Table. Positive Predictive Value, Negative Predictive Value, Sensitivity, and Specificity of Validation Through Review of Electronic Medical Record Profiles Without Free-Text Comments

	PPV			NPV[a]			Sensitivity			Specificity[a]		
Cancer Type	Num	Den	PPV (95% CI)	Num	Den	NPV (95% CI)	Num	Den	Sensitivity (95% CI)	Num	Den	Specificity (95% CI)
All (N = 168)	128	137	0.93 (0.88, 0.97)	16	31	0.52 (0.34, 0.69)	128	143	0.90 (0.84, 0.94)	16	25	0.64 (0.44, 0.81)
Bladder (n = 36)	27	29	0.93 (0.79, 0.99)	4	7	0.57 (0.22, 0.88)	27	30	0.90 (0.75, 0.97)	4	6	0.67 (0.26, 0.94)
Breast (n = 30)	27	28	0.96 (0.84, 1.00)	2	2	1.0 (0.22, 1.0)	27	27	1.0 (0.89, 1.0)	2	3	0.67 (0.13, 0.98)
Lung (n = 52)	37	40	0.93 (0.81, 0.98)	6	12	0.50 (0.23, 0.77)	37	43	0.86 (0.73, 0.94)	6	9	0.67 (0.33, 0.91)
Prostate (n = 50)	37	40	0.93 (0.81, 0.98)	4	10	0.40 (0.14, 0.71)	37	43	0.86 (0.73, 0.94)	4	7	0.57 (0.22, 0.88)

[a]The low NPV and specificity are explained by the fact that all the profiles had at least one cancer diagnosis code.
Gold standard: results from review of electronic medical records with free-text comments.
CI indicates confidence interval; Den, denominator; NPV, negative predictive value; Num, numerator; PPV, positive predictive value.

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REFERENCES

1. Independent Scientific Advisory Committee for MHRA database research (ISAC). Summary Minutes of 19 January 2016 Meeting. Available at: https://www.cprd.com/_docs/ISAC%202016%20January%20Final%20Summary%20Minutes.pdf. Accessed 16 November 2017.
2. ENCePP. Post-authorization Safety Program – Validation of the Clinical Practice Research Datalink for the Study of Cardiovascular and Neoplasm Events in Users of Treatments for Overactive Bladder (EUPAS5529). London: European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; 2016. Available at: http://www.encepp.eu/encepp/viewResource.htm?id=11107. Accessed 16 November 2017.
3. Kaye JA, Margulis AV, Fortuny J, et al. Cancer incidence after initiation of antimuscarinic medications for overactive bladder in the United Kingdom: evidence for protopathic bias. *Pharmacotherapy*. 2017;37:673–683.
4. Margulis AV, Fortuny J, Kaye JA, et al. Validation of cancer cases using primary care, cancer registry, and hospitalization data in the UK. *Epidemiology*. 2017 [Epub ahead of print].
5. Boggon R, van Staa TP, Chapman M, Gallagher AM, Hammad TA, Richards MA. Cancer recording and mortality in the General Practice Research Database and linked cancer registries. *Pharmacoepidemiol Drug Saf*. 2013;22:168–175.
6. Cea Soriano L, Soriano-Gabarró M, García Rodríguez LA. Validity and completeness of colorectal cancer diagnoses in a primary care database in the United Kingdom. *Pharmacoepidemiol Drug Saf*. 2016;25:385–391.

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Long Working Hours and Risk of Venous Thromboembolism

We are unable to provide direct access to the data from the single studies analyzed here. Code is available on request.
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To the Editor:

Venous thromboembolism (VTE) results from a blood clot that forms within a vein.[1] It includes two subtypes: deep-vein thrombosis (a clot in a deep-vein, usually in the leg) and pulmonary embolism (a sudden blockage in a lung artery). Studies of people sleeping in deck chairs in air-raid shelters during the second world war and, more recently, those of passengers on long-haul flights have linked extended periods of sitting to increased VTE risk.[2] It is also the case that psychological stress can unfavorably influence blood coagulation and viscosity, potentially increasing the risk of VTE.[3,4] People working long hours are often characterized by both sedentary behavior and stress, but to our knowledge, no studies are available on the association of this working pattern with VTE. This is therefore the focus of the present analyses.

We drew individual-level data from eight prospective cohort studies participating in the Individual–Participant–Data meta-analysis in Working Populations ("IPD-Work") Consortium.[5] We excluded people not in full-time employment and those with extant disease at study baseline. Working hours and participant characteristics were assessed at baseline (total N = 77,005 to 77,291 depending on the outcome; eAppendix; http://links.lww.com/EDE/B359). All study members were followed up for VTE for a mean of 9.7 years.

As previously,[6–8] we defined ≥55 hours/week as long working hours, with

TABLE. Multivariable-adjusted Association of Weekly Working Hours with Venous Thromboembolism, Deep-Vein Thrombosis and Pulmonary Embolism[a]

Working Hours per Week	N (total)	N (events)	Hazard Ratio (95% Confidence Interval)	
			Minimally Adjusted[b]	Multivariable Adjusted[c]
Outcome: venous thromboembolism				
35–40	52,774	370	1.0 (reference)	1.0 (reference)
41–48	15,319	99	0.9 (0.7, 1.2)	0.9 (0.7, 1.2)
49–54	4615	29	1.0 (0.7, 1.5)	1.0 (0.6, 1.5)
≥55	4297	41	1.5 (1.1, 2.1)	1.5 (1.1, 2.2)
Outcome: deep-vein thrombosis				
35–40	52,804	239	1.0 (reference)	1.0 (reference)
41–48	15,327	60	0.9 (0.6, 1.3)	0.9 (0.6, 1.3)
49–54	4621	20	1.3 (0.8, 2.1)	1.4 (0.8, 2.2)
≥55	4298	31	1.7 (1.1, 2.5)	1.7 (1.1, 2.6)
Outcome: pulmonary embolism				
35–40	52,992	177	1.0 (reference)	1.0 (reference)
41–48	15,360	49	0.9 (0.6, 1.2)	0.9 (0.6, 1.3)
49–54	4627	16	1.2 (0.7, 2.0)	1.1 (0.6, 1.9)
≥55	4312	16	1.4 (0.8, 2.4)	1.4 (0.8, 2.4)

[a]We defined venous thromboembolism using the following *International Classification of Disease* codes: I80.1–I80.9, I82.1, I82.8, I82.9, O22.3, O22.9, O87.1 (version 10). The ICD codes were 451.1, 451.2, 451.8, 451.9, 453.1, 453.8, 453.9, 671.3, 671.4, 671.9 (version 9) and 451, 453, 671 (version 8) for deep-vein thrombosis and I26.0–I26.9, O88.2 (version 10), 415.1, 673.2 (version 9) and 450, 673.9 (version 8) for pulmonary embolism.
[b]Adjusted for age, sex, cohort, and socioeconomic status.
[c]Additionally adjusted for smoking, high alcohol intake, body mass index, and leisure-time physical inactivity.
ICD, *International Classification of Disease*.

a standard working week of 35–40 hours representing the reference category. Incident VTE was ascertained using linkage to electronic records for hospitalizations and deaths in national registers. We defined VTE using *International Classification of Disease* diagnostic codes (Table). During 830,550 person-years at risk, 539 VTE events were recorded: 350 with deep-vein thrombosis and 258 with pulmonary embolism (69 participants had both).

In the Table, we show associations between working hours and VTE. The hazard ratio of VTE for individuals working long hours compared with those working standard hours was 1.5 (95% confidence interval [CI] = 1.1, 2.1). The association with deep-vein thrombosis was stronger (hazard ratio = 1.7, 95% CI = 1.1, 2.5), while the association with pulmonary embolism was less robust (hazard ratio = 1.4, 95% CI = 0.8, 2.4). We found no evidence of heterogeneity across studies (I^2 = 0.0%). There was no suggestion that these associations were explained by confounding by common vascular risk factors, including smoking, high alcohol intake, BMI, or leisure-time physical inactivity.

Long working hours have been shown to be associated with increased risk of arrhythmias.[7] Irregular rhythm—by disrupting the flow of circulation—can cause blood to pool in the left atrial appendage, contributing to clot formation, especially in the presence of hypercoagulability, a condition also underlying VTE.[1,2] The clot can then travel from the heart to the brain and result in a stroke.[1,2] In agreement with this link is the observation of increased stroke risk in individuals who work long hours.[6] The present study completes the picture by reporting an association between long working hours and hypercoagulability on the venous side of the circulation, as indicated by increased risk of VTE, in particularly deep-vein thrombosis.

These results should be viewed with the following limitations in mind. While we took into account a wide array of covariates, including lifestyle variables and occupational group, we did not have data on prior surgery, major trauma, or blood conditions that increase the tendency toward blood clotting, all of which increase the likelihood of VTE.[2] Lack of adjustment for these characteristics, given that they are linked with reduced rather than increased working hours, may have led to an underestimation of the association with VTE. Unmeasured variation in working hours over time, if random, may also have attenuated observed associations by increasing exposure misclassification. Despite these concerns, our results nonetheless suggest that individuals who work long hours may experience an elevated risk of VTE.

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REFERENCES

1. Di Nisio M, van Es N, Büller HR. Deep vein thrombosis and pulmonary embolism. *Lancet*. 2016;388:3060–3073.

2. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet*. 2012;379:1835–1846.
3. Fang F, Fall K, Mittleman MA, et al. Suicide and cardiovascular death after a cancer diagnosis. *N Engl J Med*. 2012;366:1310–1318.
4. Kivimäki M, Steptoe A. Effects of stress on the development and progression of cardiovascular disease. *Nat Rev Cardiol*. 2018;15:215–229.
5. Kivimäki M, Nyberg ST, Batty GD, et al.; IPD-Work Consortium. Job strain as a risk factor for coronary heart disease: a collaborative meta-analysis of individual participant data. *Lancet*. 2012;380:1491–1497.
6. Kivimäki M, Jokela M, Nyberg ST, et al.; IPD-Work Consortium. Long working hours and risk of coronary heart disease and stroke: a systematic review and meta-analysis of published and unpublished data for 603,838 individuals. *Lancet*. 2015;386:1739–1746.
7. Kivimäki M, Nyberg ST, Batty GD, et al.; IPD-Work consortium. Long working hours as a risk factor for atrial fibrillation: a multi-cohort study. *Eur Heart J*. 2017;38:2621–2628.
8. Sokejima S, Kagamimori S. Working hours as a risk factor for acute myocardial infarction in Japan: case-control study. *BMJ*. 1998;317:775–780.

Excess Risk of Fatal Road Traffic Accidents on the Day of Daylight Saving Time Change

To the Editor:

Daylight Savings Time (DST) is the practice of setting the clocks forward 1 hour from standard time during the summer months, and back again in the fall, to make better use of natural daylight. It is applied in a large number of countries worldwide affecting 1.5 billion people. Changes in light hours and sleep disruption[1,2] occurring during DST changes have been theorized to increase risk of traffic injuries. However, a recent review found inconclusive results on whether DST increased or decreased the risk of road traffic collision, especially in the short term.[3] We estimated the risk of daily fatal traffic accidents following summer and fall DST changes in Spain.

We collected all daily deaths caused by road traffic accidents (International Classification of Diseases 9th revision: E810-E819) in all the 52 Spanish provincial capital cities between 1990 and 2014, provided by the Spanish National Institute of Statistics. We also defined dummy variables to identify summer and fall DST changes, in April and October, respectively. We used an ecologic time-series design, where data were analyzed using quasi-Poisson regression with a distributed lag nonlinear model.[4] Long-term trend and seasonality were adjusted using a natural cubic spline of time with 10 degrees of freedom per year, and a categorical variable was used to control for day of the week. We modeled lagged

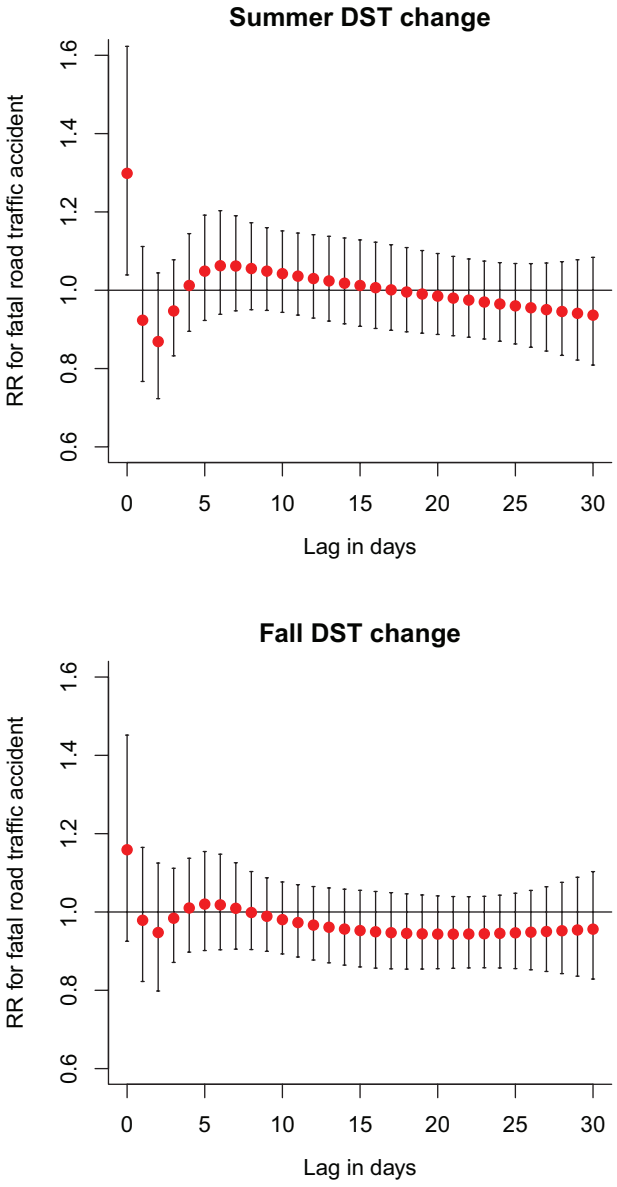

FIGURE. RR for fatal road traffic accident on the day of the daylight savings time change and lagged effects up to 30 days.

Availability of data and code for replication: The dataset generated and analyzed in the current study is not publicly available due to confidentiality agreements.

The authors report no conflicts of interest.

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