VT, knowing that she used oral contraceptives would sway her physician to refer her for diagnostic work-up, whereas the physician might not have referred her otherwise because thrombosis is unlikely in young women (2). Case–control studies enroll patients according to the diagnosis they receive and would thereby show a spurious association between oral contraceptives and VT because more case patients than controls would be using oral contraceptives. This hypothetical situation exemplifies the influence of diagnostic suspicion bias in case–control studies. One way to avoid this bias is to study only patients with severe symptoms, who would always be referred for work-up, so that diagnostic suspicion bias should play no role. The association between oral contraceptives and VT remained equally strong in studies that enrolled only women with severe symptoms (see references in Bloemenkamp and colleagues’ study [3]). Another strategy is to use referred patients as controls. If physicians preferentially refer women who use oral contraceptives and have leg symptoms, the frequency of oral contraceptive use will be the same in referred persons with and without VT—unless contraceptives are truly associated with VT. Studies that used this design yielded the same risk estimates as studies with nonreferred controls (3, 4), which suggests that diagnostic suspicion bias does not play a major role in the association of oral contraceptives with VT. Use of referred controls also helped to exclude potential bias in the association between aspirin and the Reye syndrome, another major controversy (5).

In the oral contraceptive example, we inferred that diagnostic suspicion bias was not playing a role because the strength of association did not change when the controls were referred patients. In the case of travel and VT, the association almost completely disappeared with referred controls. Does this finding mean that the association between travel and VT is due to diagnostic suspicion and referral bias? Not necessarily. A pivotal assumption when using referred controls is that the exposure (such as oral contraceptives or travel) does not cause the same signs and symptoms as the disease that defines case status (6). Oral contraceptives are very unlikely to cause acute marked edema by a nonthrombotic mechanism. However, travel, in particular long air travel, does induce edema that is similar to the swelling of leg thrombosis and may lead to referral (7, 8). In addition, all studies with referred controls included persons with a history of VT (up to 20% of both case patients and controls), which would make them prone to venous insufficiency (and therefore likely to develop edema after long periods of sitting) and easily alarmed by (and likely to seek care for) leg swelling. Because the diagnosis of recurrent thrombosis is not straightforward, adjudicated case patients and controls may be misdiagnosed, which would also bias the association of travel and VT toward the null.

Our examples of travel and oral contraceptives differ in 2 ways. First, travelers with edema that is not due to VT may be referred because they have signs and symptoms caused by travel, a mechanism that is particularly likely in persons with a history of leg thrombosis. This scenario would lead to overestimation of travel frequency among the controls and bias the association toward the null. Second, including travelers with a history of VT may lead to
diagnostic misclassification of both case patients and controls, which also causes bias toward a null association.

As a reason to exclude case-control studies that used referred controls, Chandra and colleagues (1) invoke an unspecified mechanism of an overall selection bias caused by recent travel as a reason for referral. We do not find this explanation to be compelling, because assuming that persons with mild symptoms would only be referred when they had traveled, this would augment the proportion of travelers among both the referred controls and the case patients in a similar way. However, as long as travel truly caused some cases of VT, case patients and controls would differ in their frequency of travel. Thus, the use of referred controls would only mask a true difference in travel between case patients and referred controls when travel causes a close mimic of thrombosis in the controls.

Are we certain that studies with referred controls found no association between travel and VT because travel caused the controls to have signs and symptoms that resembled thrombosis? Did inclusion of patients with a previous thrombosis lead to misclassification that further attenuated the results? We cannot be sure. To be certain, we would need to know the diagnosis assigned after testing excluded VT. In particular, did controls who had traveled receive different diagnoses than those who had not? Did such controls often have a history of VT and receive a diagnosis of postthrombotic travel edema? Restricting the analysis of case-control studies with referred controls to “first-ever VT” might increase the odds ratio, which would imply the presence of our proposed mechanisms.

The final alternative explanation is that the association between travel and VT resulted from diagnostic suspicion and referral bias. This seems unlikely. First, an early study (9) counted sudden deaths in the arrival and departure hall and found an excess of pulmonary emboli in the arrival hall; diagnostic bias is unlikely for fatal pulmonary embolism. Second, another study (10) reported that severe pulmonary embolism has a strong graded association with duration of travel. Chandra and colleagues also report a graded dose-response relationship. Finally, VT and air travel are related by several more dose-response gradients: duration of flight, number of recent flights, and recency of exposure (the incidence of VT quickly wanes after travel) (11).

In summary, Chandra and colleagues were probably right to exclude case-control studies that used referred controls, but for more complex reasons than they specified. Like any choice of controls, the use of referred controls in case-control studies can be a double-edged sword: Although it can mislead, it has the power to resolve a controversy when a postulated diagnostic referral bias does not exist or is minimal, as was the case for oral contraceptives and VT.

The importance of thinking about the proper choice of controls, and of dissecting potential bias in great detail, serves a practical purpose: If effects are rare and follow potential causes closely in time, case-control studies are the most obvious way to study a very important clinical problem: whether long-distance travel predisposes a person to VT. Therefore, it is important to know under what circumstances the results are most likely to be right. Chandra and colleagues’ meta-analysis (1) has the great merit of bringing into the open a problem that was insufficiently discussed in reviews about travel and VT and may have led previous meta-analyses to underestimate the risk.

Jan P. Vandenbroucke, MD, PhD
Suzanne C. Cannegether, MD, PhD
Frits R. Rosendaal, MD, PhD
Leiden University Medical Center
Leiden, the Netherlands

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Requests for Single Reprints: Jan P. Vandenbroucke, MD, PhD, Department of Clinical Epidemiology, Leiden University Medical Center, Box 9600, 2300 RC Leiden, the Netherlands; e-mail, j.p.vandenbroucke@lumc.nl.

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Current Author Addresses: Drs. Vandenbroucke, Cannegieter, and Rosendaal: Department of Clinical Epidemiology, Leiden University Medical Center, Box 9600, 2300 RC Leiden, the Netherlands.