Lifestyle and venous thromboembolism
A review

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Contents

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 rosuvastatin, 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. Petitti 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

(unskilled or skilled manual workers) was associated with increased risk of VTE compared with higher occupational classes.

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

1. Buller HR, Sohne M, Middeldorp S. Treatment of venous Thromboembolism. Journal of Thrombosis and Haemostasis. 2005;3:1554-60.
2. Heit JA. Venous thromboembolism: disease burden, outcomes and risk factors. J Thromb Haemost. 2005 Aug;3(8):1611-7.
3. Silverstein MD, Heit JA, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med. 1998 Mar 23;158(6):585-93.
4. Beckman MG, Hooper WC, Critchley SE, Ortel TL. Venous thromboembolism: a public health concern. Am J Prev Med. 2010 Apr;38(4 Suppl):S495-501.
5. Anderson FA, Jr., Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. Arch Intern Med. 1991 May;151(5):933-8.
6. White RH. The epidemiology of venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I4-8.
7. Rosendaal FR. Thrombosis in the young: epidemiology and risk factors. A focus on venous thrombosis. Thromb Haemost. 1997 Jul;78(1):1-6.
8. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Family history of myocardial infarction is an independent risk factor for venous thromboembolism: the Tromso study. J Thromb Haemost. 2008 Nov;6(11):1851-7.
9. Heit JA, Mohr DN, Silverstein MD, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Predictors of recurrence after deep vein thrombosis and pulmonary embolism: a population-based cohort study. Arch Intern Med. 2000 Mar 27;160(6):761-8.
10. Mohr DN, Silverstein MD, Heit JA, Petterson TM, O'Fallon WM, Melton LJ. The venous stasis syndrome after deep venous thrombosis or pulmonary embolism: a population-based study. Mayo Clin Proc. 2000 Dec;75(12):1249-56.

11. Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet. 1999 Apr 3;353(9159):1167-73.
12. Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ, 3rd. Risk factors for deep vein thrombosis and pulmonary embolism: a population-based case-control study. Arch Intern Med. 2000 Mar 27;160(6):809-15.
13. Heit JA, O'Fallon WM, Petterson TM, Lohse CM, Silverstein MD, Mohr DN, et al. Relative impact of risk factors for deep vein thrombosis and pulmonary embolism: a population-based study. Arch Intern Med. 2002 Jun 10;162(11):1245-8.
14. Heit JA. The epidemiology of venous thromboembolism in the community: implications for prevention and management. J Thromb Thrombolysis. 2006 Feb;21(1):23-9.
15. White RH, Zhou H, Romano PS. Incidence of symptomatic venous thromboembolism after different elective or urgent surgical procedures. Thromb Haemost. 2003 Sep;90(3):446-55.
16. Goldhaber SZ. Risk factors for venous thromboembolism. J Am Coll Cardiol. 2010 Jun 29;56(1):1-7.
17. Heit JA. The epidemiology of venous thromboembolism in the community. Arterioscler Thromb Vasc Biol. 2008 Mar;28(3):370-2.
18. Blom JW, Doggen CJ, Osanto S, Rosendaal FR. Malignancies, prothrombotic mutations, and the risk of venous thrombosis. JAMA. 2005 Feb 9;293(6):715-22.
19. Noble S, Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. Br J Cancer. 2010 Apr 13;102 Suppl 1:S2-9.
20. Murchison JT, Wylie L, Stockton DL. Excess risk of cancer in patients with primary venous thromboembolism: a national, population-based cohort study. Br J Cancer. 2004 Jul 5;91(1):92-5.
21. WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception. Cardiovascular disease and steroid hormone contraception. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser. 1998;877:i-vii, 1-89.
22. Middeldorp S. Epidemiology of hormone-related venous thromboembolism. Thromb Res. 2009;123 Suppl 2:S65-9.
23. Bremme KA. Haemostatic changes in pregnancy. Best Pract Res Clin Haematol. 2003 Jun;16(2):153-68.
24. James AH, Tapson VF, Goldhaber SZ. Thrombosis during pregnancy and the postpartum period. Am J Obstet Gynecol. 2005 Jul;193(1):216-9.

25. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost. 2008 Apr;6(4):632-7.
26. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med. 2003 Apr 10;348(15):1435-41.
27. Sorensen HT, Horvath-Puho E, Pedersen L, Baron JA, Prandoni P. Venous thromboembolism and subsequent hospitalisation due to acute arterial cardiovascular events: a 20-year cohort study. Lancet. 2007 Nov 24;370(9601):1773-9.
28. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM, Jr., Kastelein JJ, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med. 2009 Apr 30;360(18):1851-61.
29. Lacut K, van der Maaten J, Le Gal G, Cornily G, Mottier D, Oger E. Antiplatelet drugs and risk of venous thromboembolism: results from the EDITH case-control study. Haematologica. 2008 Jul;93(7):1117-8.
30. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):454S-545S.
31. Ansell J, Hirsh J, Hylek E, Jacobson A, Crowther M, Palareti G. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest. 2008 Jun;133(6 Suppl):160S-98S.
32. Hjelmstedt A. The pressure in the veins of the dorsum of the foot in quiet standing and during exercise in limbs without signs of venous disorder. Acta Chir Scand. 1968;134(3):235-44.
33. Kugler C, Strunk M, Rudofsky G. Venous pressure dynamics of the healthy human leg. Role of muscle activity, joint mobility and anthropometric factors. J Vasc Res. 2001 Jan-Feb;38(1):20-9.
34. Stick C, Jaeger H, Witzleb E. Measurements of volume changes and venous pressure in the human lower leg during walking and running. J Appl Physiol. 1992 Jun;72(6):2063-8.
35. van Stralen KJ, Le Cessie S, Rosendaal FR, Doggen CJ. Regular sports activities decrease the risk of venous thrombosis. J Thromb Haemost. 2007 Nov;5(11):2186-92.

36. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP, Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception. 2004 Jul;70(1):3-10.
37. Lindqvist PG, Epstein E, Olsson H. The relationship between lifestyle factors and venous thromboembolism among women: a report from the MISS study. Br J Haematol. 2009 Jan;144(2):234-40.
38. Glynn RJ, Rosner B. Comparison of risk factors for the competing risks of coronary heart disease, stroke, and venous thromboembolism. Am J Epidemiol. 2005 Nov 15;162(10):975-82.
39. van Stralen KJ, Doggen CJ, Lumley T, Cushman M, Folsom AR, Psaty BM, et al. The relationship between exercise and risk of venous thrombosis in elderly people. J Am Geriatr Soc. 2008 Mar;56(3):517-22.
40. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Polak JF, Folsom AR. Cardiovascular risk factors and venous thromboembolism incidence: the longitudinal investigation of thromboembolism etiology. Arch Intern Med. 2002 May 27;162(10):1182-9.
41. Seidell JC, Verschuren WM, van Leer EM, Kromhout D. Overweight, underweight, and mortality. A prospective study of 48,287 men and women. Arch Intern Med. 1996 May 13;156(9):958-63.
42. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999 Oct 7;341(15):1097-105.
43. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. N Engl J Med. 2006 Aug 24;355(8):763-78.
44. Juhan-Vague I, Alessi MC, Mavri A, Morange PE. Plasminogen activator inhibitor-1, inflammation, obesity, insulin resistance and vascular risk. J Thromb Haemost. 2003 Jul;1(7):1575-9.
45. Folsom AR, Qamhieh HT, Flack JM, Hilner JE, Liu K, Howard BV, et al. Plasma fibrinogen: levels and correlates in young adults. The Coronary Artery Risk Development in Young Adults (CARDIA) Study. Am J Epidemiol. 1993 Dec 15;138(12):1023-36.
46. Folsom AR. Fibrinolytic factors and atherothrombotic events: epidemiological evidence. Ann Med. 2000 Dec;32 Suppl 1:85-91.

47. Borch KH, Hansen-Krone I, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, et al. Physical activity and risk of venous thromboembolism. The Tromso study. Haematologica. 2010 Dec;95(12):2088-94.
48. Darvall KA, Sam RC, Silverman SH, Bradbury AW, Adam DJ. Obesity and thrombosis. Eur J Vasc Endovasc Surg. [Review]. 2007 Feb;33(2):223-33.
49. Nishimura S, Manabe I, Nagai R. Adipose tissue inflammation in obesity and metabolic syndrome. Discov Med. 2009 Aug;8(41):55-60.
50. Noblett KL, Jensen JK, Ostergard DR. The relationship of body mass index to intra-abdominal pressure as measured by multichannel cystometry. International urogynecology journal and pelvic floor dysfunction. 1997;8(6):323-6.
51. Willenberg T, Schumacher A, Amann-Vesti B, Jacomella V, Thalhammer C, Diehm N, et al. Impact of obesity on venous hemodynamics of the lower limbs. J Vasc Surg. [Research Support, Non-U.S. Gov't]. 2010 Sep;52(3):664-8.
52. Goldhaber SZ, Savage DD, Garrison RJ, Castelli WP, Kannel WB, McNamara PM, et al. Risk factors for pulmonary embolism. The Framingham Study. Am J Med. 1983 Jun;74(6):1023-8.
53. Goldhaber SZ, Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, et al. A prospective study of risk factors for pulmonary embolism in women. JAMA. 1997 Feb 26;277(8):642-5.
54. Borch KH, Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, et al. Anthropometric measures of obesity and risk of venous thromboembolism: the Tromso study. Arterioscler Thromb Vasc Biol. 2010 Jan;30(1):121-7.
55. Anderson FA, Jr., Spencer FA. Risk factors for venous thromboembolism. Circulation. 2003 Jun 17;107(23 Suppl 1):I9-16.
56. Barba R, Zapatero A, Losa JE, Valdes V, Todoli JA, Di Micco P, et al. Body mass index and mortality in patients with acute venous thromboembolism: findings from the RIETE registry. J Thromb Haemost. 2008 Apr;6(4):595-600.
57. Jensen RA. Postoperative thrombosis-emboli; their frequency in the period 1940-1948 at the III department of Ulveval Sykehus and the surgical department of Akers Sykehus. Acta Chir Scand. 1952 Jul 14;103(4):263-75.
58. Strøm A. Examination into the diet of Norwegian families during the war years 1942-45. Acta Med Scand Suppl. 1948;214:1-47.
59. Randall E, Marshall JR, Brasure J, Graham S. Dietary patterns and colon cancer in western New York. Nutr Cancer. 1992;18(3):265-76.

60. Trichopoulou A, Costacou T, Bamia C, Trichopoulos D. Adherence to a Mediterranean diet and survival in a Greek population. N Engl J Med. 2003 Jun 26;348(26):2599-608.
61. de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL, Monjaud I, et al. Mediterranean alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. Lancet. 1994 Jun 11;343(8911):1454-9.
62. Mezzano D, Leighton F, Martinez C, Marshall G, Cuevas A, Castillo O, et al. Complementary effects of Mediterranean diet and moderate red wine intake on haemostatic cardiovascular risk factors. Eur J Clin Nutr. 2001 Jun;55(6):444-51.
63. Mezzano D, Munoz X, Martinez C, Cuevas A, Panes O, Aranda E, et al. Vegetarians and cardiovascular risk factors: hemostasis, inflammatory markers and plasma homocysteine. Thromb Haemost. 1999 Jun;81(6):913-7.
64. Weststrate JA, van het Hof KH, van den Berg H, Velthuis-te-Wierik EJ, de Graaf C, Zimmermanns NJ, et al. A comparison of the effect of free access to reduced fat products or their full fat equivalents on food intake, body weight, blood lipids and fat-soluble antioxidants levels and haemostasis variables. Eur J Clin Nutr. 1998 Jun;52(6):389-95.
65. Braekkan SK, Mathiesen EB, Njolstad I, Wilsgaard T, Stormer J, Hansen JB. Mean platelet volume is a risk factor for venous thromboembolism: the Tromso Study, Tromso, Norway. J Thromb Haemost. 2010 Jan;8(1):157-62.
66. Folsom AR, Cushman M, Heckbert SR, Rosamond WD, Aleksic N. Prospective study of fibrinolytic markers and venous thromboembolism. J Clin Epidemiol. 2003 Jun;56(6):598-603.
67. Koster T, Rosendaal FR, Briet E, van der Meer FJ, Colly LP, Trienekens PH, et al. Protein C deficiency in a controlled series of unselected outpatients: an infrequent but clear risk factor for venous thrombosis (Leiden Thrombophilia Study). Blood. 1995 May 15;85(10):2756-61.
68. Koster T, Rosendaal FR, Reitsma PH, van der Velden PA, Briet E, Vandenbroucke JP. Factor VII and fibrinogen levels as risk factors for venous thrombosis. A case-control study of plasma levels and DNA polymorphisms--the Leiden Thrombophilia Study (LETS). Thromb Haemost. 1994 Jun;71(6):719-22.
69. Tsai AW, Cushman M, Rosamond WD, Heckbert SR, Tracy RP, Aleksic N, et al. Coagulation factors, inflammation markers, and venous thromboembolism: the longitudinal investigation of thromboembolism etiology (LITE). Am J Med. 2002 Dec 1;113(8):636-42.

70. Steffen LM, Folsom AR, Cushman M, Jacobs DR, Jr., Rosamond WD. Greater fish, fruit, and vegetable intakes are related to lower incidence of venous thromboembolism: the Longitudinal Investigation of Thromboembolism Etiology. Circulation. 2007 Jan 16;115(2):188-95.
71. Lutsey PL, Steffen LM, Virnig BA, Folsom AR. Diet and incident venous thromboembolism: the Iowa Women's Health Study. Am Heart J. 2009 Jun;157(6):1081-7.
72. Hvidtfeldt UA, Tolstrup JS, Jakobsen MU, Heitmann BL, Gronbaek M, O'Reilly E, et al. Alcohol intake and risk of coronary heart disease in younger, middle-aged, and older adults. Circulation. 2010 Apr 13;121(14):1589-97.
73. Mukamal KJ, Chen CM, Rao SR, Breslow RA. Alcohol consumption and cardiovascular mortality among U.S. adults, 1987 to 2002. J Am Coll Cardiol. 2010 Mar 30;55(13):1328-35.
74. Yarnell JW, Sweetnam PM, Rumley A, Lowe GD. Lifestyle and hemostatic risk factors for ischemic heart disease : the Caerphilly Study. Arterioscler Thromb Vasc Biol. 2000 Jan;20(1):271-9.
75. Dimmitt SB, Rakic V, Puddey IB, Baker R, Oostryck R, Adams MJ, et al. The effects of alcohol on coagulation and fibrinolytic factors: a controlled trial. Blood Coagul Fibrinolysis. 1998 Jan;9(1):39-45.
76. Mukamal KJ, Jadhav PP, D'Agostino RB, Massaro JM, Mittleman MA, Lipinska I, et al. Alcohol consumption and hemostatic factors: analysis of the Framingham Offspring cohort. Circulation. 2001 Sep 18;104(12):1367-73.
77. Pace-Asciak CR, Hahn S, Diamandis EP, Soleas G, Goldberg DM. The red wine phenolics trans-resveratrol and quercetin block human platelet aggregation and eicosanoid synthesis: implications for protection against coronary heart disease. Clin Chim Acta. 1995 Mar 31;235(2):207-19.
78. Pahor M, Guralnik JM, Havlik RJ, Carbonin P, Salive ME, Ferrucci L, et al. Alcohol consumption and risk of deep venous thrombosis and pulmonary embolism in older persons. J Am Geriatr Soc. 1996 Sep;44(9):1030-7.
79. Pomp ER, Rosendaal FR, Doggen CJ. Alcohol consumption is associated with a decreased risk of venous thrombosis. Thromb Haemost. 2008 Jan;99(1):59-63.
80. Samama MM. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med. 2000 Dec 11-25;160(22):3415-20.

81. Higdon JV, Frei B. Coffee and health: a review of recent human research. Crit Rev Food Sci Nutr. 2006;46(2):101-23.
82. Thelle DS, Arnesen E, Forde OH. The Tromso heart study. Does coffee raise serum cholesterol? N Engl J Med. 1983 Jun 16;308(24):1454-7.
83. Kawachi I, Colditz GA, Stone CB. Does coffee drinking increase the risk of coronary heart disease? Results from a meta-analysis. Br Heart J. 1994 Sep;72(3):269-75.
84. Hammar N, Andersson T, Alfredsson L, Reuterwall C, Nilsson T, Hallqvist J, et al. Association of boiled and filtered coffee with incidence of first nonfatal myocardial infarction: the SHEEP and the VHEEP study. J Intern Med. 2003 Jun;253(6):653-9.
85. Happonen P, Voutilainen S, Salonen JT. Coffee drinking is dose-dependently related to the risk of acute coronary events in middle-aged men. J Nutr. 2004 Sep;134(9):2381-6.
86. Sofi F, Conti AA, Gori AM, Eliana Luisi ML, Casini A, Abbate R, et al. Coffee consumption and risk of coronary heart disease: a meta-analysis. Nutr Metab Cardiovasc Dis. 2007 Mar;17(3):209-23.
87. Myers MG, Basinski A. Coffee and coronary heart disease. Arch Intern Med. 1992 Sep;152(9):1767-72.
88. Lopez-Garcia E, van Dam RM, Willett WC, Rimm EB, Manson JE, Stampfer MJ, et al. Coffee consumption and coronary heart disease in men and women: a prospective cohort study. Circulation. 2006 May 2;113(17):2045-53.
89. Azevedo A, Barros H. Coffee and myocardial infarction: heterogeneity of an association in Portuguese men. Eur J Cardiovasc Prev Rehabil. 2006 Apr;13(2):268-73.
90. Panagiotakos DB, Pitsavos C, Chrysohoou C, Kokkinos P, Toutouzas P, Stefanadis C. The J-shaped effect of coffee consumption on the risk of developing acute coronary syndromes: the CARDIO2000 case-control study. J Nutr. 2003 Oct;133(10):3228-32.
91. Woodward M, Tunstall-Pedoe H. Coffee and tea consumption in the Scottish Heart Health Study follow up: conflicting relations with coronary risk factors, coronary disease, and all cause mortality. J Epidemiol Community Health. 1999 Aug;53(8):481-7.
92. Wu JN, Ho SC, Zhou C, Ling WH, Chen WQ, Wang CL, et al. Coffee consumption and risk of coronary heart diseases: a meta-analysis of 21 prospective cohort studies. Int J Cardiol. 2009 Nov 12;137(3):216-25.
93. Andersen LF, Jacobs DR, Jr., Carlsen MH, Blomhoff R. Consumption of coffee is associated with reduced risk of death attributed to inflammatory and cardiovascular diseases in the Iowa Women's Health Study. Am J Clin Nutr. 2006 May;83(5):1039-46.

94. Kleemola P, Jousilahti P, Pietinen P, Vartiainen E, Tuomilehto J. Coffee consumption and the risk of coronary heart disease and death. Arch Intern Med. 2000 Dec 11-25;160(22):3393-400.
95. Lopez-Garcia E, van Dam RM, Li TY, Rodriguez-Artalejo F, Hu FB. The relationship of coffee consumption with mortality. Ann Intern Med. 2008 Jun 17;148(12):904-14.
96. van Rooij J, van der Stegen GH, Schoemaker RC, Kroon C, Burggraaf J, Hollaar L, et al. A placebo-controlled parallel study of the effect of two types of coffee oil on serum lipids and transaminases: identification of chemical substances involved in the cholesterol-raising effect of coffee. Am J Clin Nutr. 1995 Jun;61(6):1277-83.
97. Nardini M, Natella F, Scaccini C. Role of dietary polyphenols in platelet aggregation. A review of the supplementation studies. Platelets. 2007 May;18(3):224-43.
98. Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation. 2008 Jan 1;117(1):93-102.
99. Quist-Paulsen P, Naess IA, Cannegieter SC, Romundstad PR, Christiansen SC, Rosendaal FR, et al. Arterial cardiovascular risk factors and venous thrombosis: results from a population-based, prospective study (the HUNT 2). Haematologica. 2010 Jan;95(1):119-25.
100. Severinsen MT, Kristensen SR, Johnsen SP, Dethlefsen C, Tjonneland A, Overvad K. Smoking and venous thromboembolism: a Danish follow-up study. J Thromb Haemost. 2009 Aug;7(8):1297-303.
101. Hansson PO, Eriksson H, Welin L, Svardsudd K, Wilhelmsen L. Smoking and abdominal obesity: risk factors for venous thromboembolism among middle-aged men: "the study of men born in 1913". Arch Intern Med. 1999 Sep 13;159(16):1886-90.
102. Holst AG, Jensen G, Prescott E. Risk factors for venous thromboembolism: results from the Copenhagen City Heart Study. Circulation. 2010 May 4;121(17):1896-903.
103. Pomp ER, Rosendaal FR, Doggen CJ. Smoking increases the risk of venous thrombosis and acts synergistically with oral contraceptive use. Am J Hematol. 2008 Feb;83(2):97-102.
104. Tosetto A, Frezzato M, Rodeghiero F. Prevalence and risk factors of non-fatal venous thromboembolism in the active population of the VITA Project. J Thromb Haemost. 2003 Aug;1(8):1724-9.

105. Belch JJ, McArdle BM, Burns P, Lowe GD, Forbes CD. The effects of acute smoking on platelet behaviour, fibrinolysis and haemorheology in habitual smokers. Thromb Haemost. 1984 Feb 28;51(1):6-8.
106. Miller GJ, Bauer KA, Cooper JA, Rosenberg RD. Activation of the coagulant pathway in cigarette smokers. Thromb Haemost. 1998 Mar;79(3):549-53.
107. Kannel WB, D'Agostino RB, Belanger AJ. Fibrinogen, cigarette smoking, and risk of cardiovascular disease: insights from the Framingham Study. Am Heart J. 1987 Apr;113(4):1006-10.
108. Simpson AJ, Gray RS, Moore NR, Booth NA. The effects of chronic smoking on the fibrinolytic potential of plasma and platelets. Br J Haematol. 1997 Apr;97(1):208-13.
109. Allen RA, Kluft C, Brommer EJ. Effect of chronic smoking on fibrinolysis. Arteriosclerosis. 1985 Sep-Oct;5(5):443-50.
110. Ijzerman RG, Serne EH, van Weissenbruch MM, de Jongh RT, Stehouwer CD. Cigarette smoking is associated with an acute impairment of microvascular function in humans. Clin Sci (Lond). 2003 Mar;104(3):247-52.
111. Celermajer DS, Adams MR, Clarkson P, Robinson J, McCredie R, Donald A, et al. Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. N Engl J Med. 1996 Jan 18;334(3):150-4.
112. Pittilo RM, Mackie IJ, Rowles PM, Machin SJ, Woolf N. Effects of cigarette smoking on the ultrastructure of rat thoracic aorta and its ability to produce prostacyclin. Thromb Haemost. 1982 Oct 29;48(2):173-6.
113. Lutsey PL, Virnig BA, Durham SB, Steffen LM, Hirsch AT, Jacobs DR, Jr., et al. Correlates and consequences of venous thromboembolism: The Iowa Women's Health Study. Am J Public Health. 2010 Aug;100(8):1506-13.
114. Hemingway H, Marmot M. Evidence based cardiology: psychosocial factors in the aetiology and prognosis of coronary heart disease. Systematic review of prospective cohort studies. BMJ. 1999 May 29;318(7196):1460-7.
115. Clark LA, Watson D, Leeka J. Diurnal variation in the positive affects. Sep 1989. Motivation and Emotion. [Journal; Peer Reviewed Journal]. 1989;.13(3):pp.
116. Chida Y, Steptoe A. Positive psychological well-being and mortality: a quantitative review of prospective observational studies. Psychosom Med. 2008 Sep;70(7):741-56.
117. Giltay EJ, Geleijnse JM, Zitman FG, Hoekstra T, Schouten EG. Dispositional optimism and all-cause and cardiovascular mortality in a prospective cohort of elderly dutch men and women. Arch Gen Psychiatry. 2004 Nov;61(11):1126-35.

118. Nielsen NR, Kristensen TS, Schnohr P, Gronbaek M. Perceived stress and cause-specific mortality among men and women: results from a prospective cohort study. Am J Epidemiol. 2008 Sep 1;168(5):481-91; discussion 92-6.
119. Cuijpers P, Smit F. Excess mortality in depression: a meta-analysis of community studies. J Affect Disord. 2002 Dec;72(3):227-36.
120. Hawkley LC, Cacioppo JT. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. Ann Behav Med. 2010 Oct;40(2):218-27.
121. House JS, Landis KR, Umberson D. Social relationships and health. Science. 1988 Jul 29;241(4865):540-5.
122. Win S, Parakh K, Eze-Nliam CM, Gottdiener JS, Kop WJ, Ziegelstein RC. Depressive symptoms, physical inactivity and risk of cardiovascular mortality in older adults: the Cardiovascular Health Study. Heart. 2011 Mar;97(6):500-5.
123. Everson SA, Roberts RE, Goldberg DE, Kaplan GA. Depressive symptoms and increased risk of stroke mortality over a 29-year period. Arch Intern Med. 1998 May 25;158(10):1133-8.
124. Olsen RB, Olsen J, Gunner-Svensson F, Waldstrom B. Social networks and longevity. A 14 year follow-up study among elderly in Denmark. Soc Sci Med. 1991;33(10):1189-95.
125. Rosengren A, Hawken S, Ounpuu S, Sliwa K, Zubaid M, Almahmeed WA, et al. Association of psychosocial risk factors with risk of acute myocardial infarction in 11119 cases and 13648 controls from 52 countries (the INTERHEART study): case-control study. Lancet. 2004 Sep 11-17;364(9438):953-62.
126. Rugulies R. Depression as a predictor for coronary heart disease. a review and meta-analysis. Am J Prev Med. 2002 Jul;23(1):51-61.
127. Wulsin LR, Singal BM. Do depressive symptoms increase the risk for the onset of coronary disease? A systematic quantitative review. Psychosom Med. 2003 Mar-Apr;65(2):201-10.
128. Thurston RC, Kubzansky LD. Women, loneliness, and incident coronary heart disease. Psychosom Med. 2009 Oct;71(8):836-42.
129. Eaker ED, Pinsky J, Castelli WP. Myocardial infarction and coronary death among women: psychosocial predictors from a 20-year follow-up of women in the Framingham Study. Am J Epidemiol. 1992 Apr 15;135(8):854-64.
130. Kubzansky LD, Sparrow D, Vokonas P, Kawachi I. Is the glass half empty or half full? A prospective study of optimism and coronary heart disease in the normative aging study. Psychosom Med. 2001 Nov-Dec;63(6):910-6.

131. Davidson KW, Mostofsky E, Whang W. Don't worry, be happy: positive affect and reduced 10-year incident coronary heart disease: the Canadian Nova Scotia Health Survey. Eur Heart J. 2010 May;31(9):1065-70.
132. Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Arch Gen Psychiatry. 1998 Jul;55(7):580-92.
133. Rozanski A, Blumenthal JA, Davidson KW, Saab PG, Kubzansky L. The epidemiology, pathophysiology, and management of psychosocial risk factors in cardiac practice: the emerging field of behavioral cardiology. J Am Coll Cardiol. 2005 Mar 1;45(5):637-51.
134. Steptoe A, O'Donnell K, Badrick E, Kumari M, Marmot M. Neuroendocrine and inflammatory factors associated with positive affect in healthy men and women: the Whitehall II study. Am J Epidemiol. 2008 Jan 1;167(1):96-102.
135. Salovey P, Rothman AJ, Detweiler JB, Steward WT. Emotional states and physical health. Am Psychol. 2000 Jan;55(1):110-21.
136. Rosengren A, Freden M, Hansson PO, Wilhelmsen L, Wedel H, Eriksson H. Psychosocial factors and venous thromboembolism: a long-term follow-up study of Swedish men. J Thromb Haemost. 2008 Apr;6(4):558-64.
137. Clark AM, DesMeules M, Luo W, Duncan AS, Wielgosz A. Socioeconomic status and cardiovascular disease: risks and implications for care. Nat Rev Cardiol. 2009 Nov;6(11):712-22.
138. Vlismas K, Stavrinos V, Panagiotakos DB. Socio-economic status, dietary habits and health-related outcomes in various parts of the world: a review. Cent Eur J Public Health. 2009 Jun;17(2):55-63.
139. Petitti DB, Wingerd J, Pellegrin F, Ramcharan S. Oral contraceptives, smoking, and other factors in relation to risk of venous thromboembolic disease. Am J Epidemiol. 1978 Dec;108(6):480-5.
140. Albert MA, Glynn RJ, Buring J, Ridker PM. Impact of traditional and novel risk factors on the relationship between socioeconomic status and incident cardiovascular events. Circulation. 2006 Dec 12;114(24):2619-26.
141. Marmot MG, Shipley MJ, Rose G. Inequalities in death--specific explanations of a general pattern? Lancet. 1984 May 5;1(8384):1003-6.
142. Ernstsen L, Bjerkeset O, Krokstad S. Educational inequalities in ischaemic heart disease mortality in 44,000 Norwegian women and men: the influence of psychosocial and behavioural factors. The HUNT Study. Scand J Public Health. 2010 Nov;38(7):678-85.

143. Avendano M, Kunst AE, Huisman M, Lenthe FV, Bopp M, Regidor E, et al. Socioeconomic status and ischaemic heart disease mortality in 10 western European populations during the 1990s. Heart. 2006 Apr;92(4):461-7.
144. Kaplan GA, Keil JE. Socioeconomic factors and cardiovascular disease: a review of the literature. Circulation. 1993 Oct;88(4 Pt 1):1973-98.
145. Pappas G, Queen S, Hadden W, Fisher G. The increasing disparity in mortality between socioeconomic groups in the United States, 1960 and 1986. N Engl J Med. 1993 Jul 8;329(2):103-9.

Tables

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

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

Table 2. Summary of studies on Body Mass Index (BMI) and venous thromboembolism.

Reference (Year)	Study design	Purpose	Study population	Main findings
Goldhaber et al (1983)	Cohort	Assess potential risk factors for major PE	3 470 men and women, mean age 43.7 and 43.9 respectively	Increased adiposity in women is an important long-term risk factor for PE
Goldhaber et al (1997)	Cohort	Investigate risk factors for PE in women	112 822 women 30-55 years old	Obesity is associated with increased risk of PE in women
Heit et al (2000)	Nested case-control	Identify independent risk factors for VTE	625/625 men and women	BMI is not an independent risk factor for VTE
Tsai et al (2002)	Cohort	Association between traditional cardiovascular risk factors and risk for VTE	19 293 men and women 45-64 years old	BMI is a strong independent risk factor for VTE
Glynn et al (2005)	Cohort	Compare risk factors for the competing risk of CVD, stroke and VTE	18 662 male physicians 40-84 years old	Higher BMI was more strongly associated with risk of VTE than of either CVD or stroke
Barba et al (2008)	Register study	Influence of BMI on mortality in patients with acute VTE	10 114 men and women	Obese patients with acute VTE have less than half the mortality rate when compared with normal BMI patents
Borch et al (2010)	Cohort	Assess the impact of various obesity measures on identification of subjects at risk of VTE	6 708 men and women 25-84 years old	BMI is a risk factor for VTE, but waist circumference is better at identifying subjects at risk

Table 3. Summary of studies on diet and venous thromboembolism

Reference (Year)	Study design	Purpose	Study population	Main findings
Steffen et al (2007)	Cohort	Explore the relation between diet and VTE	14 962 men and women 45-64 years old	A diet including more plant food and fish and less red and processed meat is associated with lower incidence of VTE.
Lutsey et al (2009)	Cohort	Explore the role of diet in the development of VTE	37 393 women 55-69 years old	No independent association between diet and VTE

Table 4. Alcohol consumption and venous thromboembolism

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

Table 5. Coffee consumption and venous thromboembolism.

Reference (year)	Study design	Purpose	Study population	Main findings
Lutsey et al (2009)	Cohort	Explore the role of diet and food groups in the development of VTE	37 393 women ≥65 yrs	Coffee consumption was associated with reduced risk of VTE, but the association diminished when adjusting for BMI and diabetes.

Table 6. Summary of studies on smoking and venous thromboembolism

Reference (year)	Study design	Purpose	Study population	Main findings
Glynn et al (2005)	Cohort	Compare the relative risks of CHD, stroke and VTE associated with established risk factors	18662 male physicians aged 40-84 yrs	Current (HR 0.92 (0.63-1.33) nor former (HR 0.92 (0.74-1.16) smoking were not risk factors for VTE.
Tsai et al (2002)	Cohort	Determine whether atherosclerotic risk factors also are associated with VTE	19293 men and women ≥45 yrs	Smoking status and pack-years of smoking were not associated with risk of VTE.
Ageno et al (2008)	Meta-analysis	Assess the association between cardiovascular risk factors and VTE risk	63552 (21 studies included (4 cohorts)	Smoking status was not associated with VTE risk (HR 1.15 (0.92-1.44), neither in case control or cohort studies
Quist-Paulsen et al (2009)	Nested case-control study	Investigate the relation between cardiovascular risk factors and VTE risk	515 cases and 1505 controls	Smoking status is not a risk factor of VTE: HR=0.9 (0.7-1.1)
Brækkan et al (2008)	Cohort	Determine the impact of cardiovascular risk factors on risk of VTE	21330 men and women aged 25-95 yrs	Smoking status is not a risk factor of VTE (HR 1.04 (0.82-1.33)
Severinsen et al (2009)	Cohort	Investigate the relation between smoking and VTE.	57053 men and women aged 50-64 yrs	Smoking status increase risk of VTE (♀-HR: 1.52 (1.15-2.00) ♂-HR: 1.32 (1.00-1.74). Smoking >20 g tobacco/day for women and 30g/day for men increased the risk of VTE markedly.
Goldhaber et al (1997)	Cohort	Investigate risk factors of pulmonary embolism in women	112822 female nurses aged 30-55 yrs.	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).
Hansson et al (1999)	Cohort	Study long-term risk factors for VTE	855 men aged 50 at baseline.	Heavy smoking (≥15 g tobacco/day) increased the risk of VTE

				(HR=2.82 (1.30-6.13)
Holstn et al (2010)	Cohort	Study associations between cardiovascular risk factors and VTE	18954 men and women ≥20 years	≥25g tobacco/day increase risk of VTE (HR1.52 (1.15-2.01)
Lindqvist et al (2009)	Cohort	Assess the association between lifestyle factors and VTE risk	24098 women aged 25-64 years	Heavy smoking (≥100.000 cigarettes ever) increased the risk of VTE by 30% (HR=1.3 (1.0-1.7)).
Pomp et al (2008)	Case-control	Evaluate the association between smoking and VTE, with the joint effect of contraceptive pills and factor V Leiden mutation.	3989 cases and 4900 controls	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.
Tosetto et al (2003)	Case-control	Identify risk factors for VTE in a active population	116 cases and 14939 controls (18-65 yrs)	Smoking increase the risk of VTE (OR: 1.7 (1.0-2.7)
Lutsey et al (2010)	Cohort	Explore the association between demographic, lifestyle and anthropometric factors and risk of VTE	40377 women>65 yrs	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.

Table 7. Summary of studies on psychosocial factors and venous thromboembolism.

Reference (year)	Study design	Study purpose	Study population	Main findings
Rosengren et al (2002)	Cohort	Determine whether VTE is related to stress and occupational status	6958 middle-aged men	Persistent stress increase risk of PE: HR=1.80 (1.21-2.67)

Table 8. Summary of studies on socioeconomic status and venous thromboembolism.

Reference (year)	Study design	Purpose	Study population	Main findings
Petitti et al (1978)	Nested case-control	Evaluate the association of OC use, smoking and other factors, and unprovoked VTE	38 cases and 8174 controls	Education level and risk of VTE are not related.
Rosengren et al (2002)	Cohort	Determine whether VTE is related to stress and occupational status	6958 middle-aged men	Occupational status is inversely associated to risk of PE. High vs. low occupational class: HR=0.57 (0.39-0.83)
Lutsey et al (2010)	Cohort	Explore the association between demographic, lifestyle and anthropometric factors and VTE risk	40377 women ≥65 yrs.	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.
Holst et al (2010)	Cohort	Explore the association between atherosclerotic risk factors and VTE risk	18954 adult men and women ≥20 yrs	Household income is inversely related to risk of VTE. Medium vs. low income: HR= 0.82 (0.70-0.95)