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Socioeconomic factors and concomitant diseases are related to the risk for venous thromboembolism during long time follow-up.

Nazim Isma[1], Juan Merlo[3], Henrik Ohlsson[3], Peter J Svensson[1], Bengt Lindblad[2], Anders Gottsäter[2],

University of Lund [1]Centre for Thrombosis and Haemostasis, [2] Department of Vascular Diseases, [3] Unit of Social Epidemiology, Skåne University Hospital, S - 20502 Malmö, Sweden

Correspondence to:

Dr Nazim Isma

Malmö Centre for Thrombosis and Haemostasis, Skåne University Hospital
S - 20502 Malmö, Sweden

Phone: +4640331000

e-mail: nazim.isma@med.lu.se

Abstract

Background: While the risk for arterial vascular disease has been shown to be influenced by socioeconomic status (SES), there is limited information whether SES also influences the risk for venous thromboembolism (VTE).

Aims: To evaluate whether there is an association between SES and VTE incidence.

Material and methods: In 1990, all 730050 inhabitants (379465 women and 350585 men) above 25 years of age in the County of Skåne in Sweden were evaluated with regard to age, household income, marital status, country of birth, number of years of residence in Sweden, educational level, and concomitant diseases. The cohort was hereafter prospectively investigated regarding diagnosis of, or death from VTE (deep venous thrombosis [DVT] or pulmonary embolism [PE]), during 1991-2003.

The association between socioeconomic data and concomitant diseases at the baseline investigation 1990 and incidence of VTE during follow-up was examined by Cox proportional hazard models

Results: During the 13 years prospective follow-up, 10212 women and 7922 men were diagnosed with VTE. In both genders, age above 40 years at baseline, low income, single status, and a lower level of education were associated with an increased risk of VTE. However, both men and women born outside of Sweden have a lower risk for VTE during follow-up,however.

Conclusion: Age above 40 years, low income, single marital status, and lower level of education were independently related to an increased risk of VTE diagnosis during 13 years of prospective follow-up.

Introduction

Socioeconomic status (SES) is a complex multifactorial variable which has been shown to influence many aspects of human health [1-3]. For example, studies have demonstrated relationships between SES and increased risk for coronary heart disease (CHD) [4-6]. diabetes mellitus [7-9], obstructive sleep apnea syndrome (OSAS) [10], cardiovascular mortality [11-13], and cancer [11, 14].

Venous thromboembolism (VTE), manifested as deep vein thrombosis (DVT) or pulmonary embolism (PE) is a common major cause of mortality and morbidity. Although there are several studies suggesting that inflammation may trigger coagulation both in the arterial and venous circulation [15-16], arterial atherothrombotic disease and VTE are not only separate diseases but also have partly different causes [17-18]. Furthermore, the differences in the pathogenesis of this two different diseases are far from fully understood. It is therefore of great interest to know whether variables reflecting the SES of an individual are related to the risk for VTE in the same way as has been shown for different manifestations of arterial vascular disease [4-6, 11-12],

In 1981, a study by Samkoff et al demonstrated an increased rate of PE in subjects with less than 8 years of education compared to in subjects with longer education [19]. Another study by Rosengren et al [20]it showed that SES variables such as persistent stress and low occupational class were independently related to future PE, while no such significant relationship could be demonstrated between DVT and SES [20]. It is also important to note that this study [20], which to the best of our knowledge is the only that has evaluated possible associations of this kind, was performed in male subjects only.

While information on possible associations between SES and VTE are scarce, several concomitant diseases such as for example malignancy [21], inflammatory bowel disease [22], fractures and surgical procedures [23], and infection [24] have all been reported to confer an increased risk for VTE.

The aim of the present study was to assess whether both variables reflecting SES and diagnoses of concomitant diseases prospectively influence the risk for VTE during follow-up in individuals of both genders derived from a total population.

Population and methods

Description of the database and definition of the population

The present study is included within the research project "Longitudinal Multilevel Analysis in Skåne" conducted at the Unit for Social Epidemiology at the Lund University. The project has been approved by the Data Safety Committees at Statistics Sweden, the Swedish Centre for Epidemiology, and by the Regional Ethical Review Board in Lund. The personal identification number assigned to each person in Sweden was used by the Swedish authorities to link information on socioeconomic, demographic and health care variables from different registers. Once the record linkage was done the original personal identification number was encrypted to strenght the anonymity of the individuals.

According the Population Register, on the 31:st of December 1990 the County of Skåne in southern Sweden had 735050 inhabitants 25 or more years of age, 382062 women and 352988 men. In this total population 2606 (0.0068%) women and 2403 (0.0068%) men had been diagnosed with VTE, either DVT or PE during the previous three years 1987-1990, and were therefore excluded from further analysis. The remaining 379465 women and 350585 men were prospectively investigated regarding diagnosis of, or death from VTE/DVT/PE

Assessment of diagnoses

For every patient we obtained information on discharge diagnoses from the National Patient Register, and on causes of death from the National Mortality Register at the Centre for Epidemiology (Swedish National Board of Health and Welfare) (http://www.sos.se/ sose/sos/omsos/statist.htm).

We defined VTE/DVT/PE – the outcome in this study – as in hospital diagnosis or death due to VTE according the International Clasification of Diseases and Causes of Death, versions 9th and 10th (ICD9, ICD10) codes (ICD9: 451-453 & ICD10: I80-I82 or ICD9: 415 & ICD10: I26), during the period between 1st January 1991 and 31st December 2003

We defined *previous diseases* and *previous risk factors* for VTE/DVT/PE as in hospital diagnosis of VTE during 1st January 1987 to 31st December 1990 (Table 1).

Assessment of on socioeconomical and demographical variables

Statistics Sweden (http://www.scb.se/) provided information on socioeconomical and demographical variables for the year 1990, according to the Swedish census and the Population Register. We categorized *age* into five groups (25-39, 40-54, 55-64, 65-74 and 75 years or more), and used the youngest age groups as references in the comparisons.

We considered annual equalized family disposable *income* in 1990 divided into three categories (i.e., low, medium and high) using the tertiles of distribution. The highest tertile was used as reference in the analysis.

We categorized *formal educational achievement* into less than 9 years, 10 – 12 years and 13 years or more and used this last category as reference in the comparisons. Since a 16% (n = 60136) of the women and 11% (n = 37937) of the men lack information on educational achievemet we create a category of missing values.

Marital status was dichotomised into married/cohabiting and living alone (i.e., single, divorced or widowed). Married/cohabiting was used as reference in the analysis.

Country of origin was categorized into two groups (i.e., Sweden or other country)

Using information from the Population Register we calculated the number of years every individual had been registered as resident in Sweden an categorized this variable into 0-4, 5-9, 10-14 and 15 years or more. We applied this last category as reference in the comparisons.

Statistical analyses

We followed all individuals from January, 1st 1990 until December, 31st, 2003, until the first hospitalization with a DVT diagnosis or until death. We did not include any other criteria for lost of follow up since the national in hospital and mortality registries cover the whole country of Sweden and, therefore, we were able to identify those events occurring outside the county of Skåne. We assumed that migration from the country did not have any mayor effect on our estimations.

We performed a sex stratified Cox regression and obtained hazard ratios and 95% confidence intervals. We developed two different models. In model A we included only demografical and socioeconomical variables. In the expanded model B we added previous diseases and risk factors for VTE.

Results

Table 1 shows number and percentages of women and men (2.7% versus 2.3%; p<.001) who were diagnosed with or died from VTE (DVT or PE) during prospective follow-up 1991-2003. Table 2 show hazard ratios with confidence intervals (CI) for VTE diagnosis or death separately for women and men, respectively. In both genders, age above 40 years at baseline increased the risk of a VTE diagnosis, whereas age < 39 years was associated with a lower VTE risk (Table 2).

Subjects in the lowest (1.29[1.22-1.37] for women and 1.13[1.07-1.20] for men) and middle (1.12[1.06-1.19] for women and 1.09[1.03-1.16] for men) tertile concerning household income had an increased risk for VTE compared to subjects in the highest tertile (Table 2,

Figure 1). Single subjects had an increased risk for VTE-risk than married and cohabitating individuals (1.16[1.11-1.21] for women and 1.18[1.12-1.23] for men) (Table 2). Compared to those with the longest duration of education (>13 years) an increased risk for VTE both in those with less than 9 years of education (1.46[1.34-1.60] for women and 1.37[1.26-1.48] for men) and those with less than 12 years of education (1.23[1.13-1.35] for women and 1.24[1.15-1.35] for men) (Table 2). To have been born outside of Sweden, on the other hand, was associated with a lower risk for VTE during follow-up (0.91[0.84-0.99] in women and 0.78[0.71-0.86] in men), and this was most evident among subjects that had lived less than 4 years in Sweden (0.55[0.42-0.71] in women and 0.50[0.37-0.68] in men) (Table 2).
As expected, an increased risk for VTE during follow-up could be demonstrated also among subjects with a previous diagnosis of malignant disease (1.57[1.41-1.75] in women and 1.45[1.27-1.65] in men), inflammatory bowel disease (2.60[1.87-3.63] in women and 1.81[1.22-2.68] in men), or previous surgery (1.20[1.14-1.27] in women and 1.11[1.04-1.18] in men) but also among individuals with diabetes mellitus (1.51[1.31-1.73] in women and 1.6[1.38-1.85] in men), pneumonia (1.64[1.42-1.89] in women and 1.73[1.49-2.01] in men) and in women (1.22[1.09-1.36]) but not men (1.05[0.94-1.16]) with a previous ischemic heart disease (Table2 2). Moreower sepsis was not associated with increased risk for VTE during fallow-up among women (1.35[0.97-1.89]) compared to men (1.77[1.31-2.39]). (Table 2)

Discussion

VTE is associated with several anatomical, biochemical and acquired risk factors. High age is an important risk factor in many different populations [25-27], including our own [28]. This was confirmed in the present study, as higher age at baseline in both genders was associated with increased VTE-risk during follow-up.
Many other factors were also important for VTE incidence in this study, however. During a follow-up of 13 years fewer VTE-cases occurred among married subjects of both genders, as well as in subjects with higher income. Similar relationships have been demonstrated for diseases such as CHD [4, 12-13, 29] and OSAS [10]. In the Malmö population, subjects with low income also run increased risk for pre-hospital death after acute myocardial infarction [12]. Similar relationships have also been shown between these socioeconomic factors and mortality in lung cancer and COPD in the United States [14].
Furthermore, both men and women with fewer years of formal education also showed an increased VTE-incidence during follow-up, corroborating findings from studies examining

effects on education and income on incidences of type 2 diabetes and lung cancer, and on COPD mortality [7, 14].

A relationship between SES and PE has previously been demonstrated in Swedish men [20], among whom a high SES was protective against PE. We now extend this finding by confirming that SES is of relevance also among female subjects and for both DVT and PE. There might be different explanations for effects of SES on VTE incidence. A higher level of education, for example, may affect an individual in many positive ways. The subject might be more receptive to information in health matters, since this type of messages are often written in educated language making it possible for such individuals to more easily adapt to healthy behaviours. Furthermore, previous studies have shown that better education is also associated with both higher compliance [30] and commitment to medical treatment [31].

Having been born outside Sweden, on the other hand, was shown to be associated with a lower risk for VTE during follow-up for both men and women. As data were age adjusted, this could not only be a result of younger age among immigrants. Furthermore, as the risk for VTE in immigrants increased with longer inhabitance in Sweden, the results cannot be entirely explained by genetic factors either. Our results thus clarify that both environmental and genetic factors interact in VTE pathogenesis.

A high prevalence of different genetic risk factors for VTE has been described in the Skåne population [32], and the fact that we do not have data on hereditary thrombophilia in our cohort is of course a study limitation. In order to be able to present reliable data on the importance of hereditary thrombophilia for VTE diagnosis and death, we would have had to examine not only cases, however, but also controls without VTE occurrence or VTE death during follow-up. Evaluation of a cohort of over 700,000 subjects in this respect would have presented obvious practical difficulties.

The key strength of our study is the large sample size, explained by the fact that we have included the whole population above 25 years of age in the County of Skåne in 1990. Our cohort is larger than previous materials as it includes over 700000 subjects. Another difference between the present study and the study by Rosengren et al [20] is that we studied both men and women, and measured SES by income, marital status, education, country of birth and years in Sweden. In the study by Rosengren et al SES was measured by occupational class and factors reflecting stress.

As in the study by Rosengren et al [20] we found that several important concomitant diseases such as for example, malignancies, inflammatory bowel disease, and CVD at baseline was

associated with an increased risk for VTE in both genders. These diseases might of course also be more common among patients with low SES.

The well known relationship of VTE development with common risk factors at baseline such as fractures, trauma or surgery was also confirmed during follow-up in both genders, even if the confidence interval for fracture or trauma only narrowly overlapped 1.0 among females. It is important to note that our data on SES, concomitant diseases and risk factors associated with VTE-development during follow-up are derived from the period 1987-1990, and apply to the risk of VTE development and death during 1991-2003. We cannot be sure that having the same background factors in 2012 has the same implication upon VTE risk during the upcoming 13-years. We are currently following up more contemporary patient materials in order to evaluate whether our conclusions about the importance of SES, risk factors and concomitant diseases for VTE-development are relevant also for the future.

Since there are no previous prospective studies examining the role of SES in both genders in VTE-development, comparisons of our results in relation to other studies are difficult. However, Samkoff et al [19] reported a higher PE-rate in subjects with less than 8 years education compared to those with higher education.

Our study has limitations. The database includes data on the entire population in the County of Skåne, and we could not objectively verify diagnosis in all cases. Furthermore, only inhospital diagnoses were registred. As data on hereditary thrombophilia, body mass index, history of smoking and alcohol abuse are not registred by the authorities and therefore not available, it was not feasible to identify possible contribution of these variables to VTE-risk.

Conclusions

Our study demonstrated that higher age, and socioeconomic status as measured by lower income, single marital status, and lower level of education were independently related to an increased risk of VTE during prospective follow-up. Foreign ancestry, on the other hand, was related to a lower VTE risk.

Aknowledgements

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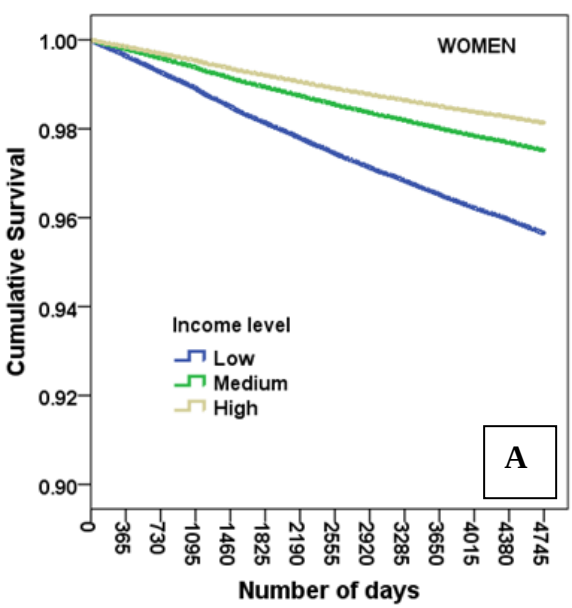
Legend to figures

Crude (A and C) and adjusted* (B and D) cumulative survival time (absolute values) free of venous thromboembolism during the 13 years follow-up period (1991-2003) related to household income in 379456 women and 350585 men, 25 years of age and older and residing in the County of Skåne, Sweden in 1990.* Adjusted according to model B in table 2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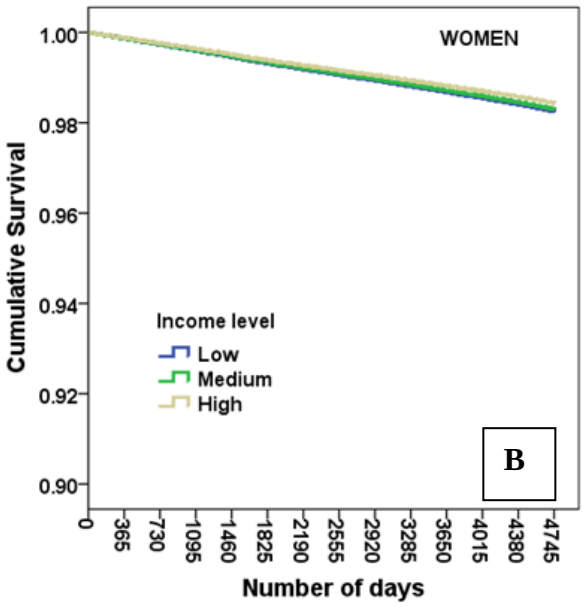
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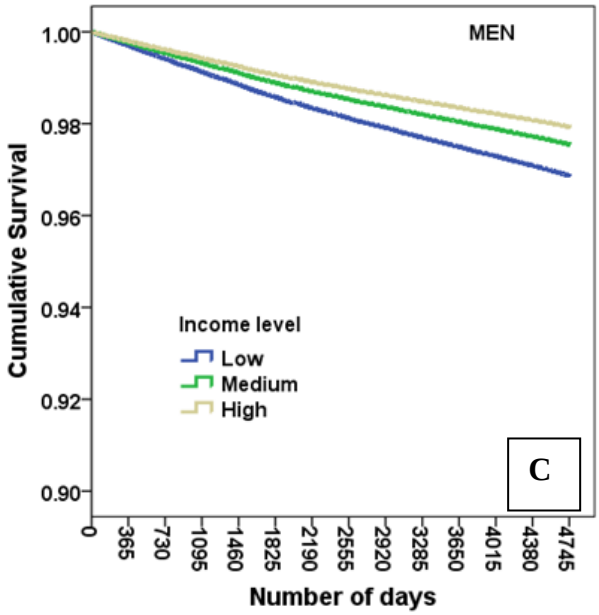
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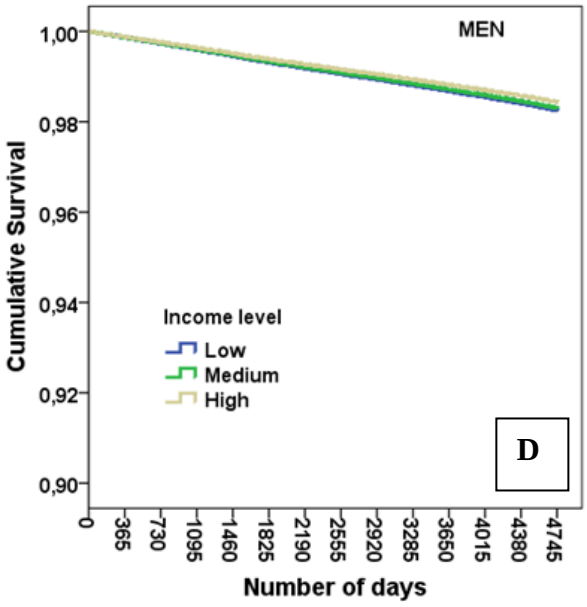
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Table 1. Characteristics of subjects with and without venous thromboembolism (VTE) during 1991-2003. Socioeconomic and demographical variables are from 1990, and data on previous diseases and risk factors refer to 1987-1990.

	Women (n = 379456)		Men (n = 350585)	
	Without VTE	With VTE (2.7%)	Without VTE	With VTE (2.3%)
Socioeconomical / demografical variables				
Mean age (years)	52.5	67.2	49.8	63.4
Income level (%)				
Low	37	52	29	34
Medium	33	28	34	34
High	31	20	37	32
Living alone (%)	43	53	38	33
Years of education (%)				
Missing data	15	36	11	22
0-9	34	39	34	41
0-12	34	19	37	27
>13	17	6	19	10
Born outside Sweden (%)	11	7	11	7
Years in Sweden (%)				
0-4	2.4	0.6	2.8	0.6
5-9	1.5	0.6	1.5	0.6
10-14	1.4	0.5	1.3	0.5
> 15 or always	95	98	94	98
Diseases and risk factors* (%)				
Chronic obstructive pulmonary disease (COPD)	0.3	0.6	0.4	1.3
Diabetes mellitus (DM)	1.1	2.2	1.2	2.4
Congestive heart disease (CHD)	0.9	1.6	0.9	2.1
Ischemic heart disease (IHD)	1.6	3.4	2.7	5.3
Cancer	1.7	3.8	1.5	3.3
Inflammatory bowel disease (IBD)	0.2	0.3	0.2	0.3
Sepsis	0.2	0.3	0.2	0.5
Pneumonia	0.9	1.9	1.0	2.4
Fracture or trauma	3.5	5.8	3.2	4.0
Surgery	19	23	12	20

*COPD (ICD9: 490-492, 496 & ICD10: J40-J44), DM (ICD9: 250 & ICD10: E10-E11), IHD (ICD9: 410-414 & ICD10: I20-I25), CHD (ICD9: 428 & ICD10: I50), cancer (ICD9: 140-208 & ICD10: C00-C97), IBD (ICD9: 555-556 & ICD10: K50-K51), sepsis (ICD9: 036C, 038 & ICD10: A327, A392-394, A40-41, A483), pneumonia (ICD9: 480-486, 510-11, 513 & ICD10: A481, B012, B015, J12-J18, J20-22, J85-86), fractures and trauma (ICD9: 8-, 91,92,95, 900-904 & ICD10:S00-T14).

Table 2. Hazard ratios (HR) and confidence intervals (CI) for incidence of venous thromboembolism in 1991-2003 in 379456 women and 350585 men > 25 years of age. Demografical and socioeconomical data are from 1990, and data on previous diseases and risk factors refer to 1987-1990.

	Model A						**Model B**					
	Women			Men			Women			Men		
	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Age (years)												
25-39	Ref.			Ref.			Ref.					
40-54	2.44	2.2	2.7	3.25	2.93	3.61	2.48	2.24	2.74	3.23	2.91	3.59
55-64	5.81	5.26	6.43	8.85	7.97	9.83	5.84	5.28	6.46	8.60	7.74	9.56
65-74	10.69	9.72	11.76	15.19	13.72	16.81	10.59	9.62	11.65	14.39	12.99	15.94
≥75	15.31	12.35	18.99	20.79	16.46	26.25	14.68	11.84	18.21	18.75	14.84	23.69
Income level												
Low	1.29	1.22	1.37	1.13	1.07	1.20	1.29	1.21	1.36	1.12	1.06	1.19
Medium	1.12	1.06	1.19	1.09	1.03	1.16	1.11	1.05	1.18	1.09	1.03	1.15
High	Ref.			Ref.			Ref.					
Marital status												
Married	Ref.			Ref.			Ref.					
Single	1.16	1.11	1.21	1.18	1.12	1.23	1.15	1.11	1.20	1.16	1.11	1.22
Education (years)												
Missing data	1.54	1.25	1.90	1.40	1.12	1.74	1.54	1.25	1.89	1.39	1.11	1.73
0-9	1.46	1.34	1.60	1.37	1.26	1.48	1.46	1.33	1.59	1.36	1.25	1.47
0-12	1.23	1.13	1.35	1.24	1.15	1.35	1.23	1.13	1.35	1.24	1.14	1.35
>13	Ref.			Ref.			Ref.					
Country of birth												
Sweden	Ref.			Ref.			Ref.					
Other	0.91	0.84	0.99	0.78	0.71	0.86	0.91	0.84	0.99	0.78	0.71	0.85
Number of years in Sweden												
0-4	0.55	0.42	0.71	0.50	0.37	0.68	0.56	0.43	0.73	0.51	0.37	0.69
5-9	0.69	0.53	0.90	0.91	0.68	1.21	0.70	0.54	0.92	0.92	0.69	1.22
10-14	0.70	0.53	0.92	0.72	0.52	1.01	0.71	0.54	0.93	0.73	0.52	1.01
≥ 15	Ref.			Ref.			Ref.					
Diseases and risk factors												
Chronic obstructive pulmonary disease							1.41	1.10	1.80	1.86	1.52	2.27
Diabetes mellitus							1.51	1.31	1.73	1.6	1.38	1.85
Congestive heart disease							1.25	1.06	1.47	1.57	1.33	1.85
Ischemic Heart Disease							1.22	1.09	1.36	1.05	0.94	1.16
Malignant disease							1.57	1.41	1.75	1.45	1.27	1.65
Inflammatory bowel disease							2.60	1.87	3.63	1.81	1.22	2.68
Sepsis							1.35	0.97	1.89	1.77	1.31	2.39
Pneumonia							1.64	1.42	1.89	1.73	1.49	2.01
Fracture or trauma							1.09	1,00	1.19	1.21	1.08	1.36
Surgery							1.20	1.14	1.27	1.11	1.04	1.18