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Risk Marker Associations with Venous Thrombotic Events: A Cross-sectional Analysis

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ABSTRACT

Objective: To examine the interrelations among, and risk marker associations for superficial and deep venous events – superficial venous thrombosis (SVT), deep venous thrombosis (DVT) and pulmonary embolism (PE).

Design: Cross-sectional Analysis

Setting: San Diego, CA

Participants: 2,404 men and women aged 40-79 years from four ethnic groups; Non-Hispanic White, Hispanic, African-American, and Asian. The study sample was drawn from current and former staff and employees of the University of California, San Diego and their spouses /significant others.

Outcome Measures: Superficial and deep venous events, specifically SVT, DVT and PE

Results: Significant correlates on multivariable analysis were, for SVT: female sex, ethnicity (African-American=protective), lower educational attainment, immobility, and family history of varicose veins. For DVT and DVE significant correlates included: heavy smoking, immobility, and family history of deep venous events (borderline for DVE). For PE, significant predictors included immobility, and, in contrast to DVT, blood pressure (BP) (systolic or diastolic). In women, oestrogen use duration for hormone replacement therapy, in all and among oestrogen users, predicted PE and DVE respectively.

Conclusions: These findings fortify evidence for known risk correlates/ predictors for venous disease, such as immobility, family history, and hormone use. In addition, new risk associations are shown. Striking among these is an association of PE, but not DVT, to elevated BP: we conjecture PE may serve as cause, rather than consequence. Future studies should evaluate temporal direction of this association.

Keywords: Cross-Sectional Studies, Vascular Diseases/epidemiology, Vascular Diseases/ethnology, Deep Venous Thrombosis, Pulmonary Embolism

ARTICLE SUMMARY:

Article Focus: We cross-sectionally examined relations between assessed physiological markers and history of venous events, including superficial venous thrombosis, deep venous thrombosis (DVT), and pulmonary embolism (PE).

Key Messages: We identified a significant correlation between superficial and deep venous events. As expected, predictors of deep venous events included smoking, immobility, and in women hormone use duration. Unexpectedly, elevated blood pressure (BP) significantly related to history of PE, but not DVT. Since DVT is typically a precursor condition to PE, we speculate that BP rises as a consequence rather than cause of PE (consistent with other evidence relating to BP elevation risk factors). To assess this further will require prospective assessment – not merely leading to, but also following, occurrence of PE.

Strengths and Limitations: Recall of events may be imperfect and fatal events are not included. Cross-sectional design does not define temporality in venous event/ risk marker relations. On the positive side, this design may enable relationships to be identified arising from effects of "events" on physiological variables: such relations may also be important, and may be missed in prospective studies that censor at occurrence of an event. However, prospective follow-up remains required, including those with and without PE, to confirm the conjectured directionality of the observed association.

Introduction

Chronic venous disease causes significant morbidity in diverse populations around the world(1-3), and it has been estimated that 1-3% of total health care expenditures are linked to venous disorders(2, 4, 5). Considerable time and resources are devoted to venous conditions in clinical practice. The San Diego Population Study (SDPS) has sought to better define venous disease prevalence and epidemiology, by clearly delineating and separately analyzing risk correlates for different elements of venous disease, irrespective of directionality of the association. The present report pertains to a history of venous thrombotic events, including superficial venous thrombosis (SVT), deep venous thrombosis (DVT), and pulmonary embolism (PE). It assesses the relation of age, sex, and other potential risk factors to a history of these events.

Materials and Methods

Subjects

2,404 men and women aged 40-79 years from four ethnic groups (Non-Hispanic White, Hispanic, African-American, and Asian), comprising current and former staff/ employees of the University of California, San Diego and their spouses/significant others, were targeted for participation in the SDPS. Inclusion of spouses/significant others modestly extended the age range of participants (29-91 years). Subjects represented a spectrum of socioeconomic status, including unemployed and retired as well as working persons. A full description of the SDPS population, which collected data from 1994-8, is available elsewhere(6, 7). The study was approved by the UCSD Human Research Protection Program, and all subjects gave written informed consent.

Outcomes

SVT, DVT and PE were ascertained by self-report. Questions elicited a history of "a blood clot in a leg vein" and "phlebitis or inflamed vein in your leg," stratified by whether the problem was in a superficial or deep vein and queried separately for each leg; "pulmonary embolism or blood clot in lung;" and "heparin or coumadin/ warfarin therapy for a problem with your veins." Because PEs are pathophysiologically linked to DVTs, DVT and PE were analyzed both separately, and conjointly as deep venous events (DVE: DVT and/or PE).

Independent Variables

Variables evaluated for their relation to SVT, DVT and PE included self-reported age, sex, ethnicity, smoking status, alcohol consumption, self-reported activity level, education level (ranked from 1=grade school or less to 9=doctoral degree), occupation (categorical), hormone use in females, history of immobility, and family history of superficial and deep events. Systolic and diastolic brachial blood pressure (SBP and DBP, respectively) was assessed using the subject's right arm after the subject sat quietly for five minutes. Ethnicity, determined by self-report, was categorized as above as Non-Hispanic White (hereafter referred to as Caucasian), Hispanic, African-American, or Asian. Alcohol measures examined included drinking status (none vs. present), days per week of alcohol consumption, and highest number of drinks in a day. Smoking information included current smoking status, years of smoking, average packs/day during time smoked (allowing calculation of pack years of smoking), and heavy smoker status (defined as ≥40 cigarettes/day average during time smoked). Activity was coded into 5 levels, assessed relative to others of the same age and sex. Responses ranged from "much less active" to "much more active." In analyses examining venous outcomes in women, oestrogen use duration and other hormone measures were also evaluated as potential risk factors.

Analyses

Subject characteristics were tabulated as a function of venous event status – no event, SVT, DVT, or PE. The (unadjusted) relationship of demographic and potential risk variables to each event type was ascertained, using t-test of difference in mean values for continuous variables and chi-squared testing for categorical variables. Relationships between SVT, DVT and PE were evaluated.

For multivariable analyses, following examination of correlations among predictor variables to assist in assessing issues of collinearity, logistic regression was performed. Age- and sex-adjusted regressions were followed by multivariable regressions including all variables shown for bivariable analysis ("full model"). (Where several measures tapping the same variable were appraised, e.g. pack years of smoking vs. heavy smoking, the variable that bore the stronger apparent relationship to the outcome was employed in multivariable analyses.) A "final" regression model was then determined for each venous event outcome, adjusted for potential predictor variables identified from bivariable and age-sex adjusted or fully adjusted analyses. This assessed the multivariable relationship of candidate risk factors to events, controlling for potential confounders. Variables that approached significance on age-sex adjusted and/or fully adjusted analysis (P<0.2) were tested for inclusion in the final model. Those retaining potential predictive value (P<~0.2) were retained in the final model. All logistic regression analyses were performed with and without stratification by sex; results of stratified analyses are presented only where effect modification by sex was present.

Sensitivity analyses were conducted adding back non-significant variables, but typically the final model variables were robustly supported (with exceptions specified). Significance was designated as two-sided P<0.05. Analyses employed Stata version 8.0 (College Station, TX).

Results

Population Characteristics

Sixty-six percent of subjects were female (1580 women vs. 824 men). Female participants were minimally but significantly younger on average than males (58.9 years vs. 60.1 years; P=0.012). Average values of predictor variables in this population, stratified by venous event status, are shown in **Tables 1a** and **1b**. Variables that differed significantly in those with SVT vs. no events (on unadjusted analysis) were male sex, African-American ethnicity (protective), lower education level, drinkers who did not specify maximum alcohol consumption, and family history of venous disease. For DVT, significant factors were age, Caucasian ethnicity (with African-American ethnicity somewhat protective), family history of venous disease, heavy smoking, and high maximum alcohol consumption (≥7 drinks per day). For PE, significant factors were heavy smoking, Caucasian ethnicity, SBP, DBP; and among women, oestrogen use duration for hormone replacement therapy (HRT) *among all females*, and oestrogen use duration *among oestrogen users* for HRT.

Relationships Among Events

The fraction of the population with superficial or deep venous events or PE is shown in **Table 2**. 142 had at least one type of thrombotic event (SVT, DVT, or PE), including 11 in whom both lower extremity (DVT) and pulmonary thrombotic events were reported. A total of 132 people had at least one SVT or DVT. Of these, 29 people reported bilateral events of one or both types, 2 citing both (data not shown in table),

More than half of those with a PE were aware of having had a DVT (52.4%). This contrasts with only 2.65% of those without a PE being aware of a prior DVT. 14.9% of those with a DVT had experienced a PE while only 0.43% of those with no reported DVT reported a PE. Thus, the expected relationship of DVT to PE (i.e. increased likelihood of PE in presence vs. absence of reported DVT, and vice versa) was upheld (χ^2=172.1, P<0.001).

A significant relationship (χ^2 analysis) was also seen between experiencing an SVT and a DVT (P<0.001), as well as between experiencing an SVT and a PE (P=0.010).

Multivariable Analyses by Event Type

SVT (**Table 3**): Female sex, lower educational attainment, failure to specify level of maximum alcohol consumption, history of immobility, and family history of first-degree relatives with varicose veins showed significant (or for immobility, borderline significant, P<0.1) positive relations, while African-American ethnicity appeared protective, in the limited (age-sex) adjustment models. Each was significant in the final model.

DVT (**Table 4**): For DVT, significance on multivariable regression was seen for heavy smoker status; history of immobility; and family history of first-degree relatives with DVE. In addition to these variables, Caucasian ethnicity, age, and family history of superficial venous events appeared significant in the limited (age-sex) adjustment model, but lost significance on multivariable analysis.

PE (**Table 4**): For PE, significance on multivariable analysis was seen for: BP; history of immobility; and for women, duration of oestrogen use for HRT. Caucasian ethnicity and heavy smoking, with ORs exceeding 2.5, were retained in the final model, but did not meet criteria for significance, reflecting the modest number of PEs (n=21). We underscore that SBP and/or DBP, *though not related to DVT or SVT in any adjustment scenario*, were significantly related to PE on unadjusted and adjusted analysis.

DVE (DVT and/or PE; **Table 4**): As for DVT, age and Caucasian ethnicity, though significant in the limited adjustment model, lost significance with further adjustment. Significance was seen for heavy smoker status; and history of immobility; and for women, oestrogen use duration *among oestrogen users* for HRT. Family history of DVE, with an OR of 2.49, was also retained in the final model. This variable approached but did not meet criteria for significance (P=0.057).

Discussion

This is the first study to characterize, in a population sample, the relationships between superficial and deep venous events, and between DVTs and PEs; and to characterize the risk correlates for SVT, DVT, PE, and DVE. Some anticipated relationships were confirmed; and some intriguing differences in statistical correlates of SVT vs. DVT; and for DVT vs. PE were revealed.

The expected significant relationship between DVT and PE was upheld(8). There was also a significant relationship between risk of SVT and risk of DVT, as well as risk of PE(9).

Regarding sex differences, females were confirmed to have strongly and significantly higher rates of SVTs than males. Oestrogen use duration for HRT showed a link to DVE in women, consistent with existing findings(9-12).

History of heavy smoking was not associated with SVT, but was a strong risk factor for DVT and DVE. Smoking is often not reported as a risk factor for venous thrombosis, though it has been recognized to amplify risk in the setting of oral contraceptive use(13), perhaps contributing to its association to venous thromboembolism in studies of women of reproductive age(14). Moreover, some studies do report an association of smoking to venous thromboembolism extending to older samples and men as well as women(15, 16).

Caucasian ethnicity bore an apparent relationship to DVT, PE and DVE; that was, however, extinguished with multivariable adjustment. Some other studies have also reported a relation of ethnicity to DVT to be extinguished with adjustment for other factors(17). Family history showed an association to DVT that accounted for the ethnicity association and is also consistent with existing data on genetic variation in clotting factors(10, 18).

Immobility, a known risk factor for venous events(10, 11, 17, 19-21), was affirmed here to be a strong predictor for DVT, PE, and DVE. It was also a predictor, though less potent, for superficial events. Many factors associated with thrombosis entail periods of immobility: these range from nursing home confinement(9) and hospitalization(9, 17, 20), to peri-surgical, neurological and injury states(9, 18-20).

Among the most interesting findings, SBP and DBP, though unrelated to DVT, were strongly related to PE. We suggest that, because risk marker data were procured after event occurrence, PE could drive subsequent elevations in BP. Transient hypoxia in settings like sleep apnea promotes BP elevation(22, 23). The possibility cannot be excluded that even focal pulmonary infarction might reduce efficiency of oxygen transfer to blood sufficiently to influence BP in some instances. Potentially compatible information derives from data that initial DVT accompanied by PE is a risk factor for *recurrence* of DVT(24); and that arterial hypertension is a risk factor for *recurrent* DVT(25), which we hypothesize could be a marker for prior overt or occult PE.

Longitudinal study assessing change in risk markers *following* events is seldom undertaken. Therefore cross-sectional designs' lack of "temporality" may serve here not as a fault but an advantageous feature, enabling *event-factor* as well as *factor-event* relations to be uncovered. However prospective studies are desired to confirm hypothesized "reverse" directionality. Whether elevated BP ultimately proves to be a risk factor for, or a consequence of PE, the relationship will be important to understand.

This study has limitations, including those pertaining to all cross-sectional studies. Though the sample was economically broad and ethnically diverse, findings for this population need not generalize to all others; however, affirmation of many known associations reduces concerns regarding generalizability. The study measures historical occurrence rather than prospective incidence. There is inherent potential for omitted variable bias, which can influence the apparent relationship of tested variables to the outcome of interest. Fatal events as well as clinically silent ones were not included in our analyses. Most of the retained variables showed relationships robust across sensitivity analyses, supporting relevance of the variables identified. Exceptions

arose with inclusion/exclusion of ethnicity and family history. In this as in all studies, apparent ethnic and family relationships may represent proxies for (measured and) unmeasured variables with which ethnicity (or family) correlate. There were few cases of current cancer in our sample; cancer has elsewhere been reported to predict venous events(9, 19). Finally, events have already occurred when risk markers were measured. For modifiable risk factors, the events could drive the factors rather than the converse, as discussed for the association of PE to increased SBP and DBP.

This study confirms relationships of sex, history of immobility, heavy smoking, and duration of HRT to venothrombotic events. Family history was also affirmed to bear a strong relation to venous events, consistent with recognized genetic risk factors. In addition, an intriguing association of systolic and diastolic blood pressure to PE, but not to DVT, was identified, which merits further evaluation.

Contributorship statement: MC and BG conceived the idea for the study. MC acquired and provided the data. JD managed data, developed data dictionary, and contributed to analysis review. VC, BG, and SK conducted statistical analyses. Manuscript was drafted by BG and VC. All authors contributed to revision to the manuscript for intellectual content and approved the final manuscript.

Data sharing: There are no additional data available.

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Legends

Table 1a. Legend

DBP – diastolic blood pressure; DVT – deep venous thrombosis; HDL – high-density lipoprotein cholesterol; HRT – postmenopausal hormone replacement therapy; PE – pulmonary embolism; SBP – systolic blood pressure; SD – standard deviation; SVT – superficial venous thrombosis.

* P<0.05; ** P<0.01; *** P<0.001

† Ordinal rather than continuous: Ranked from 1 = Grade school or less to 9 = Doctoral Degree.

‡ This correlated well with pack years, which showed a similar relationship to venous events; but variable transformations more suitably satisfied regression constraints for this variable, and the impact of this variable was more potent than that of pack years for deep events, the category of events for which it was predictive.

§ Pack years was calculated by multiplying years smoked by the average number of cigarettes per day divided by 20 (the average number of cigarettes in one pack).

¶ Rated relative to others your age, 1-5 with 5 being most active.

∫ Only females were included in this portion of the analysis.

Table 1b. Legend

DBP – diastolic blood pressure; DVT – deep venous thrombosis; PE – pulmonary embolism; SBP – systolic blood pressure; SVT – superficial venous thrombosis.

* P<0.05; ** P≤0.010; *** P≤0.001

† Hypertension: SBP ≥ 140 or DBP ≥ 90.

Table 2. Legend

DVT – deep venous thrombosis; PE – pulmonary embolism; SVT – superficial venous thrombosis.

Recall: Some variables had missing data; and some subjects had multiple types of events.

Table 3. Legend

DBP – diastolic blood pressure; DVE – deep venous event; SBP – systolic blood pressure; OR – odds ratio.

* Age variable was adjusted for sex only; and sex variable was adjusted for age only.

† Instead of including both SBP and DBP, we used DBP and the residual of regression of SBP on DBP, so as not to double-count the shared (collinear) contribution by the SBP and DBP values.

Table 4. Legend

DBP – diastolic blood pressure; DVE – deep venous event; DVT – deep venous thrombosis; OR – odds ratio; PE – pulmonary embolism; SBP – systolic blood pressure; SVT – superficial venous thrombosis.

* Age variable was adjusted for sex only; and sex variable was adjusted for age only.

† Instead of including both SBP and DBP, we used DBP and the residual of regression of SBP on DBP, so as not to double-count the shared (collinear) contribution by the SBP and DBP values.

‡ Although some variables lose significance in the fully adjusted model due to collinearity, variables which were of significance or borderline significance in unadjusted or age/sex adjusted model were added back to the final model. When Caucasian ethnicity and heavy smoking were included without one another in the final model, they resumed significance or borderline significance.

§ In the final model, either one of the blood pressure measures – SBP or DBP – could be included and remained statistically significant. (Only one of the two blood pressure variables was included because of collinearity.)

|| Female specific analysis. Excludes family history of first deep events (see comment for PE). The final female-specific model included age and history immobilization, the sole other variables with $P<0.2$ (neither <0.1).

Note: Caucasian ethnicity shows significant relationship to DVT if not adjusted for family history of DVE (OR=2.15, $P=0.008$). If both Caucasian ethnicity and family history of DVE are included, Caucasian ethnicity

loses significance (OR 1.29, *P*=0.659) but family history of deep events retains significance (OR 3.17, *P*=0.026).

Note: Age (OR=1.02,*P*=0.035) and Caucasian ethnicity (OR=1.97,*P*=0.015) show a significant relationship to combined deep events in the final model if family history of venous events is excluded.

Note: For combined DVT and/or PE oestrogen use for HRT was tested as a predictor in women but was not significant. For oestrogen use duration (per 10 years) ORs (*P* -values) for age-adjusted and final models, were 0.532 (0.534) and 0.523 (0.611). For oestrogen use duration (per 10 years) *among oestrogen users*, ORs (*P*-values) for age-adjusted and final models were 0.948 (0.955); and 0.767 (0.756). In the latter case, family history of first deep events was excluded from the final model or the oestrogen variable was dropped due to collinearity. Of note, the resulting modified final model (which included the oestrogen variable) dropped the heavy smoking variable.

Table 1a. Summary of Demographic and Predictor Variables by Venous Event Status (continuous variables):

Variables	**No Event** N=2262 Mean (SD)	**SVT** N=63 Mean (SD)	**DVT** N=74 Mean (SD)	**PE** N=21 Mean (SD)
Age	59.1 (11.4)	60.5 (10.7)	61.9 (11.7)*	61.5 (10.2)
Education†	5.78 (1.73)	5.11 (1.89)***	5.73 (1.67)	5.29 (1.79)
Highest number of drinks per day	2.70 (3.13)	2.24 (2.51)	3.32 (3.76)	3.06 (2.84)
Cigarettes/ day averaged over years totaled‡	6.99 (11.5)	7.73 (14.1)	12.0 (16.1)***	13.2 (14.9)*

Pack years§	7.22 (14.9)	7.38 (18.7)	13.9 (22.3)***	16.5 (20.9)**
SBP (mmHg)	131 (20.3)	132 (22.4)	133 (20.9)	143.0 (21.0)**
DBP (mmHg)	76.8 (11.3)	76.6 (10.8)	78.2 (9.67)	82.5 (7.69)*
Total Cholesterol (mg/dl)	210 (41.3)	207 (38.4)	211 (43.2)	209.2 (42.3)
HDL (mg/dl)	54.5 (17.0)	51.4 (11.3)	50.9 (15.6)	49.9 (16.5)
Activity Level¶	3.71 (1.16)	3.69 (1.19)	3.53 (1.22)	3.40 (1.27)
Number of times in a week engaging in ≥ 20 min of vigorous activity	3.60 (2.51)	3.78 (2.66)	3.52 (2.53)	3.40 (2.54)
Longest period of immobility (days)	11.0 (110)	5.38 (11.9)	17.8 (51.8)	31.4 (84.5)
Oestrogen use duration for HRT *among all females*∫ (years)	0.743 (3.73)	0.882 (3.04)	0.313 (1.60)	5.92 (13.9)***
Oestrogen use duration *among oestrogen users* for HRT∫ (years)	9.82 (9.79)	6.43 (5.97)	7.50 (3.54)	35.5 (3.54)***

Table 1b. Summary of Demographic and Predictor Variables by Venous Event Status (categorical variables)**:**

Variables		**No Event** (%)	**SVT** (%)	**DVT** (%)	**PE** (%)
Male		34.5	19.0**	35.1	42.9
Hypertension†		35.9	28.6	32.4	42.9
Drinker (any alcohol)		93.4	87.3	95.9	90.5
Maximum alcohol consumption ≥7 drinks per day		7.42	7.31	14.3*	16.7
Drinkers who did not specify maximum level of alcohol consumption		8.49	22.6***	11.1	10.5
Current smoker		6.02	3.17	9.46	9.52
Heavy smoker (≥40 cigarettes per day during time smoked)		3.85	3.17	14.9***	14.3*
Ethnicity	Caucasian	58.9	65.1	78.4***	81.0*
	Hispanic	14.7	20.6	9.46	4.76
	African American	13.9	4.76*	8.11*	9.52
	Asian	12.5	9.52	4.05	4.76
Occupation	Professional	26.4	21.1	26.1	20.0
	Technical, Administrative, or Managerial	40.9	38.6	40.6	45.0
	Clerical and Skilled	26.8	29.8	30.4	25.0

	Semi-skilled	3.85	8.77	2.90	5.00
	Laborer	2.07	1.75	0.00	5.00
Family history of venous diseases		57.2	76.2**	71.6*	57.1
Oral contraceptive use (ever; female)		58.1	56.0	54.4	58.3

Table 2. Venous Events in Studied Population

Venous Condition	All Subjects: N (%)	If SVT: N (%)	If DVT: N (%)	If PE: N (%)
SVT	63 (2.68)	*63 (100)*	5 (22.7)	2 (13.3)
DVT	74 (3.09)	5 (8.33)	*74 (100)*	11 (52.4)
PE	21 (0.87)	2 (3.17)	11 (14.9)	*21 (100)*
Any deep event (DVT or PE)	84 (3.50)	5 (8.33)	*74 (100)*	*21 (100)*
Any event (SVT or DVT or PE)	142 (5.91)	*63 (100)*	*74 (100)*	*21 (100)*

Table 3. Multivariate Analyses for SVT

	Age-Sex Adjusted* OR (*P* -value)	**Fully Adjusted** OR (*P*-value)	**Final Model** OR (*P* -value)
Age	1.01 (0.306)	1.03 (0.224)	-
Male sex	0.437 (0.011)	0.275 (0.042)	0.470 (0.028)
African American ethnicity	0.290 (0.038)	0.378 (0.204)	0.305 (0.047)
Education	0.821 (0.015)	0.805 (0.079)	0.801 (0.007)
Activity Level	0.971 (0.796)	0.931 (0.686)	-
Heavy Smoking (≥40 cigarettes per day during time smoked)	0.913 (0.901)	0.977 (0.983)	-
DBP (per 20mmHg)	1.03 (0.894)	2.14 (0.227)	-
SBP (per 20mmHg)	1.01 (0.942)	- †	-
Drinkers who did not specify their maximum alcohol consumption per day	4.37 (<0.001)	4.65 (0.011)	3.33 (<0.001)
History of immobility (>1day)	1.55 (0.091)	2.53 (0.015)	1.71 (0.043)
Family history of first-degree relatives with superficial venous events	1.54 (0.301)	1.55 (0.520)	-
Family history of first-degree relatives with varicose veins	2.30 (0.002)	1.25 (0.706)	2.02 (0.009)
Family history of first-degree	1.74 (0.177)	1.25 (0.637)	-

relatives with DVE			

Table 4. Multivariate Analyses for DVT, PE, and Combined Deep Venous Events

	DVT OR (*P* -value)			PE OR (*P* -value)			DVT and PE OR (*P* -value)		
	Age-Sex Adjusted*	**Fully Adjusted**	**Final Model**	**Age-Sex Adjusted***	**Fully Adjusted**	**Final Model**	**Age-Sex Adjusted***	**Fully Adjusted**	**Final Model**
Age	1.02 (0.047)	1.05 (0.162)	-	1.02 (0.404)	0.977 (0.621)	-	1.03 (0.004)	1.04 (0.202)	-
Male sex	1.01 (0.955)	0.479 (0.312)	-	1.41 (0.435)	0.778 (0.795)	-	1.15 (0.548)	0.773 (0.662)	-
Caucasian ethnicity	2.35 (0.003)	0.754 (0.674)	-	2.68 (0.083)	5.77 (0.149)	2.58 (0.096) ‡	2.26 0.003)	0.936 (0.913)	-
Activity Level	0.827 (0.059)	0.819 (0.418)	-	0.771 (0.163)	0.986 (0.971)	-	0.846 (0.081)	0.909 (0.672)	-
Heavy Smoking (≥40 cigarettes per day during time smoked)	4.19 (<0.001)	10.1 (0.007)	16.6 (<0.001)	3.50 (0.052)	5.21 (0.191)	2.73 (0.121) ‡	3.38 (<0.001)	6.92 (0.013)	12.5 (<0.001)
DBP (per 20mmHg)	1.28 (0.227)	0.442 (0.445)	-	2.06 (0.014)	3.20 (0.419)	2.29 (0.010) §	1.39 (0.077)	0.764 (0.766)	-

SBP (per 20mmHg)	0.996 (0.975)	- †	-	1.59 (0.012)	- †	- §	1.05 (0.643)	- †	-
Drinkers who did not specify their maximum alcohol consumption per day	1.74 (0.170)	1.46 (0.739)	-	1.63 (0.534)	2.70 (0.447)	-	1.61 (0.235)	1.09 (0.939)	-
History of immobility (>1day)	2.17 (0.001)	5.32 (0.008)	4.30 (0.006)	4.44 (0.002)	4.21 (0.114)	4.07 (0.004)	2.23 (<0.001)	3.80 (0.013)	3.48 (0.008)
Family history of first-degree relatives with superficial venous events	3.32 (0.024)	0.719 (0.643)	-	1.51 (0.600)	0.730 (0.754)	-	2.52 (0.036)	0.626 (0.449)	-
Family history of first-degree relatives with DVE	4.41 (0.003)	3.51 (0.066)	3.28 (0.020)	0.855 (0.889)	0.431 (0.491)	-	3.42 (0.010)	2.85 (0.100)	2.49 (0.057)
Oestrogen use duration for HRT‖ (per 10 years)	-	-	-	2.73 (0.000)	3.73 (0.000)	2.63 (0.001)			
Oestrogen use duration	-	-	-	-	-	-	4.67	5.22	4.74

among oestrogen users for HRT (per 10 years)							(0.018)	(0.018)	(0.016)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			8-10
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Risk Marker Associations with Venous Thrombotic Events: A Cross-sectional Analysis

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Risk Marker Associations with Venous Thrombotic Events: A Cross-sectional Analysis

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ABSTRACT

Objective: To examine the interrelations among, and risk marker associations for superficial and deep venous events – superficial venous thrombosis (**SVT**), deep venous thrombosis (**DVT**) and pulmonary embolism (**PE**).

Design: Cross-sectional Analysis

Setting: San Diego, CA

Participants: 2,404 men and women aged 40-79 years from four ethnic groups; Non-Hispanic White, Hispanic, African-American, and Asian. The study sample was drawn from current and former staff and employees of the University of California, San Diego and their spouses /significant others.

Outcome Measures: Superficial and deep venous events, specifically SVT, DVT, PE, and combined deep venous events **(DVE)** comprising DVT and PE.

Results: Significant correlates on multivariable analysis were, for SVT: female sex, ethnicity (African-American=protective), lower educational attainment, immobility, and family history of varicose veins. For DVT and DVE significant correlates included: heavy smoking, immobility, and family history of deep venous events (borderline for DVE). For PE, significant predictors included immobility, and, in contrast to DVT, blood pressure (**BP**) (systolic or diastolic). In women, oestrogen use duration for hormone replacement therapy, in all and among oestrogen users, predicted PE and DVE respectively.

Conclusions: These findings fortify evidence for known risk correlates/ predictors for venous disease, such as family history, hormone use, and immobility. New risk associations are shown. Striking among these is an association of PE, but not DVT, to elevated BP: we conjecture PE may serve as cause, rather than consequence. Future studies should evaluate temporal direction of this association. Oxidative stress and cell energy compromise are proposed to explain and predict many risk factors, operating through cell-death mediated triggering of coagulation activation.

Article Summary

Article Focus: We cross-sectionally examined relations between assessed physiological markers and history of venous events, including superficial venous thrombosis, deep venous thrombosis (**DVT**), and pulmonary embolism (**PE**).

Key Messages: We identified a significant correlation between superficial and deep venous events. As expected, predictors of deep venous events included smoking, immobility, and in women hormone use duration. Unexpectedly, elevated blood pressure (**BP**) significantly related to history of PE, but not DVT. Since DVT is typically a precursor condition to PE, we speculate that BP rises as a consequence rather than cause of PE (consistent with other evidence relating to BP-elevation risk factors). To assess this further will require longitudinal assessment – not merely leading to, but also following, occurrence of PE.

Strengths and Limitations: Recall may be imperfect and fatal events are not included. Cross-sectional design does not define temporality in venous event/ risk marker relations. On the positive side, this design may enable relationships to be identified arising from effects of "events" on physiological variables: such relations may also be important, and may be missed in prospective studies that censor follow-up at occurrence of an event. Longitudinal assessment, continued after PE occurrence, is required to confirm the conjectured directionality of the observed association.

Introduction

Chronic venous disease causes significant morbidity in diverse populations around the world[1-5] and costs are material, with estimates suggesting that up to several percent of total health care expenditures are linked to venous disorders[2 6-9]. Considerable time and resources are devoted to venous conditions in clinical practice. The San Diego Population Study (**SDPS**) has sought to better define venous disease prevalence and epidemiology[10 11], by clearly delineating and separately analyzing risk correlates for different elements of venous disease, irrespective of directionality of the association. The present report pertains to a history of venous thrombotic events, including superficial venous thrombosis (**SVT**), deep venous thrombosis (**DVT**), and pulmonary embolism (**PE**). It assesses the relation of age, sex, and other potential risk factors to a history of these events.

Materials and Methods

Subjects

2,404 men and women aged 40-79 years from four ethnic groups (Non-Hispanic White, Hispanic, African-American, and Asian), comprising current and former staff/ employees of the University of California, San Diego and their spouses/significant others, were targeted for participation in the SDPS. Inclusion of spouses/significant others modestly extended the age range of participants (29-91 years). Subjects represented a spectrum of socioeconomic status, including unemployed and retired as well as working persons. A description of the SDPS population, which collected data from 1994-8, is available elsewhere[10]. The study's primary aims related to prevalence, and the study was powered such that 95% confidence limits for prevalence for each sex were less than ±3.3%; and for subgroups of e.g. n=200, less than ±7%. The study was approved by the UCSD Human Research Protection Program, and all participants gave written informed consent.

Outcomes

SVT, DVT and PE were ascertained by self-report. Questions elicited a history of "a blood clot in a leg vein" and "phlebitis or inflamed vein in your leg," stratified by whether the problem was in a superficial or deep vein and queried separately for each leg; "pulmonary embolism or blood clot in lung;" and "heparin or coumadin/ warfarin therapy for a problem with your veins." Because PEs are pathophysiologically linked to DVTs, DVT and PE were analyzed both separately, and conjointly as deep venous events (**DVE**: DVT and/or PE).

Independent Variables

Variables evaluated for their relation to SVT, DVT, PE and DVE included self-reported age, sex, ethnicity, smoking status, alcohol consumption, self-reported activity level, education level (ranked from 1=grade school or less to 9=doctoral degree), occupation (categorical), hormone use in females (including oral contraceptive use (and if so, # years); and postmenopausal hormone replacement therapy use (and if so, # of years), and history of immobility (i.e. bedrest) for >1 day. Assessment of family history of venous events inquired regarding each qualifying venous condition in each first degree relative (parents, siblings, children), such that a positive family history of deep venous events required one or more qualifying deep venous event in one or more first degree relatives. Systolic and diastolic brachial blood pressure (SBP and DBP, respectively) were assessed using the subject's right arm after the subject sat quietly for five minutes. Ethnicity, determined by self-report, was categorized as above as Non-Hispanic White (hereafter referred to as Caucasian), Hispanic, African-American, or Asian. Alcohol measures examined included drinking status (none vs. present), days per week of alcohol consumption, and highest number of drinks in a day. Smoking information included current smoking status, years of smoking, average packs/day during time smoked (allowing calculation of pack years of smoking), and heavy smoker status (defined as ≥40 cigarettes/day average during time smoked). Activity was coded into 5 levels, assessed relative to others of the same age and sex. Responses ranged from "much less

active" to "much more active." In analyses examining venous outcomes in women, oestrogen use duration and other hormone measures were also evaluated as potential risk factors.

Analyses

Subject characteristics were tabulated as a function of venous event status – no event, SVT, DVT, or PE. The unadjusted relationship of demographic and potential risk variables to each event type was ascertained, using t-test of difference in mean values for continuous variables and chi-squared testing for categorical variables. Relationships between SVT, DVT and PE were also evaluated.

For multivariable analyses, following examination of correlations among predictor variables to assist in assessing issues of collinearity, logistic regression was performed. Age- and sex-adjusted regressions were followed by multivariable regressions including all variables for which a relationship was supported in bivariable analysis ("full model"). Where several measures tapping the same variable were appraised, e.g. pack years of smoking vs. heavy smoking, the variable that bore the stronger apparent relationship to the outcome was employed in multivariable analyses. A "final" regression model was then determined for each venous event outcome, adjusted for potential predictor variables identified from bivariable and age-sex adjusted or fully adjusted analyses. This assessed the multivariable relationship of candidate risk factors to events, controlling for potential confounders. Variables that approached significance on age-sex adjusted and/or fully adjusted analysis (P<0.2) were tested for inclusion in the final model. Those retaining potential predictive value (P<~0.2) were retained in the final model. All logistic regression analyses were performed with and without stratification by sex; results of stratified analyses are presented only where effect modification by sex was present.

Sensitivity analyses were conducted adding back non-significant variables, but typically the final model variables were robustly supported (with exceptions specified). Significance was designated as two-sided P<0.05. Analyses employed Stata version 8.0 (College Station, TX).

Results

Population Characteristics

Sixty-six percent of subjects were female (1,580 women vs. 824 men). Female participants were minimally but significantly younger on average than males (58.9 years vs. 60.1 years; *P*=0.012). Average values of predictor variables in this population, stratified by venous event status, are shown in **Tables 1a** and **1b**. Variables that differed significantly in those with SVT vs. no events (on unadjusted analysis) were male sex, African-American ethnicity (protective), lower education level, drinkers who did not specify maximum alcohol consumption, and family history of venous disease. For DVT, significant factors were age, Caucasian ethnicity (with African-American ethnicity somewhat protective), family history of venous disease, heavy smoking, and high maximum alcohol consumption (≥7 drinks per day). For PE, significant factors were heavy smoking, Caucasian ethnicity, SBP, DBP; and among women, oestrogen use duration for hormone replacement therapy (**HRT**) among all females..

Relationships Among Events

The fraction of the population with superficial or deep venous events or PE is shown in **Table 2**. 142 had at least one type of thrombotic event (SVT, DVT, or PE), including 11 in whom both lower extremity (DVT) and pulmonary thrombotic events were reported. A total of 132 people had at least one SVT or DVT. Of these, 29 people reported bilateral events of one or both types, 2 citing both (data not shown in table),

More than half of those with a PE were aware of having had a DVT (52.4%). This contrasts with only 2.65% of those without a PE being aware of a prior DVT. 14.9% of those with a DVT had experienced a PE while only 0.43% of those with no reported DVT reported a PE. Thus, the expected relationship of DVT to PE

(i.e. increased likelihood of PE in presence vs. absence of reported DVT, and vice versa) was upheld (χ^2=172.1, P<0.001).

A significant relationship (χ^2 analysis) was also seen between experiencing an SVT and a DVT (P<0.001), as well as between experiencing an SVT and a PE (P=0.010).

Multivariable Analyses by Event Type

SVT (**Table 3**): Female sex, lower educational attainment, failure to specify level of maximum alcohol consumption, history of immobility, and family history of first-degree relatives with varicose veins showed significant (or for immobility, borderline significant, P<0.1) positive relations, while African-American ethnicity appeared protective, in the limited (age-sex) adjustment models. Each was significant in the final model.

DVT (**Table 4**): For DVT, significance on multivariable regression was seen for heavy smoker status; history of immobility; and family history of first-degree relatives with DVE. In addition to these variables, Caucasian ethnicity, age, and family history of superficial venous events appeared significant in the limited (age-sex) adjustment model, but lost significance on multivariable analysis.

PE (**Table 4**): For PE, significance on multivariable analysis was seen for: BP; history of immobility; and for women, duration of oestrogen use for HRT. Caucasian ethnicity and heavy smoking, with ORs exceeding 2.5, were retained in the final model, but did not meet criteria for significance, reflecting the modest number of PEs (n=21). We underscore that SBP and/or DBP, *though not related to DVT or SVT in any adjustment scenario*, were significantly related to PE on unadjusted and adjusted analysis.

DVE (DVT and/or PE; **Table 4**): As for DVT, age and Caucasian ethnicity, though significant in the limited adjustment model, lost significance with further adjustment. Significance was seen for heavy smoker

status; and history of immobility. Family history of DVE, with an OR of 2.49, was also retained in the final model. This variable approached but did not meet criteria for significance (P=0.057).

Discussion

This study characterizes, in a population sample, the relationships between superficial and deep venous events, and between DVTs and PEs; and characterizes the risk correlates for SVT, DVT, PE, and DVE. Some anticipated relationships were confirmed; and some intriguing differences in statistical correlates of SVT vs. DVT; and for DVT vs. PE were revealed.

The expected significant relationship between DVT and PE was upheld[12]. There was also a significant relationship between risk of SVT and risk of DVT, as well as of PE, as others have recently reported[13-16].

Regarding sex differences, females were confirmed to have strongly and significantly higher rates of SVTs than males. Oestrogen use duration for HRT showed a link to DVE in women, consistent with existing findings[13 17-19].

History of heavy smoking was not associated with SVT, but was a strong risk factor for DVT and DVE. Smoking has been inconsistently reported as a risk factor for venous thrombosis[20], though it has been recognized to amplify risk in the setting of oral contraceptive use[21], perhaps contributing to its association to venous thromboembolism in studies of women of reproductive age[22]. Moreover, some studies do report an association of smoking to venous thromboembolism extending to older samples and men as well as women[23 24].

Caucasian ethnicity bore an apparent relationship to DVT, PE and DVE that was, however, extinguished with multivariable adjustment. The demographics of San Diego are such that ethnic minorities are more strongly represented in younger ages. Consistent with this, Caucasians were on average older than other study participants. Some other studies have also reported a relation of ethnicity to DVT to be extinguished with

adjustment for other factors[25]. Family history showed an association to DVT that is also consistent with existing documentation of genetic variation in venous thrombosis risk[17 26-30].

Immobility, a known risk factor for venous events[17 26 31-36] was affirmed here to be a strong predictor for DVT, PE, and DVE. It was also a predictor, though less potent, for superficial events. Many factors elsewhere reported to be associated with thrombosis entail periods of immobility: these range from nursing home confinement[13] and hospitalization [13 25 37], to perisurgical, neurological and injury states [13 25 37 38]; factors also extend to prolonged sitting in the work environment[31-33 35].

High maximum alcohol consumption was linked to DVT. High maximum alcohol use (such as binge drinking) is the pattern most linked to blackouts[39-41], and thus immobilization. This alcohol finding coheres with a recent report of an association of venous thromboembolism to hard liquor consumption and binge drinking (contrasted with a protective association for wine consumption)[42].

We suggest, in addition, that many (if not most) risk factors for venous thromboembolism, those identified here and elsewhere, share in common an association to elevated risk of cell death, through oxidative stress or adverse cell energy supply-demand balance. Cell death is a consideration with immobilization (leading to focal ischemia), heavy smoking (oxidative stress[43-45] triggers apoptosis[46]), heavy alcohol (promoting oxidative stress[47-50] and mitochondrial toxicity[51-55] as well as ischemia from immobilization). Cancer, trauma, surgery, and the puerpuerium are associated with tissue injury and cell death. Pregnancy is associated with diversion of blood and energy substrates to the fetus, as well as potential for ischemic compression, which can promote cell death. We observe that *cell death triggers coagulation activation*, via exposure at the cell surface of phosphatidylserine[56], and hypothesize that ultimately numerous additional factors, sharing in common elevated risk of cell death (with oxidative stress and/or cell energy supply-demand frequently involved), or correlation to these, will be identified in the future as risk factors for venous thromboembolism. Indeed, the observation that initial DVT accompanied by PE is a risk factor for recurrence of DVT[57] also fits this theme:

PE, by affecting oxygen transfer, has prospects to tip the energy adequacy balance, particularly in settings of energy compromise from other sources. Also relevant, central obesity is linked to oxidative stress and cell energy inadequacy[58], and has shown a reported link to thromboembolism risk[23].

Perhaps the most novel findings from this analysis were that SBP and DBP, though unrelated to DVT, were strongly related to PE. We suggest that given absence of a relation of blood pressure, in this sample, to the requisite precursor event DVT, and given measurement of BP after venous event occurrence, causality could operate in the reverse direction: PE, known to be a risk factor for pulmonary hypertension[59-64], could drive elevation in arterial BP. Indeed, transient hypoxemia in other settings (such as sleep apnea) promotes BP elevation[13 26 37 65 66 67 68 69]. Even modest reduction in oxygen transfer, arising from pulmonary embolism, might influence BP adversely – concordant with assembled evidence that a range of factors that impair cell energy, promote hypertension (and other metabolic syndrome factors) [58]. Additional potentially compatible information derives from data that initial DVT accompanied by PE is a risk factor for *recurrence* of DVT[57]; and that arterial hypertension is a risk factor for *recurrent* DVT[70], which we hypothesize could be a marker for prior overt or occult PE.

Longitudinal studies assessing change in risk markers *following* events are seldom undertaken. Therefore cross-sectional designs' lack of "temporality" may serve here not as a fault but an advantageous feature, enabling *event-factor* as well as *factor-event* relations to be uncovered. However prospective studies are desired to confirm hypothesized "reverse" directionality. Irrespective of whether elevated BP ultimately proves to be a consequence of PE, as we propose, the relationship will be important to understand.

This study has limitations, including those pertaining to all cross-sectional studies. Though the sample was diverse economically and ethnically, findings for this population need not generalize to all others; however, reproduction in this sample of many previously reported associations reduces concerns regarding generalizability of the findings. The study measures historical occurrence rather than prospective incidence.

Neither fatal events nor clinically silent ones were included in our analyses. Assessment is by self-report, which may involve recall and reporting bias; however self-report of venous events has been used in other studies[71]. In one study, it was shown that most self-reported DVTs were corroborated by surgeons' report (via phone call), and concordance was particularly strong for PE[72]. Most significantly, numerous associations identified here, both among venous outcomes, and between risk factors and venous outcomes, cohere with associations reported in other studies using alternate event assessment modalities, providing strong convergent validation for the findings. An additional limitation, as in all observational studies, is inherent potential for omitted variable bias, which can influence the apparent relationship of tested variables to the outcome of interest. Most of the retained variables showed relationships robust across sensitivity analyses, supporting relevance of the variables identified. Exceptions arose with inclusion/exclusion of ethnicity and family history. In this as in all studies, apparent ethnic and family relationships may represent proxies for (measured and) unmeasured variables with which ethnicity (or family) correlate. There were few cases of current cancer in our sample; cancer has elsewhere been reported to predict venous events[13 65 73-76]. Finally, events had already occurred when risk markers were measured. For modifiable risk factors, the events could drive the factors rather than the converse, as discussed for the association of PE to increased SBP and DBP.

This study supports previously reported relationships of sex, history of immobility, heavy smoking, and duration of HRT to venothrombotic events. It supports recent evidence for a relation of heavy maximal alcohol consumption to venous thromboses, consistent with prior evidence linking binge drinking to venous events[42]. Family history was also affirmed to bear a strong relation to venous events, consistent with (but not exclusive to) recognized genetic risk factors. An intriguing association of systolic and diastolic blood pressure to PE, but not to DVT, was identified. This novel finding is illuminated by, and simultaneously contributes to, an emerging body of evidence linking mediators of cell energy compromise to increased risk of hypertension – and to other metabolic syndrome factors [58]. It is also observed, to our knowledge for the first time, that factors promoting

cell death – including factors that contribute to (or reflect) cell energy compromise or oxidative stress – may be expected to dispose to venous thromboembolism, explaining many observed risk factors[23], and predicting numerous additional ones[58].

Contributorship statement: MC and BG conceived the idea for the study. MC acquired and provided the data. JD managed data, developed the data dictionary, and contributed to analysis review. VC, BG, and SK conducted statistical analyses. The manuscript was drafted by BG and VC. All authors contributed to revision to the manuscript for intellectual content and approved the final manuscript.

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Legends

Table 1. Legend

DBP – diastolic blood pressure; DVT – deep venous thrombosis; HDL – high-density lipoprotein cholesterol; HRT – postmenopausal hormone replacement therapy; PE – pulmonary embolism; SBP – systolic blood pressure; SD – standard deviation; SVT – superficial venous thrombosis.

* P<0.05; ** P<0.01; *** P<0.001

† Ordinal rather than continuous: Ranked from 1 = Grade school or less to 9 = Doctoral Degree.

‡ This correlated well with pack years, which showed a similar relationship to venous events; but variable transformations more suitably satisfied regression constraints for this variable, and the impact of this variable was more potent than that of pack years for deep events, the category of events for which it was predictive.

§ Pack years was calculated by multiplying years smoked by the average number of cigarettes per day divided by 20 (the average number of cigarettes in one pack).

¶ Rated relative to others your age, 1-5 with 5 being most active.

∫ Only females were included in this portion of the analysis.

‡‡ Hypertension: SBP ≥ 140 or DBP ≥ 90.

Table 2. Legend

DVT – deep venous thrombosis; PE – pulmonary embolism; SVT – superficial venous thrombosis.

Recall: Some variables had missing data; and some subjects had multiple types of events.

Table 3. Legend

DBP – diastolic blood pressure; DVE – deep venous event; SBP – systolic blood pressure; OR – odds ratio.

* Age variable was adjusted for sex only; and sex variable was adjusted for age only.

† Instead of including both SBP and DBP, we used DBP and the residual of regression of SBP on DBP, so as not to double-count the shared (collinear) contribution by the SBP and DBP values.

Table 4. Legend

DBP – diastolic blood pressure; DVE – deep venous event; DVT – deep venous thrombosis; OR – odds ratio; PE – pulmonary embolism; SBP – systolic blood pressure; SVT – superficial venous thrombosis.

* Age variable was adjusted for sex only; and sex variable was adjusted for age only.

† Instead of including both SBP and DBP, we used DBP and the residual of regression of SBP on DBP, so as not to double-count the shared (collinear) contribution by the SBP and DBP values.

‡ Although some variables lose significance in the fully adjusted model due to collinearity, variables which were of significance or borderline significance in unadjusted or age/sex adjusted model were added back to the final model. When Caucasian ethnicity and heavy smoking were included without one another in the final model, they resumed significance or borderline significance.

§ In the final model, either one of the blood pressure measures – SBP or DBP – could be included and remained statistically significant. (Only one of the two blood pressure variables was included because of collinearity.)

|| Female specific analysis. Excludes family history of first deep events (see comment for PE). The final female-specific model included age and history immobilization, the sole other variables with $P<0.2$ (neither <0.1).

Note: Caucasian ethnicity shows significant relationship to DVT if not adjusted for family history of DVE (OR=2.15, $P=0.008$). If both Caucasian ethnicity and family history of DVE are included, Caucasian ethnicity loses significance (OR 1.29, $P=0.659$) but family history of deep events retains significance (OR 3.17, $P=0.026$).

Note: Age (OR=1.02,$P=0.035$) and Caucasian ethnicity (OR=1.97,$P=0.015$) show a significant relationship to combined deep events in the final model if family history of venous events is excluded.

Note: For combined DVT and/or PE oestrogen use for HRT was tested as a predictor in women but was not significant. For oestrogen use duration (per 10 years) ORs (*P* -values) for age-adjusted and final models, were 0.532 (0.534) and 0.523 (0.611).

Table 1a. Summary of Demographic and Predictor Variables by Venous Event Status (continuous variables):

Variables	No Event N=2262 Mean (SD)	SVT N=63 Mean (SD)	DVT N=74 Mean (SD)	PE N=21 Mean (SD)
Age	59.1 (11.4)	60.5 (10.7)	61.9 (11.7)*	61.5 (10.2)
Education†	5.78 (1.73)	5.11 (1.89)***	5.73 (1.67)	5.29 (1.79)
Highest number of drinks per day	2.70 (3.13)	2.24 (2.51)	3.32 (3.76)	3.06 (2.84)
Cigarettes/ day averaged over years totaled‡	6.99 (11.5)	7.73 (14.1)	12.0 (16.1)***	13.2 (14.9)*
Pack years§	7.22 (14.9)	7.38 (18.7)	13.9 (22.3)***	16.5 (20.9)**
SBP (mmHg)	131 (20.3)	132 (22.4)	133 (20.9)	143.0 (21.0)**
DBP (mmHg)	76.8 (11.3)	76.6 (10.8)	78.2 (9.67)	82.5 (7.69)*
Total Cholesterol (mg/dl)	210 (41.3)	207 (38.4)	211 (43.2)	209.2 (42.3)
HDL (mg/dl)	54.5 (17.0)	51.4 (11.3)	50.9 (15.6)	49.9 (16.5)
Activity Level¶	3.71 (1.16)	3.69 (1.19)	3.53 (1.22)	3.40 (1.27)
Number of times in a week engaging in ≥ 20 min of vigorous activity	3.60 (2.51)	3.78 (2.66)	3.52 (2.53)	3.40 (2.54)
Longest period of immobility (days)	11.0 (110)	5.38 (11.9)	17.8 (51.8)	31.4 (84.5)
Oestrogen use duration for HRT among all females∫ (years)	0.743 (3.73)	0.882 (3.04)	0.313 (1.60)	5.92 (13.9)***

Table 1b. Summary of Demographic and Predictor Variables by Venous Event Status (categorical variables)

Variables		No Event (%)	SVT (%)	DVT (%)	PE (%)
Male		34.5	19.0**	35.1	42.9
Hypertension‡‡		35.9	28.6	32.4	42.9
Drinker (any alcohol)		93.4	87.3	95.9	90.5
Maximum alcohol consumption ≥7 drinks per day		7.42	7.31	14.3*	16.7
Drinkers who did not specify maximum level of alcohol consumption		8.49	22.6***	11.1	10.5
Current smoker		6.02	3.17	9.46	9.52
Heavy smoker (≥40 cigarettes per day during time smoked)		3.85	3.17	14.9***	14.3*
Ethnicity	Caucasian	58.9	65.1	78.4***	81.0*
	Hispanic	14.7	20.6	9.46	4.76
	African American	13.9	4.76*	8.11*	9.52
	Asian	12.5	9.52	4.05	4.76
Occupation	Professional	26.4	21.1	26.1	20.0
	Technical, Administrative, or Managerial	40.9	38.6	40.6	45.0
	Clerical and Skilled	26.8	29.8	30.4	25.0

	Semi-skilled	3.85	8.77	2.90	5.00
	Laborer	2.07	1.75	0.00	5.00
Family history of venous diseases (Venous condition in any first degree relative)		57.2	76.2**	71.6*	57.1
Oral contraceptive use (ever; female)		58.1	56.0	54.4	58.3

Table 2. Venous Events in Studied Population

Venous Condition	All Subjects: N (%)	If SVT: N (%)	If DVT: N (%)	If PE: N (%)
SVT	63 (2.68)	*63 (100)*	5 (22.7)	2 (13.3)
DVT	74 (3.09)	5 (8.33)	*74 (100)*	11 (52.4)
PE	21 (0.87)	2 (3.17)	11 (14.9)	*21 (100)*
Any deep event (DVT or PE)	84 (3.50)	5 (8.33)	*74 (100)*	*21 (100)*
Any event (SVT or DVT or PE)	142 (5.91)	*63 (100)*	*74 (100)*	*21 (100)*

Table 3. Multivariate Analyses for SVT

	Age-Sex Adjusted* OR (*P* -value)	**Fully Adjusted** OR (*P*-value)	**Final Model** OR (*P* -value)
Age	1.01 (0.306)	1.03 (0.224)	-
Male sex	0.437 (0.011)	0.275 (0.042)	0.470 (0.028)
African American ethnicity	0.290 (0.038)	0.378 (0.204)	0.305 (0.047)
Education	0.821 (0.015)	0.805 (0.079)	0.801 (0.007)
Activity Level	0.971 (0.796)	0.931 (0.686)	-
Heavy Smoking (≥40 cigarettes per day during time smoked)	0.913 (0.901)	0.977 (0.983)	-
DBP (per 20mmHg)	1.03 (0.894)	2.14 (0.227)	-
SBP (per 20mmHg)	1.01 (0.942)	- †	-
Drinkers who did not specify their maximum alcohol consumption per day	4.37 (<0.001)	4.65 (0.011)	3.33 (<0.001)
History of immobility (>1day)	1.55 (0.091)	2.53 (0.015)	1.71 (0.043)
Family history of first-degree relatives with superficial venous events	1.54 (0.301)	1.55 (0.520)	-
Family history of first-degree relatives with varicose veins	2.30 (0.002)	1.25 (0.706)	2.02 (0.009)
Family history of first-degree	1.74 (0.177)	1.25 (0.637)	-

relatives with DVE			

Table 4. Multivariate Analyses for DVT, PE, and Combined Deep Venous Events

	DVT OR (*P* -value)			PE OR (*P* -value)			DVT and PE OR (*P* -value)		
	Age-Sex Adjusted*	**Fully Adjusted**	**Final Model**	**Age-Sex Adjusted***	**Fully Adjusted**	**Final Model**	**Age-Sex Adjusted***	**Fully Adjusted**	**Final Model**
Age	1.02 (0.047)	1.05 (0.162)	-	1.02 (0.404)	0.977 (0.621)	-	1.03 (0.004)	1.04 (0.202)	-
Male sex	1.01 (0.955)	0.479 (0.312)	-	1.41 (0.435)	0.778 (0.795)	-	1.15 (0.548)	0.773 (0.662)	-
Caucasian ethnicity	2.35 (0.003)	0.754 (0.674)	-	2.68 (0.083)	5.77 (0.149)	2.58 (0.096) ‡	2.26 0.003)	0.936 (0.913)	-
Activity Level	0.827 (0.059)	0.819 (0.418)	-	0.771 (0.163)	0.986 (0.971)	-	0.846 (0.081)	0.909 (0.672)	-
Heavy Smoking (≥40 cigarettes per day during time smoked)	4.19 (<0.001)	10.1 (0.007)	16.6 (<0.001)	3.50 (0.052)	5.21 (0.191)	2.73 (0.121) ‡	3.38 (<0.001)	6.92 (0.013)	12.5 (<0.001)
DBP (per 20mmHg)	1.28 (0.227)	0.442 (0.445)	-	2.06 (0.014)	3.20 (0.419)	2.29 (0.010) §	1.39 (0.077)	0.764 (0.766)	-

SBP (per 20mmHg)	0.996 (0.975)	- †	-	1.59 (0.012)	- †	- §	1.05 (0.643)	- †	-
Drinkers who did not specify their maximum alcohol consumption per day	1.74 (0.170)	1.46 (0.739)	-	1.63 (0.534)	2.70 (0.447)	-	1.61 (0.235)	1.09 (0.939)	-
History of immobility (>1day)	2.17 (0.001)	5.32 (0.008)	4.30 (0.006)	4.44 (0.002)	4.21 (0.114)	4.07 (0.004)	2.23 (<0.001)	3.80 (0.013)	3.48 (0.008)
Family history of first-degree relatives with superficial venous events	3.32 (0.024)	0.719 (0.643)	-	1.51 (0.600)	0.730 (0.754)	-	2.52 (0.036)	0.626 (0.449)	-
Family history of first-degree relatives with DVE	4.41 (0.003)	3.51 (0.066)	3.28 (0.020)	0.855 (0.889)	0.431 (0.491)	-	3.42 (0.010)	2.85 (0.100)	2.49 (0.057)
Oestrogen use duration for HRT‖ (per 10 years)	-	-	-	2.73 (0.000)	3.73 (0.000)	2.63 (0.001)			
Oestrogen use duration	-	-	-	-	-	-	4.67	5.22	4.74

among oestrogen users for HRT (per 10 years)							(0.018)	(0.018)	(0.016)

Risk Marker Associations with Venous Thrombotic Events:

A Cross-sectional Analysis

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ABSTRACT

Objective: To examine the interrelations among, and risk marker associations for superficial and deep venous events – superficial venous thrombosis (**SVT**), deep venous thrombosis (**DVT**) and pulmonary embolism (**PE**).

Design: Cross-sectional Analysis

Setting: San Diego, CA

Participants: 2,404 men and women aged 40-79 years from four ethnic groups; Non-Hispanic White, Hispanic, African-American, and Asian. The study sample was drawn from current and former staff and employees of the University of California, San Diego and their spouses /significant others.

Outcome Measures: Superficial and deep venous events, specifically SVT, DVT**, PE, and combined deep venous events (DVE) comprising DVT and PE** ~~and PE~~.

Results: Significant correlates on multivariable analysis were, for SVT: female sex, ethnicity (African-American=protective), lower educational attainment, immobility, and family history of varicose veins. For DVT and DVE significant correlates included: heavy smoking, immobility, and family history of deep venous events (borderline for DVE). For PE, significant predictors included immobility, and, in contrast to DVT, blood pressure (**BP**) (systolic or diastolic). In women, oestrogen use duration for hormone replacement therapy, in all and among oestrogen users, predicted PE and DVE respectively.

Conclusions: These findings fortify evidence for known risk correlates/ predictors for venous disease, such as ~~immobility,~~ family history, ~~and~~ hormone use**, and immobility.** ~~In addition, n~~New risk associations are shown. Striking among these is an association of PE, but not DVT, to elevated BP: we conjecture PE may serve as cause, rather than consequence. Future studies should evaluate temporal direction of this association. **Oxidative**

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stress and cell energy compromise are proposed to explain and predict many risk factors, operating through cell-death mediated triggering of coagulation activation.

Keywords: Cross-Sectional Studies, Vascular Diseases/epidemiology, Vascular Diseases/ethnology, Deep Venous Thrombosis, Pulmonary Embolism

Article Summary

Article Focus: We cross-sectionally examined relations between assessed physiological markers and history of venous events, including superficial venous thrombosis, deep venous thrombosis (**DVT**), and pulmonary embolism (**PE**).

Key Messages: We identified a significant correlation between superficial and deep venous events. As expected, predictors of deep venous events included smoking, immobility, and in women hormone use duration. Unexpectedly, elevated blood pressure (**BP**) significantly related to history of PE, but not DVT. Since DVT is typically a precursor condition to PE, we speculate that BP rises as a consequence rather than cause of PE (consistent with other evidence relating to BP-elevation risk factors). To assess this further will require **longitudinal**~~prospective~~ assessment – not merely leading to, but also following, occurrence of PE.

Strengths and Limitations: Recall ~~of events~~ may be imperfect and fatal events are not included. Cross-sectional design does not define temporality in venous event/ risk marker relations. On the positive side, this design may enable relationships to be identified arising from effects of "events" on physiological variables: such relations may also be important, and may be missed in prospective studies that censor **follow-up** at occurrence of an event. **Longitudinal assessment, continued after PE occurrence, is** ~~However, prospective follow-up remains~~ required~~, including those with and without PE,~~ to confirm the conjectured directionality of the observed association.

Introduction

Chronic venous disease causes significant morbidity in diverse populations around the world[1-5]~~,~~ and **costs are material, with estimates suggesting**~~it has been estimated~~ that **up to several percent**~~1-3%~~ of total health care expenditures are linked to venous disorders[2 6-9]. Considerable time and resources are devoted to venous conditions in clinical practice. The San Diego Population Study (**SDPS**) has sought to better define venous disease prevalence and epidemiology[10 11], by clearly delineating and separately analyzing risk correlates for different elements of venous disease, irrespective of directionality of the association. The present report pertains to a history of venous thrombotic events, including superficial venous thrombosis (**SVT**), deep venous thrombosis (**DVT**), and pulmonary embolism (**PE**). It assesses the relation of age, sex, and other potential risk factors to a history of these events.

Materials and Methods

Subjects

2,404 men and women aged 40-79 years from four ethnic groups (Non-Hispanic White, Hispanic, African-American, and Asian), comprising current and former staff/ employees of the University of California, San Diego and their spouses/significant others, were targeted for participation in the SDPS. Inclusion of spouses/significant others modestly extended the age range of participants (29-91 years). Subjects represented a spectrum of socioeconomic status, including unemployed and retired as well as working persons. A ~~full~~ description of the SDPS population, which collected data from 1994-8, is available elsewhere[10]**. The study's primary aims related to prevalence, and the study was powered such that 95% confidence limits for prevalence for each sex were less than ±3.3%; and for subgroups of e.g. n=200, less than ±7%.**~~(6, 7).~~ The

study was approved by the UCSD Human Research Protection Program, and all **participants**~~subjects~~ gave written informed consent.

Outcomes

SVT, DVT and PE were ascertained by self-report. Questions elicited a history of "a blood clot in a leg vein" and "phlebitis or inflamed vein in your leg," stratified by whether the problem was in a superficial or deep vein and queried separately for each leg; "pulmonary embolism or blood clot in lung;" and "heparin or coumadin/ warfarin therapy for a problem with your veins." Because PEs are pathophysiologically linked to DVTs, DVT and PE were analyzed both separately, and conjointly as deep venous events (**DVE**: DVT and/or PE).

Independent Variables

Variables evaluated for their relation to SVT, DVT**, PE** and **DVE**~~PE~~ included self-reported age, sex, ethnicity, smoking status, alcohol consumption, self-reported activity level, education level (ranked from 1=grade school or less to 9=doctoral degree), occupation (categorical), hormone use in females **(including oral contraceptive use (and if so, # years); and postmenopausal hormone replacement therapy use (and if so, # of years), and**~~,~~ history of immobility **(i.e. bedrest) for >1 day. Assessment of** ~~, and~~ family history of **venous** ~~superficial and deep~~ events **inquired regarding each qualifying venous condition in each first degree relative (parents, siblings, children), such that a positive family history of deep venous events required one or more qualifying deep venous event in one or more first degree relatives.**~~.~~ Systolic and diastolic brachial blood pressure (**SBP** and **DBP**, respectively) **were**~~was~~ assessed using the subject's right arm after the subject sat quietly for five minutes. Ethnicity, determined by self-report, was categorized as above as Non-Hispanic White (hereafter referred to as Caucasian), Hispanic, African-American, or Asian. Alcohol measures

examined included drinking status (none vs. present), days per week of alcohol consumption, and highest number of drinks in a day. Smoking information included current smoking status, years of smoking, average packs/day during time smoked (allowing calculation of pack years of smoking), and heavy smoker status (defined as ≥40 cigarettes/day average during time smoked). Activity was coded into 5 levels, assessed relative to others of the same age and sex. Responses ranged from "much less active" to "much more active." In analyses examining venous outcomes in women, oestrogen use duration and other hormone measures were also evaluated as potential risk factors.

Analyses

Subject characteristics were tabulated as a function of venous event status – no event, SVT, DVT, or PE. The ~~(~~unadjusted~~)~~ relationship of demographic and potential risk variables to each event type was ascertained, using t-test of difference in mean values for continuous variables and chi-squared testing for categorical variables. Relationships between SVT, DVT and PE were **also** evaluated.

For multivariable analyses, following examination of correlations among predictor variables to assist in assessing issues of collinearity, logistic regression was performed. Age- and sex-adjusted regressions were followed by multivariable regressions including all variables ~~shown~~ for **which a relationship was supported in** bivariable analysis ("full model"). ~~(~~Where several measures tapping the same variable were appraised, e.g. pack years of smoking vs. heavy smoking, the variable that bore the stronger apparent relationship to the outcome was employed in multivariable analyses.~~)~~ A "final" regression model was then determined for each venous event outcome, adjusted for potential predictor variables identified from bivariable and age-sex adjusted or fully adjusted analyses. This assessed the multivariable relationship of candidate risk factors to events, controlling for potential confounders. Variables that approached significance on age-sex adjusted and/or fully adjusted analysis (P<0.2) were tested for inclusion in the final model. Those retaining potential predictive value (P<~0.2) were

retained in the final model. All logistic regression analyses were performed with and without stratification by sex; results of stratified analyses are presented only where effect modification by sex was present.

Sensitivity analyses were conducted adding back non-significant variables, but typically the final model variables were robustly supported (with exceptions specified). Significance was designated as two-sided $P<0.05$. Analyses employed Stata version 8.0 (College Station, TX).

Results

Population Characteristics

Sixty-six percent of subjects were female (1,580 women vs. 824 men). Female participants were minimally but significantly younger on average than males (58.9 years vs. 60.1 years; $P=0.012$). Average values of predictor variables in this population, stratified by venous event status, are shown in **Tables 1a** and **1b**. Variables that differed significantly in those with SVT vs. no events (on unadjusted analysis) were male sex, African-American ethnicity (protective), lower education level, drinkers who did not specify maximum alcohol consumption, and family history of venous disease. For DVT, significant factors were age, Caucasian ethnicity (with African-American ethnicity somewhat protective), family history of venous disease, heavy smoking, and high maximum alcohol consumption (≥7 drinks per day). For PE, significant factors were heavy smoking, Caucasian ethnicity, SBP, DBP; and among women, oestrogen use duration for hormone replacement therapy (**HRT**) among all females~~, and oestrogen use duration among oestrogen users for HRT~~.

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Relationships Among Events

The fraction of the population with superficial or deep venous events or PE is shown in **Table 2**. 142 had at least one type of thrombotic event (SVT, DVT, or PE), including 11 in whom both lower extremity

(DVT) and pulmonary thrombotic events were reported. A total of 132 people had at least one SVT or DVT. Of these, 29 people reported bilateral events of one or both types, 2 citing both (data not shown in table),

More than half of those with a PE were aware of having had a DVT (52.4%). This contrasts with only 2.65% of those without a PE being aware of a prior DVT. 14.9% of those with a DVT had experienced a PE while only 0.43% of those with no reported DVT reported a PE. Thus, the expected relationship of DVT to PE (i.e. increased likelihood of PE in presence vs. absence of reported DVT, and vice versa) was upheld (χ^2=172.1, P<0.001).

A significant relationship (χ^2 analysis) was also seen between experiencing an SVT and a DVT (P<0.001), as well as between experiencing an SVT and a PE (P=0.010).

Multivariable Analyses by Event Type

SVT (**Table 3**): Female sex, lower educational attainment, failure to specify level of maximum alcohol consumption, history of immobility, and family history of first-degree relatives with varicose veins showed significant (or for immobility, borderline significant, P<0.1) positive relations, while African-American ethnicity appeared protective, in the limited (age-sex) adjustment models. Each was significant in the final model.

DVT (**Table 4**): For DVT, significance on multivariable regression was seen for heavy smoker status; history of immobility; and family history of first-degree relatives with DVE. In addition to these variables, Caucasian ethnicity, age, and family history of superficial venous events appeared significant in the limited (age-sex) adjustment model, but lost significance on multivariable analysis.

PE (**Table 4**): For PE, significance on multivariable analysis was seen for: BP; history of immobility; and for women, duration of oestrogen use for HRT. Caucasian ethnicity and heavy smoking, with ORs exceeding 2.5, were retained in the final model, but did not meet criteria for significance, reflecting the modest

number of PEs (n=21). We underscore that SBP and/or DBP, *though not related to DVT or SVT in any adjustment scenario*, were significantly related to PE on unadjusted and adjusted analysis.

DVE (DVT and/or PE; **Table 4**): As for DVT, age and Caucasian ethnicity, though significant in the limited adjustment model, lost significance with further adjustment. Significance was seen for heavy smoker status; and history of immobility~~; and for women, oestrogen use duration *among oestrogen users* for HRT~~. Family history of DVE, with an OR of 2.49, was also retained in the final model. This variable approached but did not meet criteria for significance (*P*=0.057).

Discussion

This ~~is the first~~ study **characterizes,**~~to characterize,~~ in a population sample, the relationships between superficial and deep venous events, and between DVTs and PEs; and **characterizes**~~to characterize~~ the risk correlates for SVT, DVT, PE, and DVE. Some anticipated relationships were confirmed; and some intriguing differences in statistical correlates of SVT vs. DVT; and for DVT vs. PE were revealed.

The expected significant relationship between DVT and PE was upheld[12]. There was also a significant relationship between risk of SVT and risk of DVT, as well as ~~risk~~ of PE**, as others have recently reported**[13-16].

Regarding sex differences, females were confirmed to have strongly and significantly higher rates of SVTs than males. Oestrogen use duration for HRT showed a link to DVE in women, consistent with existing findings[13 17-19].

History of heavy smoking was not associated with SVT, but was a strong risk factor for DVT and DVE. Smoking **has been inconsistently** ~~is often not~~ reported as a risk factor for venous **thrombosis**[20]**,** ~~thrombosis,~~ though it has been recognized to amplify risk in the setting of oral contraceptive use[21]**, perhaps contributing to its association to venous thromboembolism in studies of women of reproductive age**[22]**. Moreover, some**

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studies do report an~~, perhaps contributing to its~~ association of smoking to venous thromboembolism extending to older samples and men as well as ~~in studies of~~ women ~~of reproductive age~~[23 24].

Caucasian ethnicity bore an apparent relationship to DVT, PE and DVE that was, however, extinguished with multivariable adjustment. The demographics of San Diego are such that ethnic minorities are more strongly represented in younger ages. Consistent with this, Caucasians were on average older than other study participants. Some other studies have also reported a relation of ethnicity to DVT to be extinguished with adjustment for other factors~~. Moreover, some studies do report an association of smoking to venous thromboembolism extending to older samples and men as well as women~~[25].

Family history showed

~~Caucasian ethnicity bore~~ an association~~apparent relationship~~ to DVT~~, PE and DVE;~~ that is~~was, however, extinguished with multivariable adjustment. Some other studies have~~ also consistent with existing documentation~~reported a relation~~ of genetic variation in venous thrombosis risk~~ethnicity to DVT to be extinguished with adjustment for other factors~~[17 26-30].

Immobility, a known risk factor for venous events~~. Family history showed an association to DVT that accounted for the ethnicity association and is also consistent with existing data on genetic variation in clotting factors~~[17 26 31-36] was affirmed here to be a strong predictor for DVT, PE, and DVE.~~

~~Immobility, a known risk factor for venous events~~ It was also a predictor, though less potent, for superficial events. Many factors elsewhere reported to be associated with thrombosis entail periods of immobility: these range from nursing home confinement[13]~~, was affirmed here to be a strong predictor for DVT, PE, and DVE. It was also a predictor, though less potent, for superficial events.~~ and hospitalization ~~Many factors associated with thrombosis entail periods of immobility: these range from nursing home confinement~~[13 25 37], to perisurgical, neurological and injury states ~~and hospitalization~~[13 25 37 38]; factors also extend to prolonged sitting in the work environment[31-33 35].

10

High maximum alcohol consumption was linked to DVT. High maximum alcohol use (such as binge drinking) is the pattern most linked to blackouts[39-41], and thus immobilization. This alcohol finding coheres with a recent report of an association of venous thromboembolism to hard liquor consumption and binge drinking (contrasted with a protective association for wine consumption)[42].

We suggest, in addition, that many (if not most) risk factors for venous thromboembolism, those identified here and elsewhere, share in common an association to elevated risk of cell death, through oxidative stress or adverse cell energy supply-demand balance. Cell death is a consideration with immobilization (leading to focal ischemia), heavy smoking (oxidative stress[43-45] triggers apoptosis[46]), heavy alcohol (promoting oxidative stress[47-50] and mitochondrial toxicity[51-55] as well as ischemia from immobilization). Cancer, trauma, surgery, and the puerpuerium are associated with tissue injury and cell death. Pregnancy is associated with diversion of blood and energy substrates to the fetus, as well as potential for ischemic compression, which can promote cell death. We observe that *cell death triggers coagulation activation*, via exposure at the cell surface of phosphatidylserine[56], and hypothesize that ultimately numerous additional factors, sharing in common elevated risk of cell death (with oxidative stress and/or cell energy supply-demand frequently involved), or correlation to these, will be identified in the future as risk factors for venous thromboembolism. Indeed, the observation that initial DVT accompanied by PE is a risk factor for recurrence of DVT[57] also fits this theme: PE, by affecting oxygen transfer, has prospects to tip the energy adequacy balance, particularly in settings of energy compromise from other sources. Also relevant, central obesity is linked to oxidative stress and cell energy inadequacy[58], and has shown a reported link to thromboembolism risk[23].

Perhaps the most novel findings from this analysis were that SBP and DBP, though unrelated to DVT, were strongly related to PE. We suggest that given absence of a relation of blood pressure, in this sample, to the requisite precursor event DVT, and given measurement of BP after venous event

occurrence, causality could operate in the reverse direction: PE, known to be a risk factor for pulmonary hypertension[59-64], could drive elevation in arterial BP. Indeed, transient hypoxemia in other settings (such as sleep apnea) promotes BP elevation~~, to peri-surgical, neurological and injury states[13 26 37 65]~~**.**

~~Among the most interesting findings, SBP and DBP, though unrelated to DVT, were strongly related to PE. We suggest that, because risk marker data were procured after event occurrence, PE could drive subsequent elevations in BP. Transient hypoxia in settings like sleep apnea promotes BP elevation[66 67]. The possibility cannot be excluded that even focal pulmonary infarction might reduce efficiency of oxygen transfer to blood sufficiently to influence BP in some instances. Potentially compatible information derives from data that initial DVT accompanied by PE is a risk factor for *recurrence* of DVT[68 69]~~**. Even modest reduction in oxygen transfer, arising from pulmonary embolism, might influence BP adversely – concordant with assembled evidence that a range of factors that impair cell energy, promote hypertension (and other metabolic syndrome factors)** ~~; and that arterial hypertension is a risk factor for *recurrent* DVT[58]~~**. Additional potentially compatible information derives from data that initial DVT accompanied by PE is a risk factor for *recurrence* of DVT[57]; and that arterial hypertension is a risk factor for *recurrent* DVT[70], which we hypothesize could be a marker for prior overt or occult PE.**

~~, which we hypothesize could be a marker for prior overt or occult PE.~~

Longitudinal **studies**~~study~~ assessing change in risk markers *following* events **are**~~is~~ seldom undertaken. Therefore cross-sectional designs' lack of "temporality" may serve here not as a fault but an advantageous feature, enabling *event-factor* as well as *factor-event* relations to be uncovered. However prospective studies are desired to confirm hypothesized "reverse" directionality. **Irrespective of whether**~~Whether~~ elevated BP ultimately proves to be a ~~risk factor for, or a~~ consequence of PE, **as we propose,** the relationship will be important to understand.

This study has limitations, including those pertaining to all cross-sectional studies. Though the sample was **diverse economically and ethnically, findings for this population need not generalize to all others; however, reproduction in this sample of many previously reported associations reduces concerns regarding generalizability of the findings. The study measures historical occurrence rather than prospective incidence. Neither fatal events nor clinically silent ones were included in our analyses. Assessment is by self-report, which may involve recall and reporting bias; however self-report of venous events has been used in other studies[71]. In one study, it was shown that most self-reported DVTs were corroborated by surgeons' report (via phone call), and concordance was particularly strong for PE[72]. Most significantly, numerous associations identified here, both among venous outcomes, and between risk factors and venous outcomes, cohere with associations reported in other studies using alternate event assessment modalities, providing strong convergent validation for the findings. An additional limitation, as in all observational studies,** ~~economically broad and ethnically diverse, findings for this population need not generalize to all others; however, affirmation of many known associations reduces concerns regarding generalizability. The study measures historical occurrence rather than prospective incidence. There~~ is inherent potential for omitted variable bias, which can influence the apparent relationship of tested variables to the outcome of interest. ~~Fatal events as well as clinically silent ones were not included in our analyses.~~ Most of the retained variables showed relationships robust across sensitivity analyses, supporting relevance of the variables identified. Exceptions arose with inclusion/exclusion of ethnicity and family history. In this as in all studies, apparent ethnic and family relationships may represent proxies for (measured and) unmeasured variables with which ethnicity (or family) correlate. There were few cases of current cancer in our sample; cancer has elsewhere been reported to predict venous events[13 65 73-76]. Finally, events **had**~~have~~ already occurred when risk markers were measured. For modifiable risk factors, the events could drive the factors rather than the converse, as discussed for the association of PE to increased SBP and DBP.

This study supports previously reported~~confirms~~ relationships of sex, history of immobility, heavy smoking, and duration of HRT to venothrombotic events. It supports recent evidence for a relation of heavy maximal alcohol consumption to venous thromboses, consistent with prior evidence linking binge drinking to venous events[42]. Family history was also affirmed to bear a strong relation to venous events, consistent with (but not exclusive to) recognized genetic risk factors. ~~In addition, a~~An intriguing association of systolic and diastolic blood pressure to PE, but not to DVT, was identified. This novel finding is illuminated by, and simultaneously contributes to, an emerging body of evidence linking mediators of cell energy compromise to increased risk of hypertension – and to other metabolic syndrome factors[58] ~~, identified, which merits further evaluation.~~ It is also observed, to our knowledge for the first time, that factors promoting cell death – including factors that contribute to (or reflect) cell energy compromise or oxidative stress – may be expected to dispose to venous thromboembolism, explaining many observed risk factors[23] , and predicting numerous additional ones[58] .

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Contributorship statement: MC and BG conceived the idea for the study. MC acquired and provided the data. JD managed data, developed the data dictionary, and contributed to analysis review. VC, BG, and SK conducted statistical analyses. The manuscript~~Manuscript~~ was drafted by BG and VC. All authors contributed to revision to the manuscript for intellectual content and approved the final manuscript.

Data sharing: There are no additional data available.

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15

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16

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18

Legends

Table 1. Legend

DBP – diastolic blood pressure; DVT – deep venous thrombosis; HDL – high-density lipoprotein cholesterol; HRT – postmenopausal hormone replacement therapy; PE – pulmonary embolism; SBP – systolic blood pressure; SD – standard deviation; SVT – superficial venous thrombosis.

* P<0.05; ** P<0.01; *** P<0.001

† Ordinal rather than continuous: Ranked from 1 = Grade school or less to 9 = Doctoral Degree.

‡ This correlated well with pack years, which showed a similar relationship to venous events; but variable transformations more suitably satisfied regression constraints for this variable, and the impact of this variable was more potent than that of pack years for deep events, the category of events for which it was predictive.

§ Pack years was calculated by multiplying years smoked by the average number of cigarettes per day divided by 20 (the average number of cigarettes in one pack).

¶ Rated relative to others your age, 1-5 with 5 being most active.

∫ Only females were included in this portion of the analysis.

‡‡ Hypertension: SBP ≥ 140 or DBP ≥ 90.

Table 2. Legend

DVT – deep venous thrombosis; PE – pulmonary embolism; SVT – superficial venous thrombosis.

Recall: Some variables had missing data; and some subjects had multiple types of events.

Table 3. Legend

DBP – diastolic blood pressure; DVE – deep venous event; SBP – systolic blood pressure; OR – odds ratio.

* Age variable was adjusted for sex only; and sex variable was adjusted for age only.

20

† Instead of including both SBP and DBP, we used DBP and the residual of regression of SBP on DBP, so as not to double-count the shared (collinear) contribution by the SBP and DBP values.

Table 4. Legend

DBP – diastolic blood pressure; DVE – deep venous event; DVT – deep venous thrombosis; OR – odds ratio; PE – pulmonary embolism; SBP – systolic blood pressure; SVT – superficial venous thrombosis.

* Age variable was adjusted for sex only; and sex variable was adjusted for age only.

† Instead of including both SBP and DBP, we used DBP and the residual of regression of SBP on DBP, so as not to double-count the shared (collinear) contribution by the SBP and DBP values.

‡ Although some variables lose significance in the fully adjusted model due to collinearity, variables which were of significance or borderline significance in unadjusted or age/sex adjusted model were added back to the final model. When Caucasian ethnicity and heavy smoking were included without one another in the final model, they resumed significance or borderline significance.

§ In the final model, either one of the blood pressure measures – SBP or DBP – could be included and remained statistically significant. (Only one of the two blood pressure variables was included because of collinearity.)

‖ Female specific analysis. Excludes family history of first deep events (see comment for PE). The final female-specific model included age and history immobilization, the sole other variables with $P<0.2$ (neither <0.1).

Note: Caucasian ethnicity shows significant relationship to DVT if not adjusted for family history of DVE (OR=2.15, P=0.008). If both Caucasian ethnicity and family history of DVE are included, Caucasian ethnicity loses significance (OR 1.29, P=0.659) but family history of deep events retains significance (OR 3.17, P=0.026).

Note: Age (OR=1.02,P=0.035) and Caucasian ethnicity (OR=1.97,P=0.015) show a significant relationship to combined deep events in the final model if family history of venous events is excluded.

20

Note: For combined DVT and/or PE oestrogen use for HRT was tested as a predictor in women but was not significant. For oestrogen use duration (per 10 years) ORs (*P* -values) for age-adjusted and final models, were 0.532 (0.534) and 0.523 (0.611). ~~For oestrogen use duration (per 10 years) *among oestrogen users*, ORs (*P* -values) for age-adjusted and final models were 0.948 (0.955); and 0.767 (0.756). (0.756). In the latter case, family history of first deep events was excluded from the final model or the oestrogen variable was dropped due to collinearity. Of note, the resulting modified final model (which included the oestrogen variable) dropped the heavy smoking variable.~~

Table 1a. Summary of Demographic and Predictor Variables by Venous Event Status (continuous variables):

Variables	No Event N=2262 Mean (SD)	SVT N=63 Mean (SD)	DVT N=74 Mean (SD)	PE N=21 Mean (SD)
Age	59.1 (11.4)	60.5 (10.7)	61.9 (11.7)*	61.5 (10.2)
Education†	5.78 (1.73)	5.11 (1.89)***	5.73 (1.67)	5.29 (1.79)
Highest number of drinks per day	2.70 (3.13)	2.24 (2.51)	3.32 (3.76)	3.06 (2.84)
Cigarettes/ day averaged over years totaled‡	6.99 (11.5)	7.73 (14.1)	12.0 (16.1)***	13.2 (14.9)*
Pack years§	7.22 (14.9)	7.38 (18.7)	13.9 (22.3)***	16.5 (20.9)**
SBP (mmHg)	131 (20.3)	132 (22.4)	133 (20.9)	143.0 (21.0)**
DBP (mmHg)	76.8 (11.3)	76.6 (10.8)	78.2 (9.67)	82.5 (7.69)*
Total Cholesterol (mg/dl)	210 (41.3)	207 (38.4)	211 (43.2)	209.2 (42.3)
HDL (mg/dl)	54.5 (17.0)	51.4 (11.3)	50.9 (15.6)	49.9 (16.5)
Activity Level¶	3.71 (1.16)	3.69 (1.19)	3.53 (1.22)	3.40 (1.27)
Number of times in a week engaging in ≥ 20 min of vigorous activity	3.60 (2.51)	3.78 (2.66)	3.52 (2.53)	3.40 (2.54)
Longest period of immobility (days)	11.0 (110)	5.38 (11.9)	17.8 (51.8)	31.4 (84.5)
Oestrogen use duration for HRT among all females∫ (years)	0.743 (3.73)	0.882 (3.04)	0.313 (1.60)	5.92 (13.9)***

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~~Oestrogen use duration *among oestrogen users* for HRT~~ ~~(years)~~	~~9.82 (9.79)~~	~~6.43 (5.97)~~	~~7.50 (3.54)~~	~~15.5 (3.54)*****~~

23

Table 1b. Summary of Demographic and Predictor Variables by Venous Event Status (categorical variables)‡

Variables		No Event (%)	SVT (%)	DVT (%)	PE (%)
Male		34.5	19.0**	35.1	42.9
Hypertension‡‡		35.9	28.6	32.4	42.9
Drinker (any alcohol)		93.4	87.3	95.9	90.5
Maximum alcohol consumption ≥7 drinks per day		7.42	7.31	14.3*	16.7
Drinkers who did not specify maximum level of alcohol consumption		8.49	22.6***	11.1	10.5
Current smoker		6.02	3.17	9.46	9.52
Heavy smoker (≥40 cigarettes per day during time smoked)		3.85	3.17	14.9***	14.3*
Ethnicity	Caucasian	58.9	65.1	78.4***	81.0*
	Hispanic	14.7	20.6	9.46	4.76
	African American	13.9	4.76*	8.11*	9.52
	Asian	12.5	9.52	4.05	4.76
Occupation	Professional	26.4	21.1	26.1	20.0
	Technical, Administrative, or Managerial	40.9	38.6	40.6	45.0
	Clerical and Skilled	26.8	29.8	30.4	25.0

	Semi-skilled	3.85	8.77	2.90	5.00
	Laborer	2.07	1.75	0.00	5.00
Family history of venous diseases (Venous condition in any first degree relative)		57.2	76.2**	71.6*	57.1
Oral contraceptive use (ever; female)		58.1	56.0	54.4	58.3

Table 2. Venous Events in Studied Population

Venous Condition	All Subjects: N (%)	If SVT: N (%)	If DVT: N (%)	If PE: N (%)
SVT	63 (2.68)	*63 (100)*	5 (22.7)	2 (13.3)
DVT	74 (3.09)	5 (8.33)	*74 (100)*	11 (52.4)
PE	21 (0.87)	2 (3.17)	11 (14.9)	*21 (100)*
Any deep event (DVT or PE)	84 (3.50)	5 (8.33)	*74 (100)*	*21 (100)*
Any event (SVT or DVT or PE)	142 (5.91)	*63 (100)*	*74 (100)*	*21 (100)*

Table 3. Multivariate Analyses for SVT

	Age-Sex Adjusted* OR (*P* -value)	**Fully Adjusted** OR (*P*-value)	**Final Model** OR (*P* -value)
Age	1.01 (0.306)	1.03 (0.224)	-
Male sex	0.437 (0.011)	0.275 (0.042)	0.470 (0.028)
African American ethnicity	0.290 (0.038)	0.378 (0.204)	0.305 (0.047)
Education	0.821 (0.015)	0.805 (0.079)	0.801 (0.007)
Activity Level	0.971 (0.796)	0.931 (0.686)	-
Heavy Smoking (≥40 cigarettes per day during time smoked)	0.913 (0.901)	0.977 (0.983)	-
DBP (per 20mmHg)	1.03 (0.894)	2.14 (0.227)	-
SBP (per 20mmHg)	1.01 (0.942)	- †	-
Drinkers who did not specify their maximum alcohol consumption per day	4.37 (<0.001)	4.65 (0.011)	3.33 (<0.001)
History of immobility (>1day)	1.55 (0.091)	2.53 (0.015)	1.71 (0.043)
Family history of first-degree relatives with superficial venous events	1.54 (0.301)	1.55 (0.520)	-
Family history of first-degree relatives with varicose veins	2.30 (0.002)	1.25 (0.706)	2.02 (0.009)
Family history of first-degree	1.74 (0.177)	1.25 (0.637)	-

relatives with DVE			

28

Table 4. Multivariate Analyses for DVT, PE, and Combined Deep Venous Events

	DVT OR (*P* -value)			PE OR (*P* -value)			DVT and PE OR (*P* -value)		
	Age-Sex Adjusted*	**Fully Adjusted**	**Final Model**	**Age-Sex Adjusted***	**Fully Adjusted**	**Final Model**	**Age-Sex Adjusted***	**Fully Adjusted**	**Final Model**
Age	1.02 (0.047)	1.05 (0.162)	-	1.02 (0.404)	0.977 (0.621)	-	1.03 (0.004)	1.04 (0.202)	-
Male sex	1.01 (0.955)	0.479 (0.312)	-	1.41 (0.435)	0.778 (0.795)	-	1.15 (0.548)	0.773 (0.662)	-
Caucasian ethnicity	2.35 (0.003)	0.754 (0.674)	-	2.68 (0.083)	5.77 (0.149)	2.58 (0.096) ‡	2.26 0.003)	0.936 (0.913)	-
Activity Level	0.827 (0.059)	0.819 (0.418)	-	0.771 (0.163)	0.986 (0.971)	-	0.846 (0.081)	0.909 (0.672)	-
Heavy Smoking (≥40 cigarettes per day during time smoked)	4.19 (<0.001)	10.1 (0.007)	16.6 (<0.001)	3.50 (0.052)	5.21 (0.191)	2.73 (0.121) ‡	3.38 (<0.001)	6.92 (0.013)	12.5 (<0.001)
DBP (per 20mmHg)	1.28 (0.227)	0.442 (0.445)	-	2.06 (0.014)	3.20 (0.419)	2.29 (0.010) §	1.39 (0.077)	0.764 (0.766)	-

SBP (per 20mmHg)	0.996 (0.975)	- †	-	1.59 (0.012)	- †	- §	1.05 (0.643)	- †	-
Drinkers who did not specify their maximum alcohol consumption per day	1.74 (0.170)	1.46 (0.739)	-	1.63 (0.534)	2.70 (0.447)	-	1.61 (0.235)	1.09 (0.939)	-
History of immobility (>1day)	2.17 (0.001)	5.32 (0.008)	4.30 (0.006)	4.44 (0.002)	4.21 (0.114)	4.07 (0.004)	2.23 (<0.001)	3.80 (0.013)	3.48 (0.008)
Family history of first-degree relatives with superficial venous events	3.32 (0.024)	0.719 (0.643)	-	1.51 (0.600)	0.730 (0.754)	-	2.52 (0.036)	0.626 (0.449)	-
Family history of first-degree relatives with DVE	4.41 (0.003)	3.51 (0.066)	3.28 (0.020)	0.855 (0.889)	0.431 (0.491)	-	3.42 (0.010)	2.85 (0.100)	2.49 (0.057)
Oestrogen use duration for HRT‖ (per 10 years)	-	-	-	2.73 (0.000)	3.73 (0.000)	2.63 (0.001)			
Oestrogen use duration	-	-	-	-	-	-	4.67	5.22	4.74

among oestrogen users for HRT (per 10 years)							(0.018)	(0.018)	(0.016)

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	3
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	-
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4*
Bias	9	Describe any efforts to address potential sources of bias	-
Study size	10	Explain how the study size was arrived at	3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, explain how loss to follow-up was addressed	5
		(*e*) Describe any sensitivity analyses	5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6, Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Table 1
		(c) Summarise follow-up time (eg, average and total amount)	6
Outcome data	15*	Report numbers of outcome events or summary measures over time	6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
Discussion			8-10
Key results	18	Summarise key results with reference to study objectives	8-9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.