Meta-analysis: Travel and Risk for Venous Thromboembolism

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Background: The potential risk for travel-related venous thromboembolism (VTE) has become an important public health concern because of rapid increases in long-distance travel; however, previous studies on this relationship are surprisingly contradictory.

Purpose: To estimate the risk for VTE in travelers, determine whether a dose–response relationship exists, and identify reasons for the contradictory results of previous studies.

Data Sources: MEDLINE, EMBASE, BIOSIS, CINAHL, grey-literature sources, contact with investigators, and reference lists of studies, without language restrictions.

Study Selection: Reports were selected if they investigated the association between travel and VTE for persons who used any mode of transportation and if nontraveling persons were included for comparison.

Data Extraction: Data on study and patient characteristics, risk estimates, and quality were independently extracted by 2 investigators. Pooled effect estimates were obtained by using random-effect meta-analysis.

Data Synthesis: Of 1560 identified abstracts, 14 studies (11 case–control, 2 cohort, and 1 case–crossover) met inclusion criteria, including 4055 cases of VTE. Compared with nontravelers, the overall pooled relative risk for VTE in travelers was 2.0 (95% CI, 1.5 to 2.7). Significant heterogeneity was present because of the method for selecting control participants ($P = 0.008$): whether the studies used control participants who had been referred for VTE evaluation or nonreferred control participants. When the studies that used referred control participants were excluded, the pooled relative risk for VTE in travelers was 2.8 (CI, 2.2 to 3.7), without significant heterogeneity. A dose–response relationship was identified, with an 18% higher risk for VTE for each 2-hour increase in duration of travel by any mode ($P = 0.010$) and a 26% higher risk for every 2 hours of air travel ($P = 0.005$).

Limitation: All available studies were from Western countries; generalizability to non-Western populations is expected but needs confirmation.

Conclusion: Travel is associated with a nearly 3-fold higher risk for VTE, with a dose–response relationship of 18% higher risk for each 2-hour increase in travel duration. Heterogeneity in results of previous studies was due to selection bias toward the null from use of referred control participants.

Because of the rapid increase in air and other modes of travel in recent years, the potential risk for travel-related venous thromboembolism (VTE) is a growing public health concern (1). Worldwide, 2.5 billion passengers will travel by air in 2010 (2), which underscores the large global population at risk for this serious condition. In addition to the direct and indirect costs of evaluation and treatment, mortality risk is high: In ambulatory population-based cohorts, the estimated 28-day mortality for a first episode of VTE is 11% (3). Although a positive relationship between travel and VTE is often discussed and assumed to exist, the results of previous studies are surprisingly conflicting. Several epidemiologic studies have investigated this relationship over the past decade; approximately half have found no relationship between travel and VTE (4–8), whereas the rest have identified elevated risk (9–16). Demonstrating the presence and magnitude of such potential risk is crucial to determine the appropriateness of additional controlled trials or policy measures to prevent travel-related VTE. In addition, if a relationship exists, quantifying the dose–response relationship—how duration of travel relates to VTE—is central to determining the travel circumstances under which sufficient risk could be present to justify preventive interventions.

To determine whether travel is associated with risk for VTE, to quantify the dose–response relationship, and to identify reasons for the contradictory findings reported by previous studies, we performed a systematic review and meta-analysis of studies of travel and risk for VTE. We hypothesized that travel would be associated with the risk for VTE and that this risk would increase with greater duration of travel.

METHODS

We followed the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines during all stages of design, implementation, and reporting of this meta-analysis (17).

Search Strategy and Data Sources

We searched for all studies that provided an effect estimate for a potential association between travel and VTE. Inclusion criteria were observational studies or clinical trials that included patients who traveled by any mode of transportation; that used nontraveling persons for com-

Context

The body of evidence on the epidemiology of long-distance travel and venous thromboembolism (VTE) is heterogeneous and inconclusive.

Contribution

The reviewers found 14 eligible studies, which had significant between-study heterogeneity, and the pooled relative risk for VTE was 2.0 (95% CI, 1.5 to 2.7). The reviewers eliminated the heterogeneity by excluding 6 case–control studies in which control participants had been referred for VTE testing. The relative risk was 2.8 (CI, 2.2 to 3.7) in the remaining included studies and 1.2 (CI, 0.9 to 1.6) in the excluded studies.

Implication

By excluding studies with control participants who had a different risk for VTE than the source population for the case patients, the authors clarified a confusing body of evidence.

—The Editors

parison; and that diagnosed VTE by appropriate radiologic investigation (ultrasonography or venography for deep venous thrombosis [DVT] and computed tomography or ventilation–perfusion scan for pulmonary embolism [PE]), autopsy findings, or documentation of hospitalization for VTE. We excluded studies if they only evaluated treatments for VTE, rather than travel as a risk factor for VTE; if VTE was diagnosed by less rigorous criteria (such as by using only administrative codes in outpatients); or if no comparison group of nontravelers was included (which would preclude estimation of relative risks [RRs] associated with travel).

We performed our search by using MEDLINE, EMBASE, BIOSIS, CINAHL, the Cochrane library, grey-literature sources (a system for information on grey literature in Europe, a British library inside database, and dissertation abstracts online); one of the investigators also hand-searched the reference lists of identified studies. For each database, the years searched included the earliest available online year of indexing up to March 2008, without language restrictions. We exploded each search term. Our MEDLINE search terms were ((travel[MeSH Terms] OR travel[Text Word]) OR (transportation[MeSH Terms] OR transportation[Text Word]) OR journey[All Fields] OR flying[All Fields]) AND ((thrombosis[MeSH Terms] OR thrombosis[Text Word]) OR (embolism[MeSH Terms] OR embolism[Text Word]) OR DVT[All Fields] OR PE[All Fields] OR clot[All Fields]) NOT (review[Publication Type] OR review literature as topic[MeSH Terms] OR review[Text Word]) NOT (case reports[Publication Type]).

Study Selection

Of 1560 identified abstracts, we excluded 1518 on screening because they were commentaries, general reviews, or case reports (**Figure 1**). Two investigators independently examined the full text of the remaining 42 studies to confirm eligibility for inclusion. The second reviewer was blinded to the study investigators and journal of publication. Interobserver agreement between the 2 reviewers for initial study inclusion was high ($\kappa = 0.89$). We resolved disagreement by mutual discussion and, if required, by consultation with a third investigator. Of the 42 studies, we excluded 15 because they lacked a nontraveling comparison group, 11 because they evaluated preventive measures for travel-related VTE, 1 because it did not use the required criteria for VTE diagnosis (18), and 1 because no events occurred and it also lacked a nontraveling comparison group (19). This resulted in the final selection of 14 studies, including 1 prospective cohort study (15), 1 retrospective cohort study (16), 1 case–crossover study (13), and 11 case–control studies (4–12, 14, 20). The investigators can provide a complete list of abstracts searched with reasons for exclusion on request.

Data Extraction and Quality Assessment

We collected data on the year the study was performed, study design, study location, inclusion and exclusion criteria, number of participants, duration and mode of travel, duration of follow up, and adjusted relative risks and odds ratios with CIs. Two investigators performed independent data extraction by using a standardized data collection form. We resolved disagreement by mutual discussion and, if required, by consulting a third investigator. All prespecified data points were available from the pub-

Figure 1. Study flow diagram.
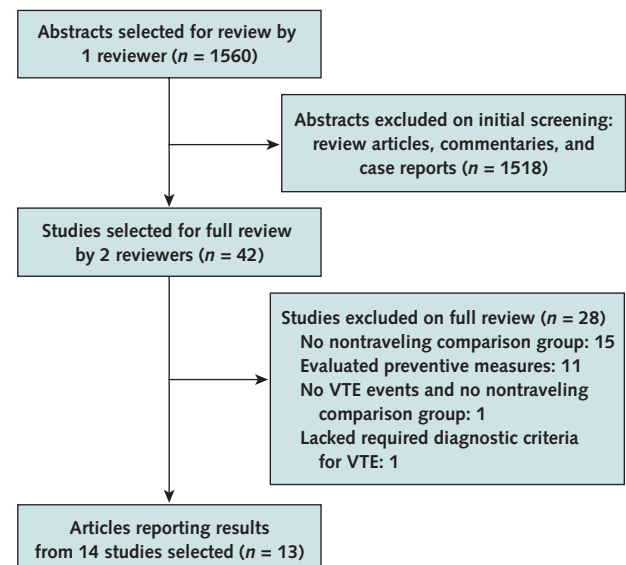
VTE = venous thromboembolism.

lished manuscripts, except for data on dose-response (duration of travel and risk for VTE) in 4 studies (11–13, 15); we contacted the investigators to request the missing data but received no responses. Because no standardized criteria have been established for judging the quality of observational studies, quality scores can differ depending on the scale chosen, and interpretation of such scores is difficult (21), we selected a priori several important design characteristics that may affect study quality to evaluate as sources of heterogeneity, including inclusion and exclusion criteria, method of travel history assessment, selection criteria for control participants, matching criteria, and control for confounding. We were particularly interested in the selection criteria for control participants in case–control studies because of the potential for selection bias that could substantially alter the validity of the obtained results. We assessed potential recall bias by the method (self-report vs. travel records) and timing (before vs. after VTE evaluation) of travel history assessment.

Statistical Analysis

We obtained pooled risk estimates for risk for VTE with travel by using random-effects models, according to the method of DerSimonian and Laird (22), with inverse-variance weighting. We used the most fully multivariable-adjusted effect estimate and recorded the included covariates. Because travel-related VTE is an uncommon outcome, odds ratios from case–control studies approximate risk ratios or relative risks (RRs) from cohort studies, and we pooled them to generate 1 common RR. Henceforth, we will refer to odds ratios from case–control studies as RRs. We assessed heterogeneity among studies by using Cochrane Q and I^2 statistics. We evaluated the following predefined sources of potential heterogeneity: study design (cohort vs. case–crossover vs. case–control), selection criteria for control participants in case–control studies (referred for VTE evaluation vs. nonreferred), study location (Europe vs. North America vs. Australia or New Zealand), minimum duration of travel required for inclusion (<8 vs.

Table 1. **Included Studies**

Study, Year (Reference)	Study Location	VTE Events, *n*	Case Confirmation	Control Group (Non–Case Patients)	Minimum Duration of Travel, *h*
Cohort studies					
Schwarz et al, 2003 (15)	Europe	7	Radiology	All non–case patients in the cohort	8
Kuipers et al, 2007 (16)	United States and Europe	22	Radiology	All non–case patients in the cohort	4
Case–crossover studies					
Kelman et al, 2003 (13)	Australia	46	Hospital admission for VTE	Within-person analysis of non–case-patient time	0
Case–control studies with nonreferred control population					
Ferrari et al, 1999 (11)	Europe	160	Radiology	Hospitalized with first episode of chest pain, arterial hypertension, or syncope‡	4
Samama, 2000 (12)	Europe	494	Radiology	Outpatients with influenza or rhinopharyngeal syndrome matched by age and sex	Not reported
Cannegieter et al, 2006 (10)	Europe	1906	Radiology	Matched partners of cases	4
Parkin et al, 2006 (9)	New Zealand	88	Autopsy§	Matched subjects from electoral roll	3
Martinelli et al, 2003 (14)	Europe	210	Radiology	Healthy volunteers	8
Case–control studies with referred control population					
Kraaijenhagen et al, 2000 (4)	Europe	186	Radiology‖	Referred for VTE but tested negative¶	3
Arya et al, 2002 (6)	Europe	185	Radiology	Referred for VTE but tested negative¶	3
Hosoi et al, 2002 (7)	Europe	101	Radiology	Referred for VTE but tested negative¶	3
ten Wolde et al (study 1), 2003 (5)	Europe	58	Radiology‖	Referred for VTE but tested negative¶	3
ten Wolde et al (study 2), 2003 (5)	Europe	233	Radiology‖	Referred for VTE but tested negative¶	3
Opatrny, 2004** (8)	Canada	359	Radiology	Referred for VTE but tested negative¶	0

DVT = deep venous thrombosis; PE = pulmonary embolism; VTE = venous thromboembolism.
* Method of ascertainment was the same for all participants in each study.
† Odds ratios for case–control and case–crossover studies and relative risks for cohort studies.
‡ We excluded patients with preexisting mobility restrictions and those who were receiving anticoagulants.
§ Eight cases were confirmed on the basis of pulmonary angiography and ventilation–perfusion scans, and 4 were confirmed by 2 internists who used standard criteria and were blinded to exposure status.
‖ Investigators also used D-dimer testing and clinical probability scores to rule out VTE in control participants.
¶ Patients were referred for radiologic work-up of suspected VTE, found to have negative test results, and included as control participants.
** This is the year of publication of the dissertation; this study has not been published in a journal.

≥8 hours), duration of follow-up after travel completed (≤3 vs. >3 weeks), type of VTE studied (DVT vs. PE), mode of travel (air vs. surface [land or sea]), exposure assessment (self-report vs. travel records), and number of included covariates. We obtained effect estimates by mode of travel from the individual studies or, when such estimates were unavailable, from previously reported pooled estimates (5). We used meta-regression to examine sources of heterogeneity by using the Wald test in random-effects meta-regression models. We also used meta-regression to test for a dose–response relationship between duration of travel and risk for VTE. We assessed potential publication bias by visually examining a funnel plot with the Begg test (23), a statistical analogue of the visual funnel graph, and the Egger test (24). We used STATA, version 9.0 (Stata-Corp, College Station, Texas), for all analyses. We defined statistical significance as a 2-tailed α value less than 0.05.

Role of the Funding Source

Our study received no outside funding.

RESULTS

Table 1 summarizes the characteristics of the 14 included studies. We identified 4055 cases of VTE, including 3980 cases in the 11 case–control studies (with 5413 control participants), 29 in the 2 cohort studies (10 932 participants), and 46 in the case–crossover study (5408 participants). Seven of the studies reported statistically significant associations between travel and VTE and 7 reported no significant association, which highlights the heterogeneity of the individual study results.
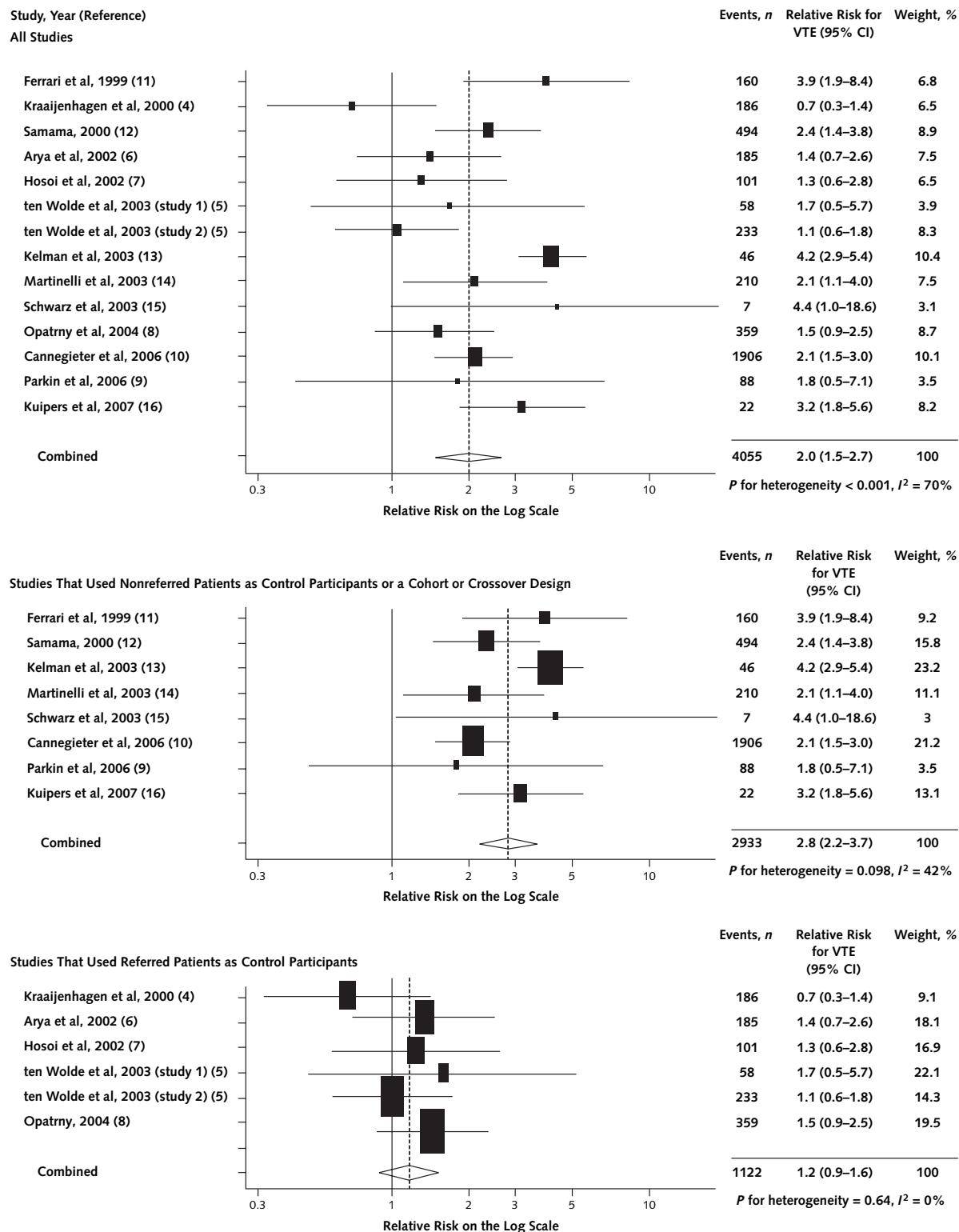
Description of Studies

We identified 3 study designs: cohort, case–control, and case–crossover. Two cohort studies evaluated large groups in specific populations, ascertained cases of VTE, and ascertained exposure (travel) status. These cohort designs allowed direct calculation of risk for VTE among those with versus those without exposure and minimized selection and recall bias. Conversely, given the infrequency

Mode of Travel	Travel History*	Follow-up, wk	Type of VTE	Covariates in the Analysis	Effect Estimate (95% CI)†
Air	Self-report before diagnosis	4	DVT	None	4.4 (1.0–18.6)
Air	Travel records	8	DVT or PE	Age and sex	3.2 (1.8–5.6)
Air	Travel records	2	DVT or PE	Within-person analysis adjusted for all non–time-varying covariates	4.2 (2.9–5.4)
Any	Self-report on admission for VTE	4	DVT or PE	Age	3.9 (1.9–8.4)
Any	Self-report after diagnosis	3	DVT	Age and sex	2.4 (1.4–3.8)
Any	Self-report after diagnosis	8	DVT or PE	Age	2.1 (1.5–3.0)
Air	Report by next of kin after fatal PE	4	Fatal PE	Age, sex, electorate, previous VTE, body mass index, immobility >1 wk, recent admission, oral contraceptive and antipsychotic use in preceding 3 mo	1.8 (0.5–7.1)
Air	Self-report after diagnosis	4	DVT or PE	Age, sex, education, body mass index	2.1 (1.1–4.0)
Any	Self-report before diagnosis	4	DVT	Age, sex, symptom duration, previous VTE, cancer, recent surgery, immobilization	0.7 (0.3–1.4)
Any	Self-report before diagnosis	4	DVT	None	1.4 (0.7–2.6)
Any	Self-report before diagnosis	2	DVT	None	1.3 (0.6–2.8)
Any	Self-report before diagnosis	4	DVT	None	1.7 (0.5–5.7)
Any	Self-report before diagnosis	4	PE	None	1.1 (0.6–1.8)
Any	Self-report after diagnosis	4	DVT	Age, sex, family history, previous VTE, factor V Leiden, oral contraceptives, hormone replacement therapy, warfarin use, immobility, trauma	1.5 (0.9–2.5)

Table 1—Continued

Figure 2. **Forest plot of the relative risks for travel-related VTE.**

Study, Year (Reference) All Studies		Events, n	Relative Risk for VTE (95% CI)	Weight, %
Ferrari et al, 1999 (11)		160	3.9 (1.9–8.4)	6.8
Kraaijenhagen et al, 2000 (4)		186	0.7 (0.3–1.4)	6.5
Samama, 2000 (12)		494	2.4 (1.4–3.8)	8.9
Arya et al, 2002 (6)		185	1.4 (0.7–2.6)	7.5
Hosoi et al, 2002 (7)		101	1.3 (0.6–2.8)	6.5
ten Wolde et al, 2003 (study 1) (5)		58	1.7 (0.5–5.7)	3.9
ten Wolde et al, 2003 (study 2) (5)		233	1.1 (0.6–1.8)	8.3
Kelman et al, 2003 (13)		46	4.2 (2.9–5.4)	10.4
Martinelli et al, 2003 (14)		210	2.1 (1.1–4.0)	7.5
Schwarz et al, 2003 (15)		7	4.4 (1.0–18.6)	3.1
Opatrny et al, 2004 (8)		359	1.5 (0.9–2.5)	8.7
Cannegieter et al, 2006 (10)		1906	2.1 (1.5–3.0)	10.1
Parkin et al, 2006 (9)		88	1.8 (0.5–7.1)	3.5
Kuipers et al, 2007 (16)		22	3.2 (1.8–5.6)	8.2
Combined		4055	2.0 (1.5–2.7)	100

P for heterogeneity < 0.001, I^2 = 70%

Studies That Used Nonreferred Patients as Control Participants or a Cohort or Crossover Design		Events, n	Relative Risk for VTE (95% CI)	Weight, %
Ferrari et al, 1999 (11)		160	3.9 (1.9–8.4)	9.2
Samama, 2000 (12)		494	2.4 (1.4–3.8)	15.8
Kelman et al, 2003 (13)		46	4.2 (2.9–5.4)	23.2
Martinelli et al, 2003 (14)		210	2.1 (1.1–4.0)	11.1
Schwarz et al, 2003 (15)		7	4.4 (1.0–18.6)	3
Cannegieter et al, 2006 (10)		1906	2.1 (1.5–3.0)	21.2
Parkin et al, 2006 (9)		88	1.8 (0.5–7.1)	3.5
Kuipers et al, 2007 (16)		22	3.2 (1.8–5.6)	13.1
Combined		2933	2.8 (2.2–3.7)	100

P for heterogeneity = 0.098, I^2 = 42%

Studies That Used Referred Patients as Control Participants		Events, n	Relative Risk for VTE (95% CI)	Weight, %
Kraaijenhagen et al, 2000 (4)		186	0.7 (0.3–1.4)	9.1
Arya et al, 2002 (6)		185	1.4 (0.7–2.6)	18.1
Hosoi et al, 2002 (7)		101	1.3 (0.6–2.8)	16.9
ten Wolde et al, 2003 (study 1) (5)		58	1.7 (0.5–5.7)	22.1
ten Wolde et al, 2003 (study 2) (5)		233	1.1 (0.6–1.8)	14.3
Opatrny, 2004 (8)		359	1.5 (0.9–2.5)	19.5
Combined		1122	1.2 (0.9–1.6)	100

P for heterogeneity = 0.64, I^2 = 0%

VTE = venous thromboembolism.

of travel-related VTE, investigators could identify few total cases among cohorts (29 total cases among 10 932 participants), which limited statistical power.

Eleven retrospective case–control studies identified VTE cases from hospital, clinic, or death records and then selected control participants by various means (nondiseased or non–case patients) who did not have VTE for comparison of likelihood of recent travel (**Table 1**). Compared with the cohort studies, the case–control design allowed investigators to identify more cases (3980 cases in 11 studies), which increased statistical power. However, unlike cohort studies, case–control studies could not directly calculate risk for VTE among those who traveled versus those who did not. Rather, these studies calculated the odds of travel among those with versus those without VTE to infer risk for VTE among persons who traveled versus those who did not. For these 2 risks to be mathematically equivalent, the likelihood of travel among the selected control participants must be similar to the likelihood of travel in the general population (the study base) from which the case patients came (25, 26).

When selected control participants do not provide an accurate estimate of the average likelihood of travel in the study base, selection bias results. Thus, the ideal control group must be selected by using criteria unrelated to risk for exposure (in this case, travel) among the general population from which the case patients were drawn. Five of the case–control studies we identified used population- or hospital-based control participants with conditions unrelated to travel, such as upper respiratory infection (non-referred control participants). The investigators in the individual studies inferred the absence of VTE in these control participants from the lack of any symptoms or signs of VTE; in such general samples, VTE would be unlikely. Six of the case–control studies we identified used patients who had been referred for suspected VTE but who tested negative on evaluation (referred control participants). In such studies, referred control participants would be more likely to have risk factors for VTE, including likelihood of recent travel, than the true study base.

Finally, 1 study used a case–crossover approach, in which control periods were within-person to eliminate confounding by risk factors for VTE that do not change over time.

The identified studies varied by mode of travel assessed (5 assessed air only and 9 assessed air or surface travel) and minimum duration of travel required for study inclusion (range, >0 to >8 hours). Travel history was ascertained by self-report before diagnosis of VTE in 6 studies, by self-report after diagnosis of VTE in 6 studies, and from pre-existing travel records in 2 studies. One half of the studies evaluated DVT alone, 5 evaluated PE or DVT, and 2 evaluated PE alone. End point ascertainment was fairly uniform: 12 of 14 studies used standard radiologic tests to establish the diagnosis of VTE, 1 used autopsy findings, and 1 used documentation of hospitalization with a pri-

mary diagnosis of VTE. Three studies also incorporated D-dimer measurements and clinical probability scores into the VTE diagnostic algorithm (4, 5). Ten studies were in Europe, 2 were in Europe and North America, and 2 were in Australia and New Zealand.

Main Pooled Analysis and Heterogeneity

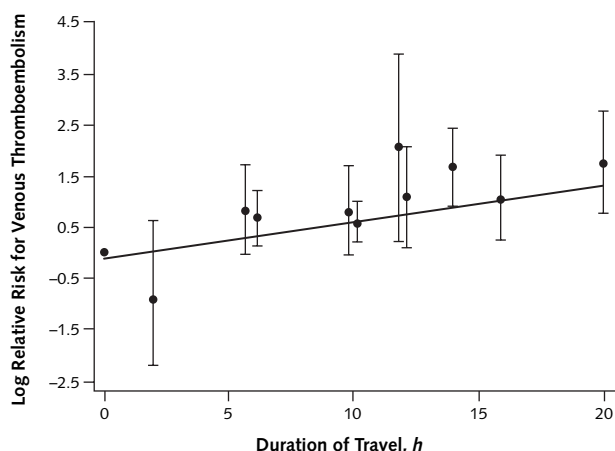The pooled relative risk for VTE among travelers across all studies was 2.0 (95% CI, 1.5 to 2.7; $P < 0.001$)

Table 2. Association Between Travel and VTE, by Prespecified Study Characteristics and Quality Criteria

Characteristic	Studies, n	Relative Risk (95% CI)	P Value for Interaction
Study design			0.008
Case–control	11	1.7 (1.3–2.2)	
Cohort	2	3.3 (2.0–5.7)	
Case–crossover	1	4.2 (3.1–5.7)	
Control participant selection in case–control studies			0.008
Participants referred for VTE evaluation	6	1.2 (0.9–1.6)	
Nonreferred control participants	5	2.3 (1.8–2.9)	
Study location			0.58
Europe	10	1.8 (1.3–2.4)	
North America	2	2.2 (1.0–4.5)	
Australia and New Zealand	2	3.5 (1.8–6.8)	
Minimum duration of travel			0.53
<8 h	2	1.9 (1.2–2.7)	
≥8 h	11	2.4 (1.3–4.3)	
Not reported	1	2.4 (1.4–3.8)	
Follow-up			0.31
≤3 wk	3	2.5 (1.4–4.7)	
>3 wk	11	1.8 (1.3–2.5)	
Type of VTE			0.030
Deep venous thrombosis	7	1.5 (1.1–2.2)	
Pulmonary embolism	2	1.1 (0.7–1.9)	
Deep venous thrombosis or pulmonary embolism	5	3.0 (2.1–4.2)	
Mode of travel*			0.143
Air	11	2.2 (1.4–3.2)	
Surface	6	1.4 (1.0–2.1)	
Source of control population for case–control studies			0.37
Hospital- or clinic-based	8	1.6 (1.1–2.2)	
Population-based	3	2.1 (1.6–2.8)	
Exposure assessment			0.57
Self-report after VTE diagnosis	6	2.1 (1.7–2.6)	
Travel records or self-report before diagnosis	8	1.8 (1.0–3.2)	
Number of covariates controlled for			0.54
0	5	1.3 (0.9–1.8)	
1–3	4	2.5 (1.9–3.2)	
>3	5	1.8 (0.9–3.6)	

VTE = venous thromboembolism.
* Studies could contribute to 1 or both estimates depending on modes of travel assessed.

Figure 3. Relationship between duration of travel and relative risk for venous thromboembolism, as reported by 4 included studies.

We also found evidence for heterogeneity by type of VTE ($P = 0.030$), with studies that evaluated DVT and PE demonstrating higher risk (RR, 3.0) than studies that evaluated DVT alone (RR, 1.5). Only 2 studies evaluated PE alone; they indicated no significant association (RR, 1.1) but had wide CIs due to the limited numbers of events in these studies (**Table 2**). We found no evidence for significant differences on the basis of study location, minimum travel duration, follow-up after travel, source of control population, method for exposure assessment, or number of potential confounders controlled for (**Table 2**). The pooled risk estimate for air travel (RR, 2.2 [CI, 1.4 to 3.2]) was somewhat higher than for surface travel (RR, 1.4 [CI, 1.0 to 2.1]), but this difference was not statistically significant (P for heterogeneity $= 0.140$).
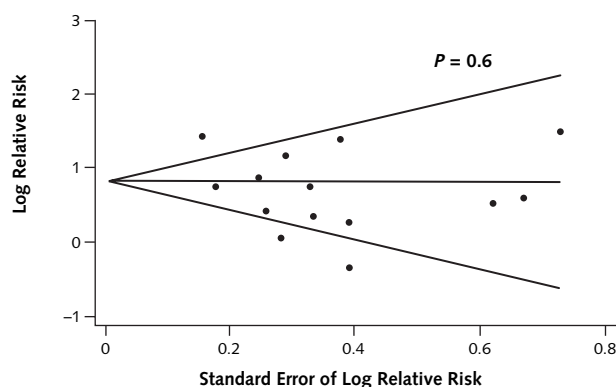
Dose–Response Relationship

We evaluated evidence for a dose–response relationship among the 8 studies that used nonreferred persons as control participants or used a cohort or case–crossover design. Data on varying risk by duration of travel were available from 4 of these 8 studies (9, 10, 14, 16). We identified a significant dose–response relationship (**Figure 3**), with an 18% higher risk for VTE for each 2-hour increase in travel duration (CI, 4% to 33%; $P = 0.010$). After we restricted this analysis to the 3 studies with available dose–response data for persons who traveled by air alone, the pooled relative risk demonstrated a 26% higher risk for VTE for each 2-hour increase in travel duration (CI, 7% to 48%; $P = 0.005$).

Publication Bias

We found no significant evidence for publication bias. Our examination of the funnel plot revealed mild asymmetry, with more negative studies published than positive—a pattern opposite to that typically seen with publication bias (**Figure 4**). This asymmetry may have been related to the several negative case–control studies that used a referred

(**Figure 2**), compared with nontravelers. However, we found significant heterogeneity (P for Q statistic < 0.001). The I^2 statistic was 70% (CI, 48% to 83%), which suggests that 70% of the total heterogeneity was due to between-study variation. When we evaluated prespecified potential sources of heterogeneity (**Table 2**), the major source was study design ($P = 0.008$), specifically the selection criteria for control participants in case–control studies ($P = 0.008$). The 6 case–control studies that used patients who had been referred for VTE evaluation (but who had tested negative) as control participants found no significant association between travel and VTE (pooled RR, 1.2 [CI, 0.9 to 1.6]), whereas the 5 case–control studies that used nonreferred control participants identified a more than 2-fold higher risk for VTE with travel (pooled RR, 2.3 [CI, 1.8 to 2.9]) (**Table 2**). When we classified all 14 studies by use of referred control participants, all but 1 of the 8 studies that used nonreferred patients as control participants or used a cohort or case–crossover design (**Figure 2**, *middle*) identified a statistically significant association between travel and VTE, with an overall pooled estimate of 2.8 (CI, 2.2 to 3.7). Among these 8 studies, statistically significant heterogeneity was not present ($P = 0.098$). Clinically relevant heterogeneity was also not present because the range of risk estimates (1.8 to 4.4) indicated clinically significant increased risk in each study. An I^2 value of 42% indicated the presence of a moderate level of statistical heterogeneity, which supports our use of a random-effects estimate. In contrast, among the 6 studies that used referred patients for control participants (**Figure 2**, *bottom*), none of the individual studies identified an association between travel and VTE, and the overall pooled estimate was 1.2 (CI, 0.9 to 1.6), with no significant heterogeneity among these studies ($P = 0.64$; $I^2 = 0\%$).

Figure 4. Funnel plot depicting results from the 13 published observational studies.

The 14th study included in the meta-analysis was unpublished. The plot shows mild asymmetry, with more negative studies being published than positive ones. We obtained the P value by using the Begg test.

population for control participants, as previously discussed. The Begg test ($P = 0.67$) and the Egger test ($P = 0.172$) also provided no statistical evidence for publication bias.

DISCUSSION

In this systematic review and meta-analysis of 14 studies that included more than 4000 cases of VTE, we identified a 2-fold higher risk for VTE in travelers than in nontravelers. Of note, significant heterogeneity was present, which was directly related to the method of selection of the comparison group in each study. In case–control studies that used individuals referred for VTE evaluation as control participants, no significant association was found. In contrast, case–control studies that used nonreferred control participants and cohort or case-only studies identified a nearly 3-fold higher risk for VTE in travelers. Our analysis confirms a substantially higher risk for VTE associated with travel and identifies the major source of conflicting results among previous individual studies.

Two previous meta-analyses (27, 28) have investigated whether travel is associated with risk for VTE. The first, which included 4 studies published before 2003, found no definitive evidence that prolonged travel, including air travel, was a risk factor for VTE (pooled odds ratio, 1.70 [CI, 0.89 to 3.22]). In a second meta-analysis, which included 6 case–control studies, the investigators concluded that air travel was not significantly associated with VTE (pooled odds ratio, 1.21 [CI, 0.95 to 1.55]), and a secondary analysis found a small increase in risk when all forms of travel were studied (pooled odds ratio, 1.46 [CI, 1.24 to 1.72]). Neither of these previous meta-analyses (27, 28) reported results in accordance with the MOOSE guidelines or evaluated selection criteria for control participants as a source of heterogeneity, and 1 did not evaluate publication bias (27). Our findings demonstrate for the first time a clear association between travel and VTE (pooled relative risk, 2.8 [CI, 2.2 to 3.7]) and also indicate that failure to consider selection criteria for control participants as a source of heterogeneity results in substantial underestimation of risk.

We identified and quantified a dose–response relationship, observing an 18% higher risk for VTE for each 2-hour increase in travel duration. Because only 4 studies had available data for this assessment, the confidence limits around this estimate are wide (4% to 33% higher risk). Two previous studies (29, 30) evaluated flight distance or duration as a risk factor for PE. These studies included only cases of PE that were brought to medical attention immediately on arrival at the airport (symptomatic PE during a flight) and did not have any information on cases of PE that were diagnosed outside the airport or on cases of DVT diagnosed at any time. Our results, which include studies of both PE and DVT diagnosed up to several weeks after travel, provide the best available estimates of the dose–response relationship between travel duration and

VTE. The demonstration of a dose–response relationship suggests a causal nature to the observed relationship between travel and VTE, particularly as related to the potential role of stasis. These findings also highlight a relevant and identifiable characteristic of travel that can predict greatest risk: longer duration of travel. Among studies that evaluated air travel alone, the dose–response relationship seemed stronger (26% higher risk per 2 hours of travel), but we had insufficient data to compare directly pooled dose–response estimates for air versus surface travel.

Several factors provide plausible biological mechanisms for an effect of travel on risk for VTE. Stasis and hypercoagulability, 2 components of the Virchow triad, are known to occur during travel and would increase the risk for VTE. Several pathophysiologic studies (31–35) have investigated the possible induction of a hypercoagulable state during travel and assessed changes in blood levels of proteins involved in thrombin generation or fibrinolysis. These studies have generally been performed in a small number of healthy volunteers who were traveling or immobilized for study purposes, and the results of these studies have been inconsistent. Further research is required to understand the effects of travel on stasis, thrombogenesis, and other risk factors for VTE and to help guide potential preventive therapies to mitigate these pathways. Such studies should test more participants during actual travel and compare the results with those of similar tests conducted during stable periods of nontravel or with results from other, nontraveling individuals.

Whereas our analysis identifies a 3-fold higher relative risk for VTE with travel, the absolute risk is also relevant to guide both policy and individual decisions about prevention. One retrospective cohort study (16) estimated the absolute risk for VTE to be 1 case in 4600 airline flights. The study drew its sample from healthy employees of multinational organizations and only included first episodes of VTE that did not result in death or loss of employment. Thus, the observed absolute risk may not be generalizable to all travelers, particularly travelers who may be at higher risk for VTE, such as older persons, pregnant women, or persons with a history of VTE. Nonetheless, the findings of this report suggest that, at least among generally healthy individuals, even a 3-fold increase in relative risk is unlikely to produce a sufficiently high absolute risk to justify higher-risk interventions, such as oral anticoagulation during travel. However, VTE is often clinically serious or fatal, and the nearly 3-fold higher relative risk our analysis demonstrates the need for better investigation of general preventive measures that could be effective, such as increased hydration or ambulation. Indirect evidence from pathophysiology studies (31, 36) suggests that dehydration and immobilization can alter serum levels of markers of thrombin generation or fibrinolysis in healthy volunteers, and investigation of whether related countermeasures can reduce risk for travel-related VTE is warranted.

Several randomized clinical trials (37–42) have evaluated the efficacy of lower-extremity elastic compression stockings for prevention of travel-related DVT. These trials have generally reported compression stockings to be effective, at least for preventing DVT in the calf, although nearly all of these trials were performed by 1 research group (37–41), whose methods for reporting of results have been questioned (43).

Our dose–response analysis indicates that general preventive measures for VTE may be particularly important as travel duration increases. In addition, researchers should consider evaluating additional preventive measures for persons who may be at higher absolute risk for VTE, such as those who have thrombophilia (14), are receiving oral contraceptives (9), or are obese (15), particularly for longer trips.

Our demonstration of heterogeneity by study design highlights the importance of basic principles in the design and evaluation of otherwise well-conceived epidemiologic studies. Studies that selected control participants on the basis of referral for VTE evaluation—because "controls should consist of people with similar signs and symptoms as cases" (4)—found no significant relationship between travel and VTE (4–7). A common misperception is that control participants in a case–control study should be as similar as possible to the case patients except for the exposure of interest. Part of this misperception may result from the concept of matching; during selection of control participants, matching on certain characteristics can increase efficiency (statistical power) during adjustment by minimizing stratified 2×2 tables that lack cases or noncases in the classical Mantel–Haenszel approach (44). Investigators commonly use important risk factors for the outcome for matching; for example, age is a common matching factor in many studies. However, matching should be used cautiously to prevent selection bias—matching on factors related to the likelihood of exposure (in this case, travel)—in the study base. This misperception may also stem from the use of the term *control participants* to describe 2 very different groups: unexposed persons in randomized trials and nondiseased persons in case–control studies. In trials, randomization to an intervention allows for untreated or unexposed persons (control participants) to be as similar as possible to treated or exposed persons in all other respects. Conversely, in a case–control study, control participants are nondiseased persons (non–case patients), not untreated or unexposed persons. In any study design—case–control, cohort, or randomized trial—persons who do not experience a disease should never be expected to be similar to the case patients; those who develop a disease will always have many more risk factors for disease than those who do not develop the disease.

In these studies, cases occurred in a particular general population (the study base). In cohort studies, this study base was explicitly identifiable as the total cohort who developed VTE. In case–control studies, the study base was conceptually identical—the general population of persons who might travel and, if they experienced VTE, be identified as a case patient in that study—but not explicitly identifiable; unlike cohort studies, no roster of persons was available to identify the study base precisely. Thus, appropriate selection of control participants was critical for these studies to accurately estimate the average exposure status in the study base. Many different selection strategies can be valid, including random-digit telephone calls or use of hospital-based control participants, as long as the methods are unrelated to the likelihood of exposure (in this case, travel) in the general population in which the cases occurred. When any of the selection criteria for control participants are related to likelihood of travel, selection bias results because the likelihood of travel in the study base is incorrectly estimated. Our findings highlight the important consequences of such selection bias. In the case of travel and risk for VTE, individuals referred for VTE evaluation would have, on average, more risk factors for VTE, including likelihood of travel, than the general population. Thus, the use of such control participants will lead to underestimation (bias toward null) of the true associations between travel and VTE because of underestimation of the true contrast between the likelihood of travel in the case-patients and the study base. Failure to recognize this selection bias would lead to erroneous conclusions regarding the presence and magnitude of travel effects on risk for VTE. Some of these referred control participants may also have had false-negative test results (they may have had VTE). Inclusion of these persons as control participants would lead to further underestimation of the true association of travel with VTE (bias toward the null due to misclassification of VTE). In contrast to the clear heterogeneity from selection criteria for control participants, the absence of heterogeneity from method or timing of exposure assessment argued against the presence of substantial recall bias in the identified studies (**Table 2**).

Our study has limitations. We may not have accounted for all sources of heterogeneity among the studies; however, after we stratified by selection criteria for control participants, our results were concordant within each of the 2 strata and neither clinical nor statistical heterogeneity was apparent. Recall bias may have affected the individual study results; however, absence of heterogeneity by method or timing of exposure assessment argues against substantial effects of recall bias. A remote possibility exists that some control participants had unrecognized VTE, a misclassification error that would result in bias toward the null. As in any meta-analysis that uses grouped data from separate published studies, we cannot be certain that our estimates are free of all confounding from individual level variables; however, we detected no heterogeneity on the basis of the number of covariates included for multivariable adjustment. The results of our meta-analysis should apply to general populations in Western countries because each of the identified studies was performed in Western popula-

tions. Although generalizability to non-Western populations should be confirmed, the biological mechanisms that predispose to travel-related VTE should be similar in most racial and ethnic groups, with the exception of such genetic risk factors as factor V Leiden. Finally, publication bias is a potential limitation of any meta-analysis, although the funnel plot and statistical evaluation in our study did not suggest any appreciable publication bias.

In conclusion, travel is associated with a 3-fold higher risk for VTE, with a dose–response relationship of 18% higher risk for each 2-hour increase in travel duration. These findings provide the strongest evidence to date of the presence and magnitude of the association between travel and VTE. They also indicate that the efficacy of low-cost and low-risk interventions, such as increased hydration and ambulation, should be investigated for all general travelers—particularly those with longer durations of travel—and that additional interventions and therapies should be evaluated for higher-risk subgroups.

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