Lifestyle and venous thromboembolism
A review

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Abstract

Introduction: The relationship between arterial cardiovascular disease (CVD) and venous thromboembolism (VTE) is debated. The knowledge about lifestyle as a risk factor for CVD is substantial, while there are few conclusions are reached on the association between lifestyle and VTE. The aim of this review was to assess whether known cardiovascular lifestyle risk factors also are associated to the risk of VTE.

Methods and results: We conducted a PubMed search of the existing literature using key words for venous thromboembolism, cardiovascular disease and lifestyle. All of the lifestyle factors are established risk factors for CVD. Studies on physical activity and VTE have diverging results; being physically active was both associated with decreased and increased risk of VTE. In contrast, body mass index (BMI) is recognized as a risk factor for VTE. Only two studies are conducted on the relationship between diet and VTE, and they reach opposite conclusions. The results on alcohol and VTE were conflicting; this is probably due to different study designs and populations. The only study done on coffee and VTE found no association. Heavy smoking yields an increased risk of VTE. Psychosocial factors have not been investigated in relation to VTE, except self-reported stress, which has been reported to increase the risk of pulmonary embolism. Lastly, high socioeconomic status was inversely associated with VTE risk.

Conclusions: BMI is the only clear common risk factor for both CVD and VTE, while more studies on general populations are needed to reach conclusions concerning the other risk factors.
Introduction
Venous thromboembolism (VTE) is the collective term for deep vein thrombosis (DVT) and pulmonary embolism (PE). Deep vein thrombosis occurs most commonly as a thrombus in the deeper veins of the lower extremity. In some cases, the thrombus becomes detached from the vessel wall, and is transported by the circulation to the pulmonary arteries as an emboli, and is known as a pulmonary embolism. Symptoms of DVTs include pain, swelling, redness and tenderness, while PE is usually presented by dyspnoe, tachypnoe and pleuritic chest pain. DVT and pulmonary embolism have the same pathophysiology and often occur at the same time. Of those presenting with an event of DVT, 50-80% have asymptomatic or major PE present. Of those presenting with PE, findings of DVT are positive in 80% of the cases (1). The incidence of VTE is 1-2 per 1000 in the Western population (2-4), and there are twice as many DVTs as pulmonary embolisms (5, 6). Several studies have reported that risk of incident VTE increase markedly with age with an incidence from 1 per 100.000 in childhood to almost 1% in old age (7). Results from the Tromsø study showed that subjects 70 years or older had an 11-fold increased risk of VTE compared to subjects younger than 50 years (8).

VTE is a substantial source to both mortality and morbidity; there are several short- and long-term complications. The mortality is about 6% and 12% within first month after the diagnosis of DVT and PE, respectively (6). Further embolization and death are short-term complications, while recurrence, post-thrombotic syndrome and pulmonary hypertension are examples of long-term complications. Venous thrombosis often recur, about 30% develop recurrence within a 10-year period (9). Furthermore, 25% of the VTE events develop post-thrombotic syndrome during a 20 year period (10) with lower leg pain, swelling, stasis dermatitis etc.

Already in the 1870, Rudolf Virchow formulated the Virchows triad, which has been the foundation in the understanding of the pathophysiology of venous thrombosis. The triad includes changes in the blood composition, alterations of blood flow and alterations of the vessel wall. To date, the pathophysiology is not fully understood, however, there is broad agreement that venous thromboembolism is a multifactorial disease involving both genetic, acquired and transient factors. These factors can all be seen in terms of the Virchows triad. The presence of several factors concurrently is often necessary for thrombosis to develop. Genetic components which increase the risk of VTE, are protein C and S deficiency, factor V
Leiden mutation, prothrombin 20210A mutation, high concentrations of factor VIII and antithrombin deficiency (11). Advancing age, chronic disease, cancer and obesity are examples of acquired factors associated with VTE occurrence.

Venous thrombosis is the leading cause of preventable in-hospital deaths in the USA (4). Confinements to hospital or nursing homes are risk factors for VTE (12), in a population-based case-control study, almost 60% of all VTE cases were attributed to institutionalization (13) where the hospitalization due to medical illnesses or due to surgery was equal. Surgery and trauma are both risk factors for venous thrombosis (11). The risk of surgery can further be stratified based on type of surgery, age, and whether cancer is present (14). Neurosurgery and hip replacements are examples of procedures with high risk of VTE (15). Chronic obstructive pulmonary disorder (COPD), congestive heart failure, chronic renal disease, malignancy, systemic lupus erythematosus (SLE), neurological disease with extremity paresis, infections and central venous catheterization or pacemaker are also associated with increased risk of VTE (4, 12, 16). Active cancer accounts for almost 20% of incident VTE events (17). The risk of VTE is 7-fold increased among cancer patients, in fact, VTE is the second leading cause of death among cancer-patients (18). In addition, chemotherapy itself increases the risk of VTE (19). Conversely, patients with idiopathic VTE have increased risk of cancer for at least 2 years after the VTE-diagnosis (20).

Among women, hormonal contraceptives (OC), hormone replacement therapy (HRT), pregnancy and puerperium are also risk factors for venous thromboembolism. Women using oral contraceptives have 3 to 6 times increased risk compared to non-users. The highest risk of VTE occur during the first year of use, but an increased risk of VTE persists until discontinuation (21). Use of hormone replacement therapy also yields a 2-3 times higher risk of VTE, and the users of HRT have an higher absolute risk of VTE compared to OC users due to higher age (22). During pregnancy, normal hematologic changes occur, with increasing levels of coagulation factors, fibrinogen and decreasing levels of anticoagulants components of the fibrinolytic system (23). This is probably a mechanism which prevents major bleedings during birth, however, pregnancy and the post-partum period are transient risk factors for venous thromboembolism. Pregnant women have 4 to 5 times higher risk of venous thrombosis than non-pregnant women, and the risk seems to be higher in the third trimester compared to the first and the second trimester (24). During the post-partum period, the risk of VTE is even higher than during pregnancy (25).
The association between venous thromboembolism and cardiovascular disease have been debated. Traditionally, arterial cardiovascular disease (CVD) and VTE are considered two different diseases with different pathophysiology, different treatment and different risk factors. However, this has been challenged over the last decade, first by a case-control study by Prandoni et al. (26), where they found higher occurrence of carotid plaques in subjects with spontaneous DVT, compared to subjects with secondary thrombosis and controls. Since then more studies have shown both that VTE is a risk factor for myocardial infarction (MI) and stroke (27), and that family history of MI is a risk factor for VTE (8). Also the treatment of the two diseases shows similarities; the JUPITER study revealed that rosvastatin, a statin traditionally used to treat high cholesterol to prevent CVD, also yielded a reduction in venous thrombotic events (28). In addition, aspirin has shown a possible preventive effect on VTE (29), low-molecular weight heparins (LMWH) is known to be effective also in the treatment of CVD (30). Lastly, warfarin is a commonly used treatment for both arterial and venous thrombosis (31).

In spite of many known risk factors, 25-50% of the VTE cases occur in the absence of any recognized risk factors (6). Further investigation of risk factors for VTE can be beneficial for risk stratification, prevention of substantial contributions to mortality and morbidity, and further understanding of the pathophysiology of venous thromboembolism. Lifestyle is known to be associated with risk of arterial cardiovascular disease, in this review we will discuss whether known lifestyle cardiovascular risk factors are related to risk of VTE based on a PubMed search of the existing literature using key words for venous thromboembolism, cardiovascular disease and lifestyle.

**Physical activity and venous thromboembolism**

As mentioned, Virchow’s triad has long been the cornerstone of understanding venous thromboembolism; he then postulated that blood stasis, which can be caused by immobilization and physical restriction, was one of the main contributors to this disease. Contrary, muscle activity yields a distinct decrease in venous pressure, elevation of the blood flow, and prevents edema (32-34). Thus, it would be reasonable to believe that physical exercise will lower the risk of VTE. However, not much research is done on this particular hypothesis, and the results of the existing research are diverging.
The MEGA-study (35) is a large population-based case-control study, including 3 608 cases and 4 252 controls aged 18-70 years (table 1). They investigated whether participating in sports activities on a regular basis was associated with the risk of VTE, and found that participating in regular sport activities at least once a week yielded a 29% reduced risk of VTE, compared to those who did not participate in sport activities. They did not find any differences in risk estimates for various frequencies, intensities or types of sport. Another case-control study (36) set out to investigate the relationship of use of oral contraceptives and risk of VTE (table 1). They included 196 cases and 746 controls aged 15-44 years. They found an increased risk associated with use of OC, but this risk was reduced among those who participated in regular and vigorous exercise. A large prospective cohort (37) including 29 518 Swedish women between 25 and 64 years, studied the relationship between several lifestyle factors and risk of VTE (table 1). One of the main findings of their study was that women who engaged in strenuous exercise (bicycling, gymnastics/dancing more than once a week) were at half the risk of VTE compared to women who led a sedentary lifestyle, whereas walking several times a week did not yield the same significant protective effect. The Physicians’ Health Study (38) compared risk factors for CVD, stroke and VTE in 18 662 healthy male physicians (table 1). Whilst they found exercise to have a protective effect on CVD and stroke, it actually yielded an increased risk of VTE, particularly for provoked events. A longitudinal study (39), investigating the impact of exercise on elderly people and the risk of VTE, reached a similar conclusion (table 1). They included 5 534 participants, aged 65 years or older and found that mild-intensity exercise such as walking gave a non-significant beneficial effect, while strenuous exercise such as jogging was associated with a greater risk of VTE compared to no exercise at all. The LITE-study (40), also studied exercise as a cardiovascular risk factor and revealed its impact on VTE (table 1). This prospective cohort, comprising of 19 293 men and women more than 45 years old found no association between physical activity and VTE, but they did reveal a tendency of increased risk with increasing levels of activity.

The reason for these very diverging results may lie in the fact that the different studies have different study designs (case-controls and cohorts), dissimilar study populations (only women, only men, only elderly etc.) and different methods for classifying physical exercise. It should be mentioned that only two case-control studies (35, 36) and one prospective study (37), which collected information on physical exercise retrospectively, found a protective effect of
exercise on VTE. To collect information retrospectively is a weakness because it could cause recall bias. Nevertheless, more studies are needed to be able to understand the relationship between physical exercise and VTE.

**Body Mass Index and venous thromboembolism**

High body mass index (BMI) is generally related to increased risk of disease, especially CVD, heart failure and death (41-43). The mechanism for the relation between high BMI and VTE is not fully understood. A French study from 2003 (44) reported a strong positive relation between plasminogen activator inhibitor-1 (PAI-1) level and BMI. Being the main fibrinolytic inhibitor, it is plausible that increased levels of PAI-1, due to high BMI, may yield an increased risk of VTE. Other studies have also suggested that increased BMI is associated with higher levels of prothrombotic factors, such as factor VII and fibrinogen (45, 46). In addition, increased levels of C-reactive protein, tumor necrosis factor alpha and interleukin-6 can cause inflammation which in turn may cause endothelial damage, promote endothelial adhesion molecule expression and increase platelet aggregation (47-50). A recent study showed that increased intraabdominal pressure (IAP) is transmitted to the lower extremities, by revealing a positive correlation between waist circumference and the femoral vein, and the fact that obese patients had higher venous outflow obstruction than lean subjects (51).

Already in 1983, the Framingham study (52) concluded that weight reduction in obese women might reduce the risk of pulmonary embolism (table 2). A decade later, the same authors again concluded that obesity was a risk factor for PE in The Nurses’ Health Study (53) (table 2). Both were prospective cohorts including women. The LITE study (40) found BMI to be a strong, independent risk factor for VTE (table 2). In concordance with the above mentioned articles about mechanisms, they suggest that this is caused by the fact that obesity is associated with venous stasis, and higher levels of prothrombotic factors, but also point out that obese individuals may be more likely to be hospitalized, and therefore immobilized. Furthermore, the Physicians’ Health Study (38) found BMI to be an even stronger risk factor for VTE than for CVD and stroke (table 2).

In The Tromsø Study (54), a prospective cohort including 6 708 men and women aged 25 to 84 years, they also found BMI to be a risk factor for VTE, but they concluded that waist circumference (WC) is a more accurate measure for obesity and the risk of VTE.
(table 2). In a review from 2003 (55), they concluded that obesity was only a weak risk factor for VTE. As a sharp contrast to previous mentioned articles, Heit et al. (12) conducted a nested case-control study, where they concluded that BMI was not a risk factor for VTE (table 2). However, they point out that their ability to identify an above-normal BMI was limited because they were missing substantial data on height and weight among controls. In a study based on the RIETE registry (56), they enrolled 10 114 patients in 2007 (table 2). Their aim was to investigate the influence of BMI on mortality in patients with VTE and they concluded that obese patients have less than half the mortality rate, compared with patients with normal BMI. With this finding, they suggest that there exists an “obese paradox” in patients with VTE. Although they point out that it is well known that underweight patients with VTE has a higher risk of major bleeding, this still does not explain the lower incidence of fatal PE, or the similar rate of VTE recurrence in all BMI groups. They are not able to suggest a pathophysiological mechanism responsible for their finding.

It is a clear overweight of those who find BMI to be an independent risk factor, and the one article who conclude that BMI is not a risk factor admits to a major weakness, they lack information on height and weight on many of the controls. Based on this it is fair to conclude that BMI is an established, independent risk factor for VTE.

**Diet and venous thromboembolism**

In 1952, Jensen (57) published an article on the decrease in postoperative thromboembolism in Norway during the Second World War. He eliminated several possible explanations for the decrease, and finally concluded that it had to be due to the altered diet during the war years (1940-45). Because of war-restrictions the diet in the Norwegian population was low in meat, high fat dairies, eggs, fruit, berries, sugar and coffee, and high in vegetables and fish (58).

Diet and arterial cardiovascular diseases (CVD) has been extensively investigated. Lately, several articles have pinpointed that studying dietary patterns has greater value than studying isolated nutrients because people usually have complex diets, and nutrients may have synergistic effects on one another (59). Dietary patterns and CVD have been shown to be strongly related (60, 61). Still, very little is known about venous thromboembolism and dietary patterns.
Not surprisingly, diet has been shown to affect several haemostatic factors like factor VIII, fibrinogen, antithrombin III, protein S (62) and platelet count and activity (63), in addition to factor VII (62, 63) and PAI-1 (62, 64). These factors are related to VTE in varying degrees (65-69). Only two articles are published studying the association between isolated nutrients and dietary patterns and risk of venous thromboembolism. The LITE-study, a prospective cohort, including almost 15 000 middle-aged adults (70), tested their hypothesis that foods rich in B vitamins and ω-3 fatty acids are negatively associated and meat intake positively associated with incident VTE (table 3). They concluded that a diet including more plant foods and fish and less red and processed meat is associated with a lower incidence of VTE. They also identified dietary patterns by using principal component analysis, and found a non-significant protective effect among those with the highest prudent dietary scores (high consumption of fish, fruit and vegetables) and a significant increased risk associated with high western dietary score (high consumption of red, processed meat and saturated fat). Another prospective cohort published two years later, also studied both isolated nutrients and dietary patterns, but their conclusion was not in concordance with LITE. The Iowa Women’s Health Study (IWHS) (71) including elderly, predominantly white women concluded that a greater intake of alcohol was associated with a lower risk of incident VTE, but found no other independent associations between diet and VTE (table 3). They also used factor analysis to identify dietary patterns. The prudent pattern was characterised by high intake of vegetables, fruit, and poultry. Those defined as having a western pattern had a greater intake of processed meat, non-cereal whole grains, and added fats and oils. They found no association between neither prudent nor western dietary patterns, and risk of VTE.

In the Iowa study (71) it was discussed why their results diverged from the results in the LITE study (70) first and foremost pointing out the age difference in the two studies. The mean age at midpoint in IWHS is 12 years older than the mean age in LITE. They point out that for example metabolism change with age, and that nutrient absorption usually declines in addition to attenuated kidney function and energy needs. Also, the follow-up in IWHS is 7 years longer than in LITE, which may have led to greater dietary misclassification in the older IWHS-population. Furthermore, they have used different questionnaires. IWHS have included 127 questions, while LITE only have 66 questions. This may lead to LITE getting less extensive information, but maybe more accurate answers because it is easier to fulfil a shorter questionnaire. The fact that the Iowa study only investigates the association in elderly women
clearly attenuates their generalizability. Only two studies, with opposite conclusions does not give us an answer to the relationship between diet and VTE.

**Alcohol and venous thromboembolism**

The association between alcohol consumption and arterial cardiovascular diseases has been extensively investigated, and the conclusion is that moderate alcohol consumption has a beneficial effect on CVD (72, 73). Several studies have also indicated that alcohol affects numerous factors involved in haemostasis, such as lowering fibrinogen (74-76), factor VII, von Willebrand factor and plasma viscosity (76), in addition to inhibiting platelet aggregation (77) and yielding an increase in levels of tissue plasminogen activator (74, 75). Still, the relationship between alcohol consumption and venous thromboembolism (VTE) is not well described, and the results from existing studies are diverging.

A prospective cohort, including predominantly elderly, white women from Iowa, New Haven and East Boston (78), found that light to moderate alcohol consumption was associated with a decreased risk of VTE (table 4). However, the finding was only significant in East Boston, due to a generally low consumption in Iowa and New Haven. Also a Swedish cohort (37), studying lifestyle factors and VTE on a population who consisted of middle-aged women, concluded that women who were non-smokers, physically active and had moderate alcohol consumption were at lower risk of VTE (table 4). The LITE-study (40), a prospective cohort with a median follow up of 8 years, including more than 19 000 middle-aged and elderly men and women, investigated the association between traditional cardiovascular risk factors and risk of VTE (table 4). In contrast to the two former mentioned studies, the LITE-study found no association between alcohol consumption and risk of VTE. Another prospective cohort studying male physicians (38), compared risk factors for coronary hearth diseases, stroke and venous thromboembolism (table 4). They found that alcohol was protective against coronary heart disease, but not associated with stroke or VTE. Two case-control studies landed on opposite conclusions. One of them, a large study on Dutch men and women (79), found that subjects with a history of previous VTE had lower alcohol intake than controls, where 2-4 glasses per day resulted in the largest beneficial effect (table 4). They also revealed that alcohol consumers had a concomitant decrease in fibrinogen; this was suggested as an explanation for the decreased risk associated with VTE. In contrast, a French case-control study (80) studying several possible risk factors for deep vein thrombosis in medical
outpatients found no association between alcohol and VTE (table 4). The only study investigating the impact of different alcohol types and risk of VTE is the Iowa Women’s Health Study (71) (table 4). This large prospective cohort on elderly women reported an observed protective effect of beer consumption only, and no association between wine or liquor and risk of VTE.

The diverging results in these studies can to a large extent be explained by different study design; most of them are prospective cohorts, but some are case-control studies. Although, the largest difference is probably the study populations; some only study elderly, white women, others only male physicians, this may have a substantial impact on the results knowing that there is generally difference in drinking patterns between elderly and middle aged and between men and women. This will attenuate the external generalizability, and make them less comparable to each other. How they classify alcohol consumption is also important, the Dutch study has more than 10 glasses of alcohol per day as their highest exposure, while the Iowa Women’s Health Study only has more than one glass per week as their highest exposure, and others use occasional or daily consumption as their only classification (38). The relation between alcohol consumption and VTE is still not understood.

**Coffee consumption and venous thromboembolism**

Consumption of coffee has been associated with many disorders (81), and there are numerous studies concerning coffee consumption and arterial cardiovascular disease. Even the University of Tromsø is recognised for the finding of the association between boiled coffee and cholesterol-levels (82). However, whether coffee is an independent risk factor for arterial cardiovascular disease remains debated. Some studies have found an increased risk of cardiovascular disease (83-86), some have not found any association (83, 86-88), while others have even found an inverse association between coffee intake and CVD incidence (89-92) and mortality (91, 93-95).

Only one observational study has investigated the relation between coffee intake and venous thromboembolism (71). The Iowa Women’s Health study is a prospective cohort study which included almost 40 000 older women, and 1950 events of VTE was registered during a follow-up of a median of 13 years (table 5). Their conclusion was that coffee was inversely associated to VTE risk in multivariable analyses (adjusted for age, kilojoules, education,
smoking status and physical activity), however, the association attenuated after further adjustments for diabetes and BMI.

Coffee is a liquid containing many different substances. What first comes to mind is caffeine, while other substances are polyphenols, diterpenes, vitamin E and B3, magnesium and potassium (81), and it is believed that coffee may have both beneficial and detrimental effects on health. Caffeine has been associated to stimulation of the central nervous system, acute elevation of blood pressure, increased diuresis and metabolic rate (81). Diterpenes (kahweol and cafestol) are present in boiled coffee, and have a cholesterol-raising effect, however, this effect can be avoided by using paper filter when preparing coffee (96). Another compound which has been studied is polyphenols. These have antioxidant properties which can affect the oxidation of LDL cholesterol, furthermore, they may influence platelet aggregation (97).

**Smoking and venous thromboembolism**
Smoking is an established risk factor for cardiovascular disease, however, the findings concerning smoking and risk of venous thrombosis are conflicting. Numerous studies have not found any association (8, 38, 40, 98, 99), while five prospective studies (37, 53, 100-102) and two case-control studies (103, 104) have found a positive association between smoking habits and venous thrombosis (table 6). Suggested underlying mechanisms for this association have been increased levels of coagulations factors and fibrinogen (105-107), defect fibrinolysis (105, 108, 109), impaired endothelial function (110-112) and possibly increased platelet aggregation (105, 112).

Among the studies reporting no association between smoking and venous thrombosis are two large cohort studies of male physicians (38) and of men and women aged ≥45 years (40). The LITE study (40) found no relation between VTE risk and smoking status or number of pack-years, while the Physicians’ Health Study (38) reported that smoking status is associated to CVD, but not to venous thrombosis. Supporting these findings is a meta-analysis published by Ageno and co-workers (98) where 21 studies were included, however, only 4 of these were prospective cohort studies. Smoking status and risk of venous thrombosis has also been investigated in the Tromsø study (8) and in the HUNT-study (99) without finding any association.
Two cohorts including middle-aged women, The Nurses’ Health Study (53) and the Swedish MISS-study (37), found smoking at least 25 cigarettes per day or more than 100,000 cigarettes ever, compared to never-smokers, was associated with increased risk of pulmonary embolism or VTE. Supporting results were reported in another Swedish cohort study including middle-aged men where smoking >15 cigarettes per day was associated with a nearly 3-times increased risk of VTE (101). The Copenhagen City Heart study found an association between VTE risk and heavy smoking (≥25 g tobacco per day vs. never smokers) (102). A large case-control study (the MEGA-study) also found increased risk of VTE among current and former smokers (103). In concordance with the others, daily amounts of cigarettes were associated to venous thrombosis in a dose-dependent manner. Increased risk of VTE was also reported in the Danish prospective study “Diet, Cancer and Health” where men and women aged 50-64 were included and followed for a median of 10.2 years (100). There was a positive association between current smoking and VTE, in addition, smoking >20 cigarettes for women, and >30 cigarettes for men, increased the risk of VTE markedly, and the authors suggest a possible threshold effect of smoking. Furthermore, the Iowa Women’s Health study, including elderly women only, reported a 20% increased risk of VTE among current and former smokers, as well as a positive association among the heavy smokers (≥20 pack-years) (113) (table 6). However, the association was restricted to provoked VTE only, and cancer-related VTE was responsible for this association (113). The association between smoking duration and risk of VTE has not been assessed (53, 100-102) or was not dose-dependently associated (103) with VTE in the abovementioned studies.

Several explanations for different results have been suggested, where different study designs and different populations are two of them. Different classification of smoking habits is another explanation. Most of the studies not finding an association have only studied the association between smoking status (current, former and never smoking) and risk of VTE, while further investigation of smoking doses has been left out. The overall conclusion of studies finding an association is that heavy smoking is associated with increased risk of venous thrombosis, although the different studies have found different thresholds. A third explanation for the conflicting results is confounding since the studies have different multivariable models. Only some of them have included important confounders such as smoking-attributable disease in the analyses. The Danish study “Diet, cancer and health” (100) included analyses for non-cancer related VTE where positive risk estimates remained, although not significant. Hansson et al. found similar results in their multivariable analyses.
where cancer, myocardial infraction, stroke and diabetes mellitus during follow-up were included (101). The Iowa Women’s Health Study was the first to report that the observed association between smoking and venous thrombosis was driven by cancer (113).

**Psychosocial factors and venous thromboembolism**

Hemingway and Marmot defines a psychosocial factor as *a measurement that potentially relates psychological phenomena to the social environment and to pathophysiological changes* (114). Some of these factors may be clinical depression and depressive symptoms, loneliness and social support, chronic stress, optimism and positive affect. Positive affect reflects an individual’s level of pleasurable engagement with the environment, and consists of terms like enthusiasm, joy, happiness, excitement and contentment (115).

Psychosocial factors have been related to health, and especially to cardiovascular disease. Positive affect and optimism have been related with beneficial effects on all-cause mortality (116) and cardiovascular mortality (117). Conversely, negative traits such as stress (118), depression, depressive symptoms, loneliness and lack of social support have been associated with higher all-cause mortality (119-121) and cardiovascular mortality (118, 122-124). Myocardial infarction has also been associated with stress, both at work and at home, financial stress and stressful life events (125). Depression and depressive symptoms have been predictive for incident coronary heart disease (CHD) (126, 127). Higher risk of CHD has been reported among chronically lonely women (128), and among female homemakers reporting loneliness during the day (129). An inverse association between CHD and optimism has been reported in cohort studies (130, 131).

There are many proposed mechanisms for the observed associations between psychosocial factors and health. Health behavioural factors may be important confounders. Cigarette smoking, dietary habits, physical activity, alcohol consumption and obesity may depend on psychosocial factors as depression or social support. Another explanation may be reverse causation. Subjects experiencing more positive traits may have a better health and less pre-existing disease. The observed associations may also be caused by biological pathways. Psychosocial factors have been associated with alterations of the autonomous nerve system, the hypothalamic-pituitary-adrenal axis, platelet function, the immune system and inflammation (120, 132-135).
Knowledge about the association between venous thromboembolism and psychosocial factors is limited. Only one observational study aimed to prospectively investigate the relation between psychosocial factors and venous thromboembolism. Rosengren and co-workers found that persistent stress increased the risk of pulmonary embolism among 7 046 middle-aged men (136) (table 7). Other psychosocial factors, such as depression and depressive symptoms, loneliness and social support, optimism and positive affect have not been investigated in association with VTE.

**Socioeconomic status and venous thromboembolism**

Socioeconomic status (SES) is the expression referring to the social position of an individual compared to other members of the same society (137). There are many indicators related to SES, however, the three most utilized concepts are education level, occupational status or income (138).

To our knowledge, there are four observational studies which have included socioeconomic status as one of the variables of interest in their investigation of the association between socioeconomic status and venous thromboembolism. Pettiti and co-workers did not find any association between education (treated as a dichotomous variable, less or more than high school level) and VTE in a nested case control with 38 cases and 8174 controls conducted in 1961-1976 among women aged 18-54 (139) (table 8). Opposite findings was found in another cohort study, The Iowa Women’s health study, where about 40,000 women were followed for a median of 13 years (113) (table 8). They found that education level of high school or higher was associated with decreased risk of VTE in analyses adjusted for age, smoking status, physical activity and BMI. Education and household income was investigated in the Danish Copenhagen City Heart study (102) (table 8). This is also a prospective cohort study including adult men and women. After a median follow-up of 19.5 years, they found an increased risk of VTE among participants with low household income compared to middle household income, and a decreased risk among those with an education of more than 11 years compared to less than 8 years of education in age- and calendar time-adjusted analyses. However, in multivariable analyses, only household income was a significant independent risk factor of venous thrombosis. A Swedish prospective study including middle-aged men only (136) found that occupational class was a risk factor of VTE (table 8). A low occupational class
Socioeconomic status has previously been associated to incident arterial cardiovascular disease (140), cardiovascular mortality (141-143) and overall mortality (144, 145) in several studies. However, explanations for these findings remain unsolved. One explanation is behavioral factors, such as smoking, diet patterns and physical exercise. It is also thought that those with higher education have more knowledge about health beneficial behavior (137). Another suggestion has been psychological factors; those in a lower social class experience more job strain, higher work demands and less individual control, financial stress, social isolation, depressive symptoms etc. than people in higher social classes. A material theory has also been discussed. People with high SES have better housing, can afford health insurances, and have resources to pay for health expenses, etc.. Type of neighborhood (e.g. exposure to air pollution, crime etc.) have also been suggested as an explanation. Furthermore, different treatment by the health services can also be a reason for the observed effects between SES and risk of CVD (115).

Discussion and conclusions
This paper has reviewed what is known about several cardiovascular lifestyle risk factors; physical activity, BMI, diet, alcohol consumption, coffee consumption, smoking, emotional states and socioeconomic status and their association to VTE. There are extensive knowledge about lifestyle factors and their association to CVD, but the knowledge about lifestyle factors and VTE is, as we have shown, scarce.

As we have seen, some of the lifestyle factors might be common risk factors for CVD and VTE. High BMI, heavy smoking, stress and low socioeconomic status seem to yield an increased risk also in VTE, and a majority of the studies find that moderate alcohol consumption is inversely associated to VTE. Other factors like physical activity have shown tendencies of opposite effects on the two diseases, considering that some of the large cohort studies find an increased risk of VTE associated with strenuous physical activity. Diet, a solid risk factor for CVD, has only been investigated by two studies who reached two opposite conclusions in regard to its relationship with VTE. Similarly, coffee and VTE have only been studied once. These are factors where it is far too early to predict anything about their
association to VTE. Furthermore, several of the existing studies are conducted on specific populations including only men or women, and/or narrow age groups. In addition, several studies are retrospective and only based on self-reported data. In order to reach a conclusion concerning all these lifestyle factors and VTE, more prospective studies on a general population are needed.

References


Table 1. Summary of studies on physical activity and venous thromboembolism

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Study design</th>
<th>Purpose</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsai et al (2002)</td>
<td>Cohort</td>
<td>Association between traditional cardiovascular risk factors and risk for VTE</td>
<td>19 293 men and women 45-64 years old</td>
<td>No relationship between arterial risk factors and risk of VTE</td>
</tr>
<tr>
<td>Glynn et al (2005)</td>
<td>Cohort</td>
<td>Compare risk factors for the competing risk of CVD, stroke and VTE</td>
<td>18 662 male physicians 40-84 years old</td>
<td>Exercise protects against CVD and stroke, but is positively associated with VTE</td>
</tr>
<tr>
<td>Sidney et al (2004)</td>
<td>Case-control</td>
<td>Relationship between oral contraceptives (OR) and risk of VTE</td>
<td>196/746 women 15-44 years old</td>
<td>The increased risk associated with use of OR was reduced among those who exercised</td>
</tr>
<tr>
<td>Van Stralen et al (2007)</td>
<td>Case-control</td>
<td>Relationship between sport activities and VTE</td>
<td>3 608/ 4 252 men and women 18-70 years old</td>
<td>Regular sport activities reduce the risk of VTE</td>
</tr>
<tr>
<td>Van Stralen et al (2008)</td>
<td>Cohort</td>
<td>Study weather exercise is associated with risk of VTE in elderly</td>
<td>5 534 men and women &gt;65 years old</td>
<td>Strenuous exercise was associated with higher risk of VTE</td>
</tr>
<tr>
<td>Lindqvist et al (2008)</td>
<td>Cohort</td>
<td>Explore the relationship between lifestyle factors and VTE in women</td>
<td>29 518 women 25-64 years old</td>
<td>Physically active women were at reduced risk of VTE</td>
</tr>
</tbody>
</table>
Table 2. Summary of studies on Body Mass Index (BMI) and venous thromboembolism.

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Study design</th>
<th>Purpose</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldhaber et al (1983)</td>
<td>Cohort</td>
<td>Assess potential risk factors for major PE</td>
<td>3 470 men and women, mean age 43.7 and 43.9 respectively</td>
<td>Increased adiposity in women is an important long-term risk factor for PE</td>
</tr>
<tr>
<td>Goldhaber et al (1997)</td>
<td>Cohort</td>
<td>Investigate risk factors for PE in women</td>
<td>112 822 women 30-55 years old</td>
<td>Obesity is associated with increased risk of PE in women</td>
</tr>
<tr>
<td>Heit et al (2000)</td>
<td>Nested case-control</td>
<td>Identify independent risk factors for VTE</td>
<td>625/625 men and women</td>
<td>BMI is not an independent risk factor for VTE</td>
</tr>
<tr>
<td>Tsai et al (2002)</td>
<td>Cohort</td>
<td>Association between traditional cardiovascular risk factors and risk for VTE</td>
<td>19 293 men and women 45-64 years old</td>
<td>BMI is a strong independent risk factor for VTE</td>
</tr>
<tr>
<td>Glynn et al (2005)</td>
<td>Cohort</td>
<td>Compare risk factors for the competing risk of CVD, stroke and VTE</td>
<td>18 662 male physicians 40-84 years old</td>
<td>Higher BMI was more strongly associated with risk of VTE than of either CVD or stroke</td>
</tr>
<tr>
<td>Barba et al (2008)</td>
<td>Register study</td>
<td>Influence of BMI on mortality in patients with acute VTE</td>
<td>10 114 men and women</td>
<td>Obese patients with acute VTE have less than half the mortality rate when compared with normal BMI patients</td>
</tr>
<tr>
<td>Borch et al (2010)</td>
<td>Cohort</td>
<td>Assess the impact of various obesity measures on identification of subjects at risk of VTE</td>
<td>6 708 men and women 25-84 years old</td>
<td>BMI is a risk factor for VTE, but waist circumference is better at identifying subjects at risk</td>
</tr>
<tr>
<td>Reference (Year)</td>
<td>Study design</td>
<td>Purpose</td>
<td>Study population</td>
<td>Main findings</td>
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</tr>
<tr>
<td>Steffen et al (2007)</td>
<td>Cohort</td>
<td>Explore the relation between diet and VTE</td>
<td>14,962 men and women 45-64 years old</td>
<td>A diet including more plant food and fish and less red and processed meat is associated with lower incidence of VTE.</td>
</tr>
<tr>
<td>Lutsey et al (2009)</td>
<td>Cohort</td>
<td>Explore the role of diet in the development of VTE</td>
<td>37,393 women 55-69 years old</td>
<td>No independent association between diet and VTE</td>
</tr>
</tbody>
</table>
Table 4. Alcohol consumption and venous thromboembolism

<table>
<thead>
<tr>
<th>Reference (Year)</th>
<th>Study design</th>
<th>Purpose</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pahor et al (1996)</td>
<td>Cohort</td>
<td>Assess whether low to moderate alcohol consumption decreases the risk of DVT and PE</td>
<td>7,959 men and women &gt;68 years old</td>
<td>Low to moderate alcohol consumption is associated with a decreased risk of VTE in older subjects</td>
</tr>
<tr>
<td>Samama et al (2000)</td>
<td>Case-control</td>
<td>Exploring risk factors for VTE in nonhospitalized subjects</td>
<td>636/636 men and women, mean age for cases and controls at baseline 59.1 and 58.1, respectively</td>
<td>No association between alcohol and VTE</td>
</tr>
<tr>
<td>Tsai et al (2002)</td>
<td>Cohort</td>
<td>Association between traditional cardiovascular risk factors and risk for VTE</td>
<td>19,293 men and women 45-64 years old</td>
<td>No relationship between arterial risk factors and risk of VTE</td>
</tr>
<tr>
<td>Glynn et al (2005)</td>
<td>Cohort</td>
<td>Compare risk factors for the competing risk of CVD, stroke and VTE</td>
<td>18,662 male physicians 40-84 years old</td>
<td>Daily alcohol consumption protects against CVD, but show no relation to VTE</td>
</tr>
<tr>
<td>Pomp et al (2007)</td>
<td>Case-control</td>
<td>Explore the relationship between alcohol consumption and VTE</td>
<td>4,423/5 235 men and women, mean age for cases and controls at baseline 48.5 46.8 respectively</td>
<td>Alcohol consumption is associated with reduced risk of VTE</td>
</tr>
<tr>
<td>Lindqvist et al (2008)</td>
<td>Cohort</td>
<td>Explore the relationship between lifestyle factors and VTE in women</td>
<td>29,518 women 25-64 years old</td>
<td>Moderate alcohol consumption is related to lower incidence of VTE in women</td>
</tr>
<tr>
<td>Lutsey et al (2009)</td>
<td>Cohort</td>
<td>Explore the role of diet in the development of VTE</td>
<td>37,393 women 55-69 years old</td>
<td>Greater intake of alcohol is associated with a lower risk of incident VTE in older women</td>
</tr>
</tbody>
</table>
Table 5. Coffee consumption and venous thromboembolism.

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Study design</th>
<th>Purpose</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lutsey et al (2009)</td>
<td>Cohort</td>
<td>Explore the role of diet and food groups in the development of VTE</td>
<td>37,393 women ≥65 yrs</td>
<td>Coffee consumption was associated with reduced risk of VTE, but the association diminished when adjusting for BMI and diabetes.</td>
</tr>
</tbody>
</table>
### Table 6. Summary of studies on smoking and venous thromboembolism

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Study design</th>
<th>Purpose</th>
<th>Study population</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glynn et al (2005)</td>
<td>Cohort</td>
<td>Compare the relative risks of CHD, stroke and VTE associated with established risk factors</td>
<td>18662 male physicians aged 40-84 yrs</td>
<td>Current (HR 0.92 (0.63-1.33) nor former (HR 0.92 (0.74-1.16) smoking were not risk factors for VTE.</td>
</tr>
<tr>
<td>Tsai et al (2002)</td>
<td>Cohort</td>
<td>Determine whether atherosclerotic risk factors also are associated with VTE</td>
<td>19293 men and women ≥45 yrs</td>
<td>Smoking status and pack-years of smoking were not associated with risk of VTE.</td>
</tr>
<tr>
<td>Ageno et al (2008)</td>
<td>Meta-analysis</td>
<td>Assess the association between cardiovascular risk factors and VTE risk</td>
<td>63552 (21 studies included (4 cohorts)</td>
<td>Smoking status was not associated with VTE risk (HR 1.15 (0.92-1.44), neither in case control or cohort studies</td>
</tr>
<tr>
<td>Quist-Paulsen et al (2009)</td>
<td>Nested case-control study</td>
<td>Investigate the relation between cardiovascular risk factors and VTE risk</td>
<td>515 cases and 1505 controls</td>
<td>Smoking status is not a risk factor of VTE: HR=0.9 (0.7-1.1)</td>
</tr>
<tr>
<td>Brækkan et al (2008)</td>
<td>Cohort</td>
<td>Determine the impact of cardiovascular risk factors on risk of VTE</td>
<td>21330 men and women aged 25-95 yrs</td>
<td>Smoking status is not a risk factor of VTE (HR 1.04 (0.82-1.33)</td>
</tr>
<tr>
<td>Severinsen et al (2009)</td>
<td>Cohort</td>
<td>Investigate the relation between smoking and VTE.</td>
<td>57053 men and women aged 50-64 yrs</td>
<td>Smoking status increase risk of VTE (♂-HR: 1.52 (1.15-2.00) ♂-HR: 1.32 (1.00-1.74). Smoking &gt;20 g tobacco/day for women and 30g/day for men increased the risk of VTE markedly.</td>
</tr>
<tr>
<td>Goldhaber et al (1997)</td>
<td>Cohort</td>
<td>Investigate risk factors of pulmonary embolism in women</td>
<td>112822 female nurses aged 30-55 yrs</td>
<td>Heavy cigarette smokers had increased risk of PE, 25-34 cig/day: HR=1.8 (1.2-2.9), ≥35 cig/day: HR=2.1 (1.2-3.6).</td>
</tr>
<tr>
<td>Hansson et al (1999)</td>
<td>Cohort</td>
<td>Study long-term risk factors for VTE</td>
<td>855 men aged 50 at baseline.</td>
<td>Heavy smoking (≥15 g tobacco/day) increased the risk of VTE.</td>
</tr>
<tr>
<td>Study (Year)</td>
<td>Study Design</td>
<td>Objective</td>
<td>Study Population</td>
<td>Findings</td>
</tr>
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<tr>
<td>Holstn et al (2010)</td>
<td>Cohort</td>
<td>Study associations between cardiovascular risk factors and VTE</td>
<td>18954 men and women ≥20 years</td>
<td>(HR=2.82 (1.30-6.13))</td>
</tr>
<tr>
<td>Lindqvist et al (2009)</td>
<td>Cohort</td>
<td>Assess the association between lifestyle factors and VTE risk</td>
<td>24098 women aged 25-64 years</td>
<td>Heavy smoking (≥100,000 cigarettes ever) increased the risk of VTE by 30% (HR=1.3 (1.0-1.7)).</td>
</tr>
<tr>
<td>Pomp et al (2008)</td>
<td>Case-control</td>
<td>Evaluate the association between smoking and VTE, with the joint effect of contraceptive pills and factor V Leiden mutation.</td>
<td>3989 cases and 4900 controls</td>
<td>Current (HR=1.43 (1.28-1.60)) and former (HR=1.23 (1.09-1.38)) smoking increased the risk of venous thrombosis, number of pack-years was associated to the risk of VTE, where youngest heavy smokers had the highest VTE risk.</td>
</tr>
<tr>
<td>Tosetto et al (2003)</td>
<td>Case-control</td>
<td>Identify risk factors for VTE in an active population</td>
<td>116 cases and 14939 controls (18-65 yrs)</td>
<td>Smoking increased the risk of VTE (OR: 1.7 (1.0-2.7))</td>
</tr>
<tr>
<td>Lutsey et al (2010)</td>
<td>Cohort</td>
<td>Explore the association between demographic, lifestyle and anthropometric factors and risk of VTE</td>
<td>40377 women&gt;65 yrs</td>
<td>Smoking status and number of pack-years were associated to risk of VTE, especially provoked VTE. The association was probably due to cancer-related VTE.</td>
</tr>
</tbody>
</table>
Table 7. Summary of studies on psychosocial factors and venous thromboembolism.

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>Study design</th>
<th>Study purpose</th>
<th>Study population</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Rosengren et al (2002)</td>
<td>Cohort</td>
<td>Determine whether VTE is related to stress and occupational status</td>
<td>6958 middle-aged men</td>
<td>Persistent stress increase risk of PE: HR=1.80 (1.21-2.67)</td>
</tr>
<tr>
<td>Reference (year)</td>
<td>Study design</td>
<td>Purpose</td>
<td>Study population</td>
<td>Main findings</td>
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<tr>
<td>Petitti et al (1978)</td>
<td>Nested case-control</td>
<td>Evaluate the association of OC use, smoking and other factors, and unprovoked VTE</td>
<td>38 cases and 8174 controls</td>
<td>Education level and risk of VTE are not related.</td>
</tr>
<tr>
<td>Rosengren et al (2002)</td>
<td>Cohort</td>
<td>Determine whether VTE is related to stress and occupational status</td>
<td>6958 middle-aged men</td>
<td>Occupational status is inversely associated to risk of PE. High vs. low occupational class: HR=0.57 (0.39-0.83)</td>
</tr>
<tr>
<td>Lutsey et al (2010)</td>
<td>Cohort</td>
<td>Explore the association between demographic, lifestyle and anthropometric factors and VTE risk</td>
<td>40377 women ≥65 yrs.</td>
<td>Education at high school level (HR=0.84 (0.75-0.94) or higher (HR=0.87 (0.77-0.97) decrease the risk of VTE compared to education less than high school.</td>
</tr>
<tr>
<td>Holst et al (2010)</td>
<td>Cohort</td>
<td>Explore the association between atherosclerotic risk factors and VTE risk</td>
<td>18954 adult men and women ≥20 yrs</td>
<td>Household income is inversely related to risk of VTE. Medium vs. low income: HR= 0.82 (0.70-0.95)</td>
</tr>
</tbody>
</table>