Lower limb venous and arterial peripheral diseases and work conditions: Systematic review

Samantha Huo Yung Kai, Jean Ferrières, Camille Carles, Marion Turpin, François-Xavier Lapébie, Frédéric Dutheil, Alessandra Bura-Rivière, Yolande Esquirol

Lower limb venous and arterial peripheral diseases and work conditions. A systematic review.

Samantha Huo Yung Kai[1*], Jean Ferrières[2], Camille Carles[3], Marion Turpin[4], François-Xavier Lapébie[5], Frederic Dutheil[6], Alessandra Bura-Riviere[7], Yolande Esquirol[8]

Corresponding author: Samantha HUO YUNG KAI, Faculté de médecine, Université Paul Sabatier III, 37 allées Jules Guesde 31000 Toulouse, France; samantha.huo-yung-kai@univ-tlse3.fr; +33561145676

[1]**Samantha Huo Yung Kai***: UMR 1027, INSERM, Université Paul Sabatier Toulouse III, 31000 Toulouse, France ; M.D., PhD student

[2]**Jean Ferrières**: UMR 1027, INSERM, Université Paul Sabatier Toulouse III, 31000 Toulouse, France. Department of Cardiology, CHU de Toulouse 31062 Toulouse, France; Professor and Research Director (M.D., PhD.)

[3]**Camille Carles**: University Bordeaux, INSERM UMR 1219, Equipe EPICENE, CHU de Bordeaux, Occupational Health Department, F33000, Bordeaux. Associated Professor (M.D, PhD.)

[4]**Marion Turpin**: Occupational Health Department, CHU-Toulouse, 31000 France, medical student.

[5]**François-Xavier Lapébie:** Service de Médecine Vasculaire, Centre Hospitalo-universitaire (CHU) ad UMR1027, Toulouse, France ; PhD student

[6] **Frederic Dutheil**: Université Clermont Auvergne, CNRS, LaPSCo, « Physiological and psychosocial stress », University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Occupational and Preventive Medicine, WittyFit, F-63000 Clermont-Ferrand, France ; Australian Catholic University, Faculty of Health, Melbourne, Victoria 3065, Australia

[7]**Alessandra Bura-Rivière :** Service de Médecine Vasculaire, Centre Hospitalo-universitaire (CHU) and Université Paul Sabatier Toulouse 3, Toulouse, France ; Professor and Research Director (M.D., PhD.)

[8]**Yolande Esquirol**: UMR 1027, INSERM, Université Paul Sabatier Toulouse III, 31000 Toulouse, France Occupational Health Department, CHU-Toulouse, 31000 France ; Associate Professor. (M.D., PhD.)

Word count: 4500

Keywords: varicose vein, venous thromboembolism, aortic dissection, aortic aneurysm, standing, work

ABSTRACT

Objectives

The individual peripheral vascular disease risk factors are well documented, but the role of work conditions remains equivocal.

This systematic review aims to assess relationships between lower limb peripheral venous diseases (lower limb varicose veins/LLVV, venous thromboembolism/VTE comprising deep vein thrombosis and pulmonary embolism), peripheral arterial disease (intermittent claudication, aortic dissection, aortic aneurysm) and occupational constraints among working adults.

Methods

Several databases were systematically searched until February 2019 for observational studies and clinical trials. PRISMA method was used for article selection. Quality assessment and risk of bias were evaluated using Strobe and Newcastle-Ottawa scales.

Results

Among the 720 screened articles, 37 remained after full-text evaluation. Among the 21 studies on LLVV, prolonged standing was significantly associated to a higher risk of varicose veins with a threshold probably around >3-4 hours/days but exposure duration in years was not sufficiently considered. Seated immobility was often observed in workers, with no sufficient evidence to prove that prolonged sitting at work is related to VTE. Carrying heavy loads, stress at work, and exposure to high temperatures have emerged more recently notably in relation to varicose veins but need to be better explored. Only three studies discussed the potential role of work on peripheral arterial disease development.

Conclusions

Although some observational studies showed that prolonged standing can be related to varicose veins and that seated immobility at work could be link to VTE, very little is known about peripheral arterial disease and occupational constraints. Clinical trials to determine preventive strategies at work are needed.

PROSPERO registration number: CRD42019127652.

Keywords varicose vein, venous thromboembolism, aortic dissection, aortic aneurysm, standing, sitting, carrying, work.

KEY MESSAGES

What is already known about this subject?

- Due to their high incidence or their poor prognostic, lower limb venous and arterial peripheral diseases remain a major concern.
- Some risk factors of arterial and venous diseases such as age, gender, smoking, and post-traumatism are well-established, but some occupational aetiologies may also be risk factors.

What are the new findings?

- This is the first systematic review on the link between several venous and arterial diseases and occupational exposures among adult working populations.
- Prolonged standing time may be associated with an increased risk of varicose veins, with possible positive exposure-response trends.
- Carrying heavy loads does not appear to be associated with varicose veins.
- Other occupational constraints such as occupational stress, high temperature, kneeling position are insufficiently documented.
- There is no sufficient evidence to prove that prolonged sitting at work is related to venous thromboembolism.

How might this impact on policy or clinical practice in the foreseeable future?

- Until more definitive research findings are available, some advice can already be reasonably proposed to workers exposed to prolonged standing: change position regularly between sitting, standing and walking, wear compression stockings, and encourage leisure physical activity.

INTRODUCTION

In Europe, the incidence rate of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is estimated between 104 and 183/100,000 person-years with a recurrence of 30% within 10 years[1]. The prevalence of lower limb varicose veins (LLVV) is about 25% of women and 15% of men[2].

The annual incidence of intermittent claudication is evaluated between 0.4 and 6/1000 men[3] and the prevalence of abdominal aortic aneurysm ranges between 1.3-12.5% in men, and up to 5.2% in women[4]. The incidence of aortic dissection is evaluated at 3.5 and 2.53/100,000 person-year, respectively in the USA and Iceland.

Although some vascular disease risk factors are well-known (age, gender, smoking, immobilisation, etc.[1 4]) occupational aetiologies remain little explored. Thus, the links between some occupational exposures and upper-extremity vascular diseases are well described (such as hand-arm vibration and Raynaud's phenomenon[5]), but the role of occupational exposures on peripheral vascular disease remains unclear and still debated. D'Souza and Al. proposed in 2005[6] a short non exhaustive overview about occupational constraints and vein varicose, without conclusive result.

This current systematic review was performed to evaluate the potential link between lower limb peripheral venous (LLVV and VTE) and arterial diseases (intermittent claudication, aortic dissection, and aortic aneurysm) and work conditions, and to summarize the current knowledge on this topic. Given that a lot of time is spent working, we hypotheses that the occupational constraints can be related to these vascular diseases. Some of occupational constraints are probably common for all these vascular diseases, while others are more specific. Determining this potential role, could be helpful to implement preventive strategies in companies.

METHODS

Search strategy

Systematic Reviews guidelines[7] were used to define the protocol of this systematic review of published studies which does not require approval by institutional and ethics committees.

A literature research in several databases including MEDLINE-PubMed, Web of Science, and ClinicalTrial.gov was conducted to identify the studies published until February the 28th 2019 and focused on the associations between the diseases of interest (LLVV, VTE, intermittent claudication, aortic dissection, aortic aneurysm) and working conditions. Moreover, added researches were performed to find unpublished articles from the System for Information on Grey Literature in Europe (‘OpenGrey.eu’). The keywords and MESH terms used are specific for each vascular disease and listed in Supplementary table 1.

Study eligibility criteria

Retrospective, prospective, cross-sectional studies, controlled trials and case reports reporting data on the potential link between each vascular event and working conditions were included. To analyse the potential role of occupational factors, only studies enrolling adult people ≥18 years old were included.

Studies written in English and in French were retained. No date selection was applied.

We excluded oral presentations, posters, opinion articles, books and when only the abstracts were available. Studies with no results concerning the potential link between occupational exposure and the studied vascular events were excluded (no assessment of risk was provided in observational studies.). Vascular diseases of the upper limbs were excluded.

Flow charts, using PRISMA method[7], summarize the different steps of the article selection for each investigated vascular diseases.

Study selection

Article selection was conducted independently by three reviewers (MT, SHYK, YE) using defined search terms. The results of the search were imported in Endnote software which was useful to delete duplicate articles. The next step consisted in selecting studies based on the screening of titles and then on abstracts independently by two reviewers (SHYK, YE) who also conducted a further selection after reading the full articles. In case of disagreement, a discussion with a third reviewer (JF) resolved it. The references listed in the included articles were compared and checked to those obtained after our selection, to ensure that we did not omit important articles.

Data extraction

A table was created for each vascular disease (LLVV, VTE, arterial diseases) to synthetize the main findings and the characteristics of each study: publication references, authors, study design, country, origin and number of participants, gender, age, study size, type of vascular events, diagnosis methods, type and methods to assess occupational constraints, confounders taken into account and the main results reported by authors.

Protocol

This systematic review was registered in the prospective register of systematic reviews (PROSPERO) (registration number CRD42019127652).

Study quality assessment – Risk of bias

To understand and assess the quality of these studies, two additional methods were applied. Firstly, criteria of Strobe[8] and CARE[9] checklists were screened to evaluate the reporting of observational studies and case reports respectively. The studies were scored to reach a maximum value of 22 and 29 points, respectively.

Secondly the quality of the studies and risk of bias were evaluated using several specific tools according to the study design.

For case reports, we applied the CARE checklist to assess their quality.

For the observational studies (prospective, retrospective, and cross-sectional studies) the Newcastle-Ottawa Scale (NOS) was used[10]. Three dimensions were evaluated: selection (representativeness of the population, ascertainment of the exposure or of case definition), comparability (control for confounding factors), and outcome (blind assessment of the outcome, adequacy of follow up etc.). Stars were assigned according to the study quality and bias risk. The total number of stars for cross-sectional studies is 10 while for case-controls and prospective studies a total of 9 could be reached. The higher the number of stars, the lower the bias risk is.

The predefinition of inclusion and exclusion criteria, the independent implication of two reviewers and a third in case of disagreement, and the several detailed tables were helpful to reduce the selection bias.

RESULTS

Characteristics of Eligible Studies

For LLVV: 457 articles were initially reported from which 138 not in English or French or on humans and 94 duplicates were excluded. Thus 225 were checked on titles and abstracts and 52 full texts were examined. Three overviews conducted in 1994 (Callam MJ.), 1997[11], and 2005[12] which provided only prevalence and incidence data were excluded. An article[13] did not fulfil the eligibility criteria because the authors did not propose results but discussed the interest of the use of their hospitalization register to explore the link between some diseases and occupational environment (Supplementary figure 1). Finally, 21 studies were included in the qualitative synthesis.

For VTE, the research yielded 535 articles, and 13 articles met all the eligibility criteria (Supplementary figure 2).

For aortic dissection and aneurysm respectively, 44 and 167 articles were retrieved, 1 and 2 articles suited the eligibility criteria, respectively (Supplementary figures 3 and 4).

For intermittent claudication, no articles explored the link between occupational environment and the disease (Supplementary figure 5).

No clinical trials were found on this topic.

Lower limb varicose veins (Table 1 and Supplementary Table 2)

Table 1: Varicose veins study characteristics.

Authors, year of publication	Study design, country, follow-up or recruitment period	Participants (gender, age)	Vascular Events	Occupational constraints and environmental exposures	Confounders	Results	Quality assessment
Stewart et al. 1955	Cross-sectional England Recruitment: 1941-1944	Three English regions ♂3,582 <45 yo	Varicose veins (Civilian Medical Board records)	Occupational status	standardized on age and region	Standardized prevalence ratios in occupational groups: Boot and Shoe: 116 (p<0.001) Clerical: 69 (p<0.001) Professional and administrative: 81 (p<0.01)	Strobe: 13/22 NOS: 4/10
Mekky et al. 1969	Cross-sectional England and Egypt Recruitment: 1964-1966	7 cotton mills ♀971	Varicose veins (clinical examination)	Position at work	none	Prevalence: 32% England, 6% Egypt Prevalence, according to working condition: English mills: Sitting: 18.2%, Walking: 28.7%, Mixed job: 35.4%, Standing: 56.6% (p<0.001) Egyptian mills: NS	Strobe: 13/22 NOS: 2/10
Abramson 1981	Cross-sectional Israel Recruitment: 1969-1971	Western Jerusalem ♂2,245 ♀2,557	Varicose veins (clinical examination)	Time spent sitting, standing, and walking during working hours; lifting or carrying of heavy weights, physical exertion (interview at home)	age, gender	Much standing (ref: Little standing): OR= 1.6 (p<0.01) Lifting or carrying of heavy weights, physical exertion at work: no significant associations	Strobe: 17/22 NOS: 7/10
Labropoulos 1995	Cross-sectional Recruitment: 1991-1994	28 vascular surgeons 25 normal volunteers men, 29-45 yo	Venous reflux in the lower extremities (colour-flow duplex imaging)	Prolonged standing	age	No venous hemodynamic abnormalities: 68% of the control group / 48% of the vascular surgeons (p=NS) Venous reflux: 32% of the control group / 52% of the vascular surgeons (p = 0.039)	Strobe: 10/22 NOS: 4/10
Tomei et al. 1999	Cross-sectional Italy	Industrial workers, stoneworkers, office workers ♂308	Chronic venous disorders (clinical examination by a trained physician)	Standing, sitting, walking during working time (questionnaire)	job classification	Prevalence: industrial workers (39.28%), stoneworkers (24.16%) and office workers (22.11%) Standing for 50% of the work shift (ref: <50%): OR= 1.07, p<0.001	Strobe: 13/22 NOS: 5/10

		mean age: 36-39 yo					
Kontosic et al. 2000	Cross-sectional Croatia	Rijeka Community ♂530 ♀794	Varicose veins (clinical examination by trained physicians)	Occupational status, standing, moving, lifting, high temperature	gender, age, BMI, flat feet, duration of fertile period/ pregnancies/deliveries, family history of varicose veins	At workplace (ref: no) Standing: ♂ OR= 2.53 (0.96, 6.73) ♀ OR= 0.67 (0.33, 1.36) Moving: ♂ OR= 1.12 (0.57, 2.17) ♀ OR= 0.63 (0.33, 1.18) Carrying heavy loads: ♂ OR= 0.82 (0.52, 1.29) ♀ OR= 0.79 (0.55, 1.13) High temperature: ♂ OR= 0.96 (0.57, 1.62) ♀ OR= 1.22 (0.79, 1.91)	Strobe: 17/22 NOS: 7/10
Fowkes et al 2001	Cross-sectional Scotland (Edinburgh Vein Study) Recruitment: 1994-1996	Registers of 12 general practices ♂609 ♀739 18-64 yo	Varicose vein (clinical examination), Venous reflux (Duplex scan)	Visual analogue scales of time spent sitting, standing, walking, and heavy lifting (never to all the time) (self-administered questionnaire)	stratified on gender; age, gastrointestinal habits, smoking, BMI	Mobility at work (ref: visual analogue scale<5) Sitting: ♂ OR= 1.09 (0.83, 1.43) ♀ OR= 0.75 (0.57, 0.99) Standing: ♂ OR= 1.04 (0.77, 1.40) ♀ OR= 1.01 (0.76, 1.34) Walking: ♂ OR= 0.93 (0.68, 1.27) ♀ OR= 0.88 (0.65, 1.18) Heavy lifting: ♂ OR= 0.96 (0.68, 1.38) ♀ OR= 1.02 (1.45, 1.54)	Strobe: 15/22 NOS: 7/10
Lee et al 2003	Cross-sectional Scotland (Edinburgh Vein Study) Recruitment: 1994-1996	Registers of 12 general practices ♂699 ♀867 18-64 yo	Varicose vein (clinical examination, Basle Study classification), Venous reflux (Duplex scan)	Visual analogue scales of time spent sitting, standing, walking, and heavy lifting (never to all the time) (self-administered questionnaire)	stratified on gender; age, diet intake, BMI, smoking	Mobility at work (ref: visual analogue scale<5) Sitting: ♂ OR= 1.34 (0.86, 2.11) ♀ OR= 0.53 (0.32, 0.87) Standing: ♂ OR= 1.12 (0.70, 1.80) ♀ OR= 1.28 (0.79, 2.08) Walking: ♂ OR= 1.16 (0.70, 1.91) ♀ OR= 0.96 (0.57, 1.60) Heavy lifting: ♂ OR= 0.90 (0.50, 1.61) ♀ OR= 1.32 (0.66, 2.62)	Strobe: 16/22 NOS: 7/10

Ziegler et al 2003	Cross-sectional Austria	Vienna's general hospital, employees ♂58 ♀161 19-60 yo	Chronic venous disease (CEAP classification)	Group 1: medical doctors and nurses Group 2: medical technician assistants, secretaries and scientific staff Group 3: cleaners and utility workers (self-questionnaire)	none	Occurrence of CVD according to groups, p<0.02: Group 1: 31% Group 2: 22% Group 3: 46% Mean period of standing at work (h/day), occurrence of CVD vs absence of CVD, p<0.02: ♂ 4.4 / 2.7 ♀3.9 / 3.2	Strobe: 13/22 NOS: 2/10
Criqui et al 2007	Cross-sectional USA Recruitment: 1994-1998	Current and retired employees of the University of California, San Diego: ♂854 ♀1,580 40-79 yo	Varicose veins (doppler examination, CEAP classification)	Occupational status (laborers, no laborers)	age, ethnicity	Laborers, men (ref: no laborer): OR= 3.24 (1.21, 8.67)	Strobe: 15/22 NOS: 6/10
Basic et al. 2014	Cross-sectional Croatia	60 dentists (median 42 yo) 60 other occupation (median 38 yo) Gender unknown	Lower limb varicose veins (questionnaire, ultrasonography)	Being a dentist	none	No statistically significant difference between-group according to the presence of varicose leg veins (p=0.835)	Strobe: 7/22 NOS: 2/10
Chen et al. 2014	Cross-sectional Southern Taiwan	♂15 ♀166 average age 45.8 yo	Lower limb varicose veins (self-administered questionnaire)	Hairdressers Prolonged standing at work (self-administered questionnaire)	stratified on age (≤45 yo, >45 yo)	Monthly standing work hours (ref <120 hours; OR for ≤ 45 yo and > 45 yo respectively): 121-168H: OR: 2.4 (0.1, 55.6) / OR: 9.7 (0.7, 132.5) 169-208H: OR: 2.0 (0.2, 24.2) / OR: 7.4 (0.6, 89.9) 209-260H: OR: 0.5 (0.0, 11.3) / OR: 6.4 (0.5, 86.2) 261-360H: OR: 5.2 (0.4, 75.8) / OR: 31.8 (1.8, 566.5)	Strobe: 14/22 NOS: 6/10
Kohno et al 2014	Cross-sectional Japan Recruitment: 2012	♂113 ♀205 ≥45 yo	Varicose veins (doppler examination, CEAP classification)	Occupation, duration of standing per day	BMI, gender, age, family history, physical activity, lumber corset, history of	Standing at work (ref: No or <5 h a day): With substantial movement: OR= 0.89 (0.40, 1.98) Upright posture: OR= 1.98 (1.04, 3.77)	Strobe: 16/22 NOS: 6/10

					cardiovascular diseases		
Ebrahimi et al 2015	Cross-sectional Iran Recruitment: 2012	♀197 (hairdresser) 18-68 yo	Varicose veins (questionnaire + standard physical examination, severity score)	Duration of standing per day	age, BMI, pregnancy, family history, high blood pressure, oral contraceptive, constipation	Duration of Standing per day (ref: ≤3 hours): > 3 hours: OR= 2.34 (1.05, 5.22)	Strobe: 17/22 NOS: 4/10
Sharif et al. 2015	Cross-sectional Iran Recruitment: 2010	Hospital nurses ♂58; ♀145 < 30 yo (n=81); 30-40 yo (n=77); > 40 yo (n=45)	Varicose veins (CEAP classification: clinical degrees, C0 to C6)	Time sitting, standing, walking posture, and overtime (self-questionnaire)	gender, age, BMI, education level, family history	Leg varicose intensity (C0-C6) and standing (ref: <2 h): 2-4 h: OR= 0.9 (0.4, 2.2) >4 h: OR= 2.3 (1.01, 5.4) Leg varicose prevalence and standing (ref: <2 h): 2-4 h: OR= 1.3 (0.4, 3.7) >4 h: OR= 3.8 (1.2, 11.9) No significant link with time spent sitting or walking Overtime (hours) (ref: no) OR= 1.02 (1.01, 1.03) Leg varicose intensity (C0-C6) and years of service: OR= 1.07 (1.03, 1.12)	Strobe: 18/22 NOS: 6/10
Yun et al. 2018	Cross-sectional Korea 2014	Nurses in a university hospital ♂7 ♀407 mean age 30 yo	Varicose veins (doppler ultrasound)	Number of daily working hours in a static standing, walking, and sitting position number of consecutive service years (questionnaire)	age, pregnancy, compression stocking period	Work posture (ref: <2h/day): Stand: 2-4h OR=1.03 (0.53, 2.0) ≥4h OR=1.53 (0.75, 3.14) Walk: 2-4h OR=0.92 (0.27, 3.14) ≥4h OR=1.70 (0.55, 5.25) Sit: 2-4h OR=0.64 (0.33, 1.25) ≥4h OR=0.58 (0.27, 1.21) Up (stand + walk, ref: ≤4h): OR=3.40 (1.27, 9.09)	Strobe: 14/22 NOS: 5/10

Tuchsen et al. 2000	Prospective Denmark Follow-up: 1991-1993	Central population register ♂727 145 ♀878 756 20-59 yo (random sample of 5,940 participants)	Varicose veins (ICD-8: 454) from hospital register	Prolonged standing at work and/or walking (questionnaire, interview by phone)	age, smoking, social group Stratified on gender	People standing more than 75% of working hours (ref: <75%): ♀ SRR=2.63 (2.25, 3.02) ♂ SRR=1.85 (1.33, 2.36)	Strobe: 21/22 NOS: 8/9
Tuchsen et al. 2005	Prospective Denmark Follow-up: 1991-2002	Central population register ♂2,939 ♀2,708 20-59 yo	Varicose veins (ICD-8: 454, ICD-10:183) from hospital register	Prolonged standing at work and/or walking; time spent carrying and lifting>20 kg (questionnaire, interview by phone)	age, smoking, social group Stratified on gender	Standing more than 75% of working hours: ♀ RR=1.82 (1.12, 2.95) ♂ RR=1.75 (0.92, 3.34) Heavy lifting (>20 kg): ♀ RR=1.16 (0.59, 2.31) ♂ RR=0.81 (0.35, 1.90)	Strobe: 21/22 NOS: 5/9
Robertson et al. 2014	Prospective Scotland (Edinburgh Vein Study) Follow-up: 13 years	Registers of 12 general practices ♂390 ♀490 18-64 yo	Varicose vein (clinical examination, Basle Study classification), Venous reflux (Duplex scan)	Visual analogue scales of >50% of time spent sitting, standing, walking, and heavy lifting (never to all the time) (self-administered questionnaire)	age, gender	Link between incidence of varicose veins and mobility at work Sitting: OR= 1.0 Standing: OR= 1.0 (0.3, 3.2) Walking: OR= 1.5 (0.6, 3.8) Heavy lifting: OR= 1.5 (0.6, 3.9)	Strobe: 16/22 NOS: 8/9
Tabatabaeifar et al. 2015	Prospective Denmark Follow-up: 1980-2011	Musculoskeletal Research Database (MRD) at the Danish Ramazzini Centre ♂16,259 ♀21,777 18-65 yo mean 42-45 yo	Varicose veins surgery (ICD-8: 454, ICD-10:183) hospital register	Time spent standing/walking and total load lifted (Lower Body Job Exposure Matrix)	age, BMI, physical activity, smoking	Standing/walking (hours/day, ref: <4): ≥4–<6: HR= ♂ 2.65 (1.52, 4.62) / ♀ 2.42 (1.91, 3.06) ≥6–≤7.3: HR=♂ 3.17 (2.06, 4.89) /♀ 2.34 (1.72, 3.19) Lifting (kg/day, ref: 0): >0-<1000: HR= ♂ 2.65 (1.63, 4.32) / ♀ 2.1 (1.6, 2.76) ≥1000–≤4900: HR= ♂ 3.95 (2.32, 6.73) / ♀ 2.54 (1.95, 3.31)	Strobe: 22/22 NOS: 8/9

Huang et al. 2017	Retrospective cohort Taiwan Period: 2007-2011	National Health Insurance Research Database: Physician ♂24,802/♀4,042 Non-physician ♂7,984/♀18,115 General population (matched 1:1)	Varicose veins (ICD-9)	Occupation: physician, non-physician health care providers	age, gender, deep venous thrombosis	Ref: general population Being a physician: OR=0.86 (0.53, 1.40) Being a non-physician: OR=1.43 (0.82, 2.50)	Strobe: 18/22 NOS: 6/9

Table 1 footnote:
♂, men
♀, women
yo, years old
NOS, Newcastle-Ottawa scale
NS, not significant
BMI, body mass index
CVD, cardiovascular disease
CEAP classification, Comprehensive Classification System for Chronic Venous Disorders
ICD, International Classification of Diseases
OR, odds ratio with 95% confidence interval
SRR, standardized risk ratio with 95% confidence interval
RR, relative risk with 95% confidence interval
HR, hazard ratio with 95% confidence interval

Twenty one studies have explored the link between OC and LLVV: 16 cross-sectional studies, enrolling from 53 to 4,802 participants[14-29], 1 retrospective study[30], with 54,943 physicians and non-physicians, and 4 prospective studies including two conducted in the same population[31-34], ranging from 5,447 to more than 1,600,000 participants from hospital registries in Denmark, and with a follow-up varying from 3 to 31 years.

Mean values and ranges obtained after the quality evaluations by NOS for the cross-sectional and prospective studies were respectively: 5.1 [2 – 8] (maximum 10), and 7 [5 – 8] (maximum 9) stars.

The mean score calculated from Strobe checklist was 15.5 and varied between 7 and 22.

The LLVV diagnosis was established with several methods: the international disease classification was used in retrospective and prospective studies, while the cross-sectional studies exploited the medical data from Doppler ultrasound, medical records or self-administered questionnaires.

Most of these studies proposed analyses adjusted on age and gender. Other well-known confounders (such as smoking status, body mass index, education level, physical activity etc.) were heterogeneously considered.

To analyse the occupational environment, two methods were used, on one hand using professional categories[15 19 20 23 25 30] such as hairdressers, dentists, nurses, physicians, secretary, scientific staff, cleaners, utility workers, and labourers, and on the other hand, using the types of constraint (standing, lifting, sitting, walking) to which the worker was exposed during the working period[16-18 21 22 24 26-29 31-35]. Regarding standing constraint, several measures of exposure duration were used such as hours/month, hours/day (with different thresholds according to the study).

Several studies exploring the link between time spent standing, expressed in hours/day or month, and LLVV found a significant dose-response effect[17 21 33 35] but not for Yun et al. study[18] and Edinburgh studies[28 29 34]. Thus, standing more than 3-4 hours/day seemed to increase the risk of LLVV in men as well as in women, compared to those less exposed (about 2.5-fold higher), and the degree of severity of the LLVV which is also associated to the number of years of service[17].

In population in age to be employed, Tuchsen 2000 at al.[32] showed that standing at work more than 75% of the time was associated with increased risk of LLVV (analyses adjusted for age, social group and smoking, respectively for men and women, RR=1.85 [95% CI 1.33-2.36] and RR=2.63 [95% CI 2.25-3.02]).

Moreover, some authors were interested by the effect of carrying or lifting heavy loads on LLVV during working period with contrasted findings. However in the most recent study conducted in a large sample involving men and women aged 18-65 years old, lifting more than 1 ton a day increase significantly the risk of LLVV[33], but only for women in Edinburgh Study.

Sitting and walking were scarcely explored, and the few results were in favour of a non-significant link with LLVV[17 18] and from the Edinburgh study, sitting time at work appeared to be protective on vein reflux only in women[28 29]

Only one study investigated the exposition to high temperatures at work with no significant association[24].

Concerning the occupational categories, compared to general population, the risk of LLVV was not increased among dentists[15], physician and non-physician[30].

Venous thromboembolism (deep vein thrombosis and pulmonary embolism)

Thirteen articles were included in the current review (Table 2 and Supplementary table 2), including four prospective studies[36-39] with large study size (up to 389,530 participants) and about 20 years of follow-up, four case-control studies, two conducted in the same initial population[40 41] including respectively 97 and 192 cases, one among insured bank staff [42], and one from clinic services[43] and five case-reports[44-48].

Table 2: Venous thromboembolism study characteristics.

Authors, year of publication	Study design, country, follow-up or recruitment period	Participants (gender, age)	Vascular Events	Occupational constraints and environmental exposures	Confounders	Results	Quality assessment
Beasley et al. 2003	Case report	♂ 32 yo	PE (pulmonary angiography)	Sitting for long periods at a computer (at work and at home)	NA	Regularly 12 h per day (up to 18 h) spent sitting at his computer	Care: 18/29
Aldington 2008	Case series	♂ 38 ♀ 23 17-64 yo	Lower limb DVT (imaging)	Prolonged seated immobility at work in the 4 weeks before VTE event	NA	21 patients with prolonged seated immobility: 8-14 hours/day, with 1 hour to 5 hours without getting up Most common jobs with prolonged seated immobility: information technology (29%), management (14%) and taxi driving (10%)	Care: 9/29
Patel et al. 2011	Case reports USA	Case 1: ♀ 38 yo Case 2: ♀ 39 yo	Case 1: lower limb DVT (doppler ultrasound) Case 2: Bilateral PE (CT scan)	Case 1: Teacher, sitting at work (computer) 8-10 hours/day, 5 days/week Case 2: Social community worker, sitting at work (computer) 10-12 hours/day, 5-6 days/week	NA	Prolonged sitting period at work, with no other known risk factors	Care: 13/29
Van Beeck et al. 2014	Case report South Africa	♂ 41 yo	Lower limb DVT (ultrasound)	Mould maker, tooling department, boat building company Prolonged kneeling	NA	Lower limb deep vein thrombosis Have worked during about 6 weeks, in a kneeling position, 8 hours/day	Care: 9/29
Doctor and Seth 2018	Case reports	Case 1: ♂ 50 yo Case 2: ♀ 18 yo	DVT (ultrasound duplex imaging)	Case 1: software professional Case 2: student	NA	Case 1: worked on his computer on average for 12 hours/day, only able to stretch regularly his right leg Case 2: spent long hours seated at her desk using her computer	Care: 16/29

Dimberg et al 2001	Case-control USA Recruitment: 1995-1998	Washington, DC World Bank staff employed and insured 111 cases (81 with definition 1, (♂ 58%), 30 with definition 2 (♂ 60%) 810 controls (♂ 50%) 22-72 yo	Phlebitis, thrombophlebitis or thromboembolism (definition 1); lower limb DVT (definition 2) (filed medical insurance claims, ICD-9)	Number of missions and travel days, Days since last mission	age, gender	No association between travel-related covariate and the risk of filing a DVT claim	Strobe: 16/22 NOS: 6/9
WEST et al. 2008	Case-control New Zealand Recruitment: 2005-2006	Wellington Hospital 97 cases (VTE clinic, ♂ 58.8%), mean age=44.9 yo (SD 13.1) 106 controls (Coronary Care Unit, ♂ 54.6%), mean age=52.4 yo (SD 9.7)	VTE (DVT, PE) (Doppler ultrasound, pulmonary angiography, scan)	Time spent seated at least 8 or 10 or 12 hours/day and associated respectively to at least 3 or 2 or 1 hours without getting up (interview, questionnaire)	age, gender, family history of VTE, medical risk factors, personal history of VTE	Maximum hours seated at work: OR=1.1 (1.0, 1.2) Maximum hours seated at work without getting up: OR=1.2 (1.0, 1.6)	Strobe: 19/22 NOS: 5/9
HEALY et al. 2010	Case-control New Zealand Recruitment: 2007-2008	Wellington Hospital 192 cases (VTE clinic, ♀ 48.7%) 195 controls (Coronary Care Unit, ♀ 26.9%) 18-50 yo	lower limb DVT, PE (Doppler ultrasound, pulmonary angiography, scan)	Prolonged work- and computer at home-related seated immobility (interviewer administered questionnaire)	age, gender, family history of VTE, medical risk factors, personal history of VTE	Prolonged work- and computer-related seated immobility: OR= 2.8 (1.2, 6.1) Per hour longer seated: Maximum work- and computer related hours seated in 24 hours: OR= 1.1 (1.0, 1.2) Maximum work- and computer related hours seated without getting up: OR= 1.2 (1.0, 1.4)	Strobe: 21/22 NOS: 5/9

Braithwaite et al. 2016	Case-control New Zealand Recruitment: 2011-2013	200 cases (Venous thromboembolism service) 200 controls (Orthopaedic service) 18-65 yo	Venous thromboembolism (Doppler ultrasound, lung scan)	Seated at work, and/or on the computer at home in a 24-h period (interviewer-administered questionnaire)	BMI, personal history of VTE, exposures within the 28 days prior to the event (immobility, surgery, cast immobilisation, air travel and/or road travel, and strenuous exercise)	Mean work/computer seated (per hour) OR= 1.08 (1.01, 1.6)	Strobe: 18/22 NOS: 6/9
Kuipers et al 2007	Prospective Follow-up: 2000-2005	International companies and organisations: 8,755 ♂ 44% ♀ 56%	DVT (compression ultrasonography or venography), PE (CT scanning)	Number of flights per employee per year (internet-based questionnaire)	age, gender	Ref: 0 flight 1 or 2: IRR= 2.5 (1.2, 4.9) 3 or 4: IRR= 4.2 (1.4, 10.3) 5 or more: IRR= 6.9 (1.3, 22.3)	Strobe: 17/22 NOS: 7/9
Rosengren et al. 2008	Prospective Sweden Mean follow-up: 22.9 years	Random sample of Göteborg men: 6,958 6,600 without VTE (mean 51.5 yo) 358 VTE (mean 51.9 yo)	Lower limb DVT, PE (ICD 8-10)	Stress (using a single question about working conditions and at home), Socio-economic index	age, diabetes, BMI, and height, treatment for hypertension, alcohol	Mental stress (ref: none or little): DVT: Moderate, HR=1.27 (0.92, 1.75) / Persistant, HR= 1.21 (0.78, 1.89) PE: Moderate, HR=1.03 (0.73, 1.45) / Persistant, HR= 1.66 (1.12, 2.48) Occupational class (ref: Unskilled + skilled manual worker): DVT: Lower officials, foremen, HR= 1.13 (0.77, 1.66) / White-collar, HR=0.81 (0.56, 1.17) PE: Lower officials, foremen, HR= 0.65 (0.42, 1.01) / White-collar, HR=0.57 (0.39, 0.83)	Strobe: 17/22 NOS: 6/9

SUADICANI et al. 2012	Prospective Danemark Follow-up: 1997-2006	Danish Occupational Hospitalisation Register 105,564 sedentary workers (♀ 5.4%) 283,966 dynamic workers (♀ 5.5 %) 20-59 yo	Death, lower limb DVT, PE (ICD 10)	Jobs encompassing prolonged sitting, drivers vs. construction workers (Statistics Denmark's Standard Classification of Occupations)	age, gender	Drivers (encompassing workers with prolonged sitting) vs. Construction workers (with dynamic occupational physical activity, ref.): Death or hospital treatment due to PE: RR= 1.28 (0.97, 1.67) Death or hospital treatment due to DVT: RR= 1.09 (0.94, 1.26)	Strobe: 14/22 NOS: 7/9
Zoller 2012	Prospective Sweden Follow-up: 1990-2007	Total Population Register and the Swedish Hospital Discharge Register ♂ 23,464 ♀ 19,599	Lower limb DVT, PE (ICD 9-10)	Socio-economic status and occupations (n=53) (Statistics Denmark's Standard Classification of Occupations)	age, time period, region of residence, immigrant status, and comorbidity stratified by gender	White-collars: ♂ SIR=0.96 (0.94, 0.99) ♀ SIR=0.93 (0.91, 0.95) Blue-collars: ♂SIR=1.03 (1.01, 1.05) ♀ SIR=1.05 (1.03, 1.08)	Strobe: 20/22 NOS: 8/9

Table 2 footnote:
♂, men
♀, women
yo, years old
NOS, Newcastle-Ottawa scale
PE, pulmonary embolism
DVT, deep vein thrombosis
VTE, venous thromboembolism
NA, not applicable
ICD, International Classification of Diseases
BMI, body mass index
OR, odds ratio with 95% confidence interval
IRR, incidence rate ratio with 95% confidence interval
HR, hazard ratio with 95% confidence interval
RR, relative risk with 95% confidence interval
SIR, standardized incidence ratio with 95% confidence interval

Case-control studies obtained 5 to 6/9 stars at NOS evaluation, while prospective studies reached 8/9 with an average of 7 stars. The scores obtained with the STROBE checklist varied between 14 and 21/22. The quality of the case reports evaluated by the CARE checklist varied between 9 and 20/29 fulfilled items.

The vascular events were diagnosed using the International Classification Diseases (ICD8-10), imaging (Doppler ultrasound, pulmonary angiography and scan) or filed medical insurance claims.

All the studies adjusted their analyses on gender and age while other confounders, known as causal risk factors of VTE, were heterogeneously considered.

Among the eight observational studies, five of them recruited participants from hospital registers.

Prolonged sitting was the most studied occupational exposure in observational studies[38 40 41 43] and case reports[44 45 47 48] with contrasted results. Only the studies undertaken from the Wellington Hospital register[40 41] and clinical services[43] analysed the number of hours spent sitting at work with around 10% increase of the risk of VTE per hour seated. Moreover, eating lunch at their desk and having their own desk at work significantly increased the risk of VTE (respectively, OR= 2.2 [95%IC 1.1-4.1] and OR= 2.1 [95%IC 1.3-3.3]), with no protective effect of adjustable chair use and stretching legs[40].

The other occupational exposures were less documented.

No link between prolonged kneeling and VTE has been clearly identified yet. But a case report was presented by van Beeck et al. in 2014[46]. A 41-year-old man presented with DVT in the left lower limb without no thrombosis risk factors. The involvement of kneeling 8 hours/day at work during the previous 6 weeks was suspected. Two of the three components of Virchow's triad may have been present: venous stasis (prolonged immobility) and vascular endothelial microtrauma (tight straps). The third component, hypercoagulability, could not be confirmed.

Rosengren et al. aimed to determine the effect of psychosocial factors on VTE[37]. The study consisted in a mean 23-year follow-up of about 7,000 men and evaluated stress comprising stress at work, stress at home, sleeping difficulties, anxiety, and irritability. Men with persistent stress had higher risk of developing PE (HR=1.66 [95% CI 1.12-2.48]) compared to men with none or little stress. No link was found for DVT.

Regarding social class, Rosengren et al.[37] found that the risk of PE was halved for white-collars (HR=0.57 [95% CI 0.39-0.83]), which was also corroborated by Zöller study[39].

Air travel is a known risk factor of DVT (2 to 4 fold risk increase)[49] for passengers but the consequences for air travel professionals has been scarcely specifically explored.

Two studies focussed on determining incidence rate of VTE among business air travellers, its relationship with duration of travel, number of long-haul flights, and with the time passed after air travel.

Kuipers et al.[36] conducted a cohort study among more than 8,000 respondents (32% response rate) and VTE was confirmed for 53 employees. Overall incidence rate was 1.4/1,000 person-years (PY) compared to 1.0/1,000 PY in individuals unexposed to air travel. Incidence rates were higher in women, with the number of flights, and with the travel time.

In Dimberg et al. case-control study[42], incidence rate (phlebitis, thrombophlebitis or thromboembolism) was 2.5/1,000 employees. DVT incidence rate was 0.9/1,000 employees.

No statistically significant associations were found between VTE and number of missions, number of travel days, or number of days since last mission.

Aortic dissection (Table 3 and supplementary table 2)

Table 3: Arterial diseases study characteristics

Authors, year of publication	Study design, country, follow-up or recruitment period	Participants (gender, age)	Vascular Events	Occupational constraints and environmental exposures	Confounders	Results	Quality assessment
Cohn 1960	Case reports (2) USA 1958	Case 1: ♂ 56 yo Case 2: ♂ 59 yo	Aortic aneurysm	Case 1: metal worker Case 2: bus mechanic	NA	Case 1: pain after heavy lifting Case 2: pain after chronic stress	Care: 10/29
Owada et al. 1999	Case-control Japan Recruitment: 1994-1998	91 sudden deaths (including 4 acute aortic dissections), ♂77/♀14 from Segamihara city 958 controls (health check) from Niigata city 20-59 yo	Aortic dissection	Duration of global stress (telephone interviews from family members)	age, sex, occupations, cardiovascular risk factors	All sudden deaths Short-term stress: OR= 1.78 (0.90, 3.5) Long-term stress: OR= 2.63 (1.30, 5.35)	Strobe: 18/22 NOS: 5/9
Aparci et al. 2013	Cross-sectional Turkey 2011	Etimesgut Military Hospital, military personnel ♂60 mean age ~38 yo	Aortic echocardiographic parameters	Physical activity during work: Ordinary activity trainers (OAT, exercise duration <2h, <2 times/week) Strenuous activity trainers (SAT, daily exercise leading 4000 kcal/day energy consumption)	none	Aortic diameters (millimetres), respectively for OAT and SAT Aortic root: 33.5±1.9 / 35.6±3.0, p=0.001 Aortic root index: 16.7±1.0 / 17.6±1.5, p=0.004 Ascending aorta: 34.4±1.9 / 36.8±3.0, p=0.001 Ascending aorta index: 17.2±1.1 / 18.2±1.5, p=0.002	Strobe: 9/22 NOS: 7/10

Table 3 footnote:
♂, men

♀, women
yo, years old
NA, not applicable
NOS, Newcastle-Ottawa scale
OR, odds ratio with 95% confidence interval

Very few studies explored the link between aortic dissection and occupational exposure.

In 1999, Owada et al.[50] aimed to determine the risk factors of sudden death among a working population with a case-control study (NOS: 5/9 stars). Among the 91 cases of sudden death, 4 (4.4%) were caused by acute aortic dissection (three men and one woman).

Occupations were only compared between all sudden deaths and controls. There was a significant difference in terms of occupations ($p<0.001$): proportion of office workers was lower in the sudden death group than in controls, while proportion of workers in manufacture, construction, transportation and telecommunication industries, manual workers, unemployed people and housewives were higher than in controls.

Aortic aneurysm (Tables 3 and supplementary table 2)

The search yielded only two references.

In a cross-sectional study (NOS evaluation: 7/10 stars), Aparci et al.[51] compared two groups: participants with daily high intensity physical activity (isometric-type strenuous training, weight lifting, benching, jumping, squatting and hanging up) necessitating at least a 4000 kcal/day energy consumption versus people who participated in physical activity no more than twice per week. They found that echocardiographic measurements of the aorta and intensity of physical activity at work were related. Patients of the first group had larger aortic root and ascending aorta diameters than those of the second group. The diameter of the ascending aorta was significantly correlated to the type of occupation. They finally suggested that some occupations (for example, members of the military or of the army, security, professional weightlifters, endurance athletes, etc.) were at a risk for the development of aortic enlargement and should initially and periodically be examined using echocardiography.

In 1960, Cohn[52] reported two cases of aortic aneurysm: one after an intense physical effort at work in a metal worker and a second exposed to chronic stress (bus mechanic).

DISCUSSION

The peripheral vascular disease can affect young workers, but there is still no study summarising the occupational factors that could participate in peripheral vascular diseases development.

The current systematic review of the literature aims to resume the relationship between lower limb peripheral venous diseases (LLVV, VTE [DVT and PE]), peripheral arterial disease (intermittent claudication, aortic dissection, and aortic aneurysm) and exposition to occupational constraints.

The link between vascular disease and work was assessed in two ways: by estimating the exposure duration to occupational constraints during a typical working period (expressed by day or month), or by using occupational social categories which allow an empirical evaluation of the exposure, usually facing the workers.

Lower limb varicose veins

The most explored potential occupational risk of varicose are prolonged standing[14 18 19 21 22 24 28 31-34], walking[18 28 33 34], sitting[17 18 26 28], working overtime[17], and heavy lifting[24 28 29 31].

While some evidence provided further weight to the hypothesis concerning the link between prolonged standing posture and varicose, the obtained results need to be considered carefully. Indeed, if the working hours/day spent standing-up act on the risk of varicose in most of the studies, the threshold which can have an adverse effect, is difficult to determine: >4 hours/day for patients recruited from hospital register[33] and for nurses[17] studies, >3 hours for hairdressers[21], 5 hours only for people who have upright standing posture without some movements in the same time for Kohno study[22]. Moreover, this link was not confirmed by Yun[18], Kontosic[24] and Edinburgh[34] studies, using dichotomized variables: > 4hours/day vs <4 hours/day or exposed vs unexposed people. Chen et al.[14] found only significant results in hairdressers aged more than 45 years old (with large confidence intervals) and Tuchsen et al.[31] only among women (population recruited from hospital register). Moreover, two explanations can be put forward. Firstly, none of the studies have considered the number of years of exposure to this occupational constraint, which can explain the inconstancy of these findings. Secondly, only two prospective studies were undertaken, both with patients from hospital registers which can lead to some bias by omitting people with no or mild symptoms and who do not need hospital care. The link between the degree of severity of varicose (assessed by the CEAP classification) and occupational constraints was considered in only one study[17] which demonstrated that being exposed to a standing-up posture more than 4 hours/day increased by two the degree of severity of varicose.

Some strong pathophysiological mechanisms can explain these links. Indeed, prolonged standing-up posture provokes an increased hydrostatic venous pressure that, combined to the incapacity to reduce venous pressure with regular stimulation of peripheral muscle pump[53] leads to venous stasis inducing a high risk of varicose veins and thrombosis. Using ultrasound Doppler, Labropoulos et al.[16] were the to demonstrate that people with occupations involving prolonged standing position (as vascular surgeons) without symptoms of venous insufficiency, had a higher risk of venous reflux in lower limbs compared to unexposed people, suggesting that prolonged standing leads to superficial venous incompetence.

Consequences of time spent sitting, walking, carrying heavy loads at work were little explored, and were not found to significantly increase the risk of varicose veins.

Walking is supposed to favour venous return due to the calf muscular contraction. Only one study considered standing and walking in the same variable. People working more than 4 hours/day were at high risk of varicose. In this study, stamping on feet rather than walking was probably considered[33]. Only one study dealing with heat exposure and varicose was retrieved, without any significant risk. It could be of interest to investigated potential occupations at risk such as cooks, bakers, dry-cleaner's or foundry employees.

Overall, these results need to be confirmed by future prospective studies.

Venous thromboembolism

Several occupational constraints have been studied in link with DVT and PE, but the types of occupational constraints and the results differ substantially from those studied for LLVV. While cases of VTE following immobility due to playing computer games (designated as 'e-thrombosis') is documented by several case reports[54], the studies specifically focused on the link between DVT/PE and working conditions imposing a prolonged sitting time are more scarce: three case-control studies[40 41 43] found an increased risk with extended sitting-time, while the only prospective study[38] did not confirm it. However, strong and complex pathophysiological mechanisms support this link. According to Virchow's triad, venous stasis is one of the main components of the thrombotic risk.

As exposure durations to prolonged sitting while playing computer (12-48 hours as described in several case-reports) are not comparable to exposure durations of prolonged sitting during working day periods (8-10 hours/day), results regarding playing computer are hard to transpose to general working population. More researches are needed to reinforce the hypothesis that sitting time at work could be considered as an occupational risk of DVT, notably by distinguishing in detail time spent sitting at work and out of work (including leisure such as gaming, reading, watching TV, eating…) and also the number of years of exposure.

If the risk of DVT in air travel for passengers in long distance flights is well documented[55], the consequences for airline cabin crew and pilots are less investigated.

Lower limb DVT and PE also appear to be related to persistent stress and low socioeconomic level[37 39]. The 2014 literature review of Austin et al.[56] on stress and hemostasis suggested that stress at work could be associated to elevated levels of fibrinogen and clotting factor VII and to decreased fibrinolysis capacity. Low socioeconomic status (before instance determined with education attainment and social class) can induce chronic stress. Low socioeconomic status has been found to be associated to elevated levels of fibrinogen, factor VII, and von Willebrand factor. Moreover, men with high job strain exposed to acute stress had higher von Willebrand factor levels. On the contrary, those who felt happy during the day at work had lower levels of fibrinogen after adjusting for sociodemographic factors and cardiovascular risk factors.

Prevention measures have been described in the literature and some recommendations for people suffering lower limb DVT or PE have been suggested: take breaks regularly in order to move the legs, and develop reminder systems to encourage to get up every 30-60 minutes[45]. Mitsuya et al.[57] have suggested to sit in a reclining posture and occasionally use a footrest, stretch the legs, and walk 10 min during breaks. However, studies to assess the effectiveness of such recommendations are still needed.

Consequences of the occupational exposure to chemical toxics on DVT or PE have been scarcely explored. However, it would be interesting to investigate this topic in future research. Indeed even if mechanisms are not fully similar with DVT or PE, occupational exposure to organic solvents has been pointed out as a potential novel risk factor for pulmonary veno-occlusive disease[58].

Arterial diseases

Few studies have explored the link between arterial disease and occupational constraints. It is surprising given that these arterial diseases are, among others, related to hypertension and that some occupational factors are suspected to increase blood pressure, notably by occupational stress.

Regarding lower limbs intermittent claudication, workers who seem to be the most affected are the manual workers. These observations are probably linked to the fact that manual worker usually have more physical activity during their job revealing by the effort ischemia, a peripheral arterial disease that can be completely asymptomatic in subjects not practicing physical efforts. Contrary to upper limbs arteritis[5], no link with vibrations has been demonstrated.

Endothelial vascular dysfunction induced by noise exposure is suspected by assuming the role of the adrenergic system[59] which can explain an increased incidence of arterial hypertension, myocardial infarction, heart failure, and stroke. However, no study has specifically explored the relation between noise exposure and peripheral arterial diseases and aneurism.

Strengths and limitation at study and outcome level

PRISMA guideline was used to select all the studies, giving transparency and homogeneity in method used, and reproducibility of searches.

Depending on the type of vascular disease or on the type of occupational exposures, the number of studies retrieved is quite different. Thirty-four studies were retained on lower limb peripheral venous diseases while there were only three studies on peripheral arterial diseases for which the potential role of occupational constraints was little explored.

No interventional trials, allowing to provide a better level of evidence than the observational studies included in this review (17 cross-sectional, 8 prospective and 6 retrospective studies, and 6 case reports), were found.

The case-control studies can induce difficulties to describe the working conditions accurately (memory bias). Moreover, the outcomes were measured differently for some vascular disease, such as varicose measured by ultrasound Doppler (which constitutes Gold standard method), or by self-questionnaires, or by phone interviews.

Given the numerous exposure assessment methods (occupational status, number of hours exposed), the few studies available for each vascular disease, the different thresholds of exposure used, and the differences in the recruitment of the studied populations, carrying out meta-analyses did not seem adapted to the included studies. But it could be conducted and be more informative if new studies, particularly prospective ones, are undertaken. Thus, the evidence of the potential associations between vascular diseases and occupational constraints were assessed based on the number and quality of the studies, and on the consistency of the results.

Strengths and limitation at review level

Only the articles written in English and French were included in this review which can induce a weak selection bias.

Publication bias cannot be excluded. Indeed, positive studies are more likely to be published, possibly explaining the small number of articles retrieved on arterial diseases. Also, the bias of multiple publications from the same study population must be considered (e.g. Danish population register[31 32]).

The quality of the studies evaluated with the most recent quality scales (NOS, CARE) and by the latest publication guidelines (Strobe checklist) often varied according to the year of publication. Indeed, we choose to include all studies whatever the date of publication, which can lead to a low-quality assessment score considering the guidelines used at this time.

The NOS is very often used in systematic review to evaluate quality of observational studies. However, there are some limits to use this scale[60]. Indeed, most of retained studies in this review are case-control studies, often undertaken in specific population with no possibility to extend to general population, leading to a lower quality score even when the results are interesting.

Moreover, quality assessment of the studies relied only the information reported in the articles which can be subject to selective presentation (e.g., omission of non-significant results evaluated as not relevant by the authors). This current review is concerned by this limitation as are most of the reviews undertaken.

CONCLUSION

In regard to the results, it seems that there are some associations between occupational exposures and peripheral vascular diseases, with more data on venous vascular diseases than arterial diseases.

Although some links between occupational conditions (as prolonged standing time and varicose or sitting time and DVT) have been suggested, there is no sufficient evidence to determine a precise threshold of exposure due to the heterogeneity of the studies. Thus, none of the concerned vascular diseases are sufficiently documented to be considered as official occupational diseases.

Some little explored occupational constraints, such as carrying heavy loads, stress at work, and exposure to high temperatures have emerged more recently notably in relation to LLVV but need to be better explored. Finally, more prospective studies on the topic are still needed, especially multidisciplinary studies encompassing vascular surgeons, vascular clinicians, occupational physicians, and general practitioners, to complete and to update the knowledge on the relationship between occupational exposures and vascular diseases.

ACKNOWLEDGMENTS

Pr Vanina Bongard for her advice.

DISCLOSURE

The authors have no conflict of interest.

SOURCES OF FUNDING

None.

AUTHOR CONTRIBUTIONS

MT, YE, SHYK, and JF: Conducted the article selection, and screening.

YE, and SHYK: Prepared the material and methods and results, and the discussion sections.

FXL, CC, FD, JF, and ABR: Contributed substantially to the discussion and reviewed all the manuscript.

All authors read and approve the final manuscript.

DATA SHARING

Data and material will be made available by the authors upon reasonable request (contact: corresponding author).

REFERENCES

1 Heit JA. Epidemiology of venous thromboembolism. *Nat Rev Cardiol* 2015;12:464-74.

2 DePopas E, Brown M. Varicose Veins and Lower Extremity Venous Insufficiency. *Semin Intervent Radiol* 2018;35:56-61.

3 Aboyans V, Sevestre MA, Desormais I, Lacroix P, Fowkes G, Criqui MH. [Epidemiology of lower extremity artery disease]. *Presse Med* 2018;47:38-46.

4 Altobelli E, Rapacchietta L, Profeta VF, Fagnano R. Risk Factors for Abdominal Aortic Aneurysm in Population-Based Studies: A Systematic Review and Meta-Analysis. *Int J Environ Res Public Health* 2018;15.

5 Nilsson T, Wahlstrom J, Burstrom L. Hand-arm vibration and the risk of vascular and neurological diseases-A systematic review and meta-analysis. *PLoS One* 2017;12:e0180795.

6 D'Souza JC, Franzblau A, Werner RA. Review of epidemiologic studies on occupational factors and lower extremity musculoskeletal and vascular disorders and symptoms. *J Occup Rehabil* 2005;15:129-65.

7 Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;339:b2535.

8 Cuschieri S. The STROBE guidelines. *Saudi J Anaesth* 2019;13:S31-S34.

9 Riley DS, Barber MS, Kienle GS et al. CARE guidelines for case reports: explanation and elaboration document. *J Clin Epidemiol* 2017;89:218-235.

10 Wells G, Shea B, O'Connell D et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.* 2016.

11 Hobson J. Venous insufficiency at work. *Angiology* 1997;48:577-82.

12 Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. *Ann Epidemiol* 2005;15:175-84.
13 Tuchsen F, Bach E. Occupation, morbidity, and hospital admission. *Scand J Public Health* 2011;39:141-6.
14 Chen CL, Guo HR. Varicose veins in hairdressers and associated risk factors: a cross-sectional study. *BMC Public Health* 2014;14:885.
15 Basic R, Rosic D, Ledinsky I, Lovricevic I. Orthostatics and chronic venous insufficiency in Croatian doctors of dental medicine. *Acta Clin Croat* 2014;53:3-6.
16 Labropoulos N, Delis KT, Nicolaides AN. Venous reflux in symptom-free vascular surgeons. *J Vasc Surg* 1995;22:150-4.
17 Sharif Nia H, Chan YH, Haghdoost AA, Soleimani MA, Beheshti Z, Bahrami N. Varicose veins of the legs among nurses: Occupational and demographic characteristics. *Int J Nurs Pract* 2015;21:313-20.
18 Yun MJ, Kim YK, Kang DM et al. A Study on Prevalence and Risk Factors for Varicose Veins in Nurses at a University Hospital. *Saf Health Work* 2018;9:79-83.
19 Ziegler S, Eckhardt G, Stoger R, Machula J, Rudiger HW. High prevalence of chronic venous disease in hospital employees. *Wien Klin Wochenschr* 2003;115:575-9.
20 Stewart AM, Webb JW, Hewitt D. Social medicine studies based on civilian medical board records. II. Physical and occupational characteristics of men with varicose conditions. *Br J Prev Soc Med* 1955;9:26-32.
21 Ebrahimi H, Amanpour F, Bolbol Haghighi N. Prevalence and risk factors of varicose veins among female hairdressers: a cross sectional study in north-east of Iran. *J Res Health Sci* 2015;15:119-23.
22 Kohno K, Niihara H, Hamano T et al. Standing posture at work and overweight exacerbate varicose veins: Shimane CoHRE Study. *J Dermatol* 2014;41:964-8.
23 Criqui MH, Denenberg JO, Bergan J, Langer RD, Fronek A. Risk factors for chronic venous disease: the San Diego Population Study. *J Vasc Surg* 2007;46:331-7.
24 Kontosic I, Vukelic M, Drescik I, Mesaros-Kanjski E, Materljan E, Jonjic A. Work conditions as risk factors for varicose veins of the lower extremities in certain professions of the working population of Rijeka. *Acta Med Okayama* 2000;54:33-8.
25 Tomei F, Baccolo TP, Tomao E, Palmi S, Rosati MV. Chronic venous disorders and occupation. *Am J Ind Med* 1999;36:653-65.
26 Mekky S, Schilling RS, Walford J. Varicose veins in women cotton workers. An epidemiological study in England and Egypt. *Br Med J* 1969;2:591-5.
27 Abramson JH, Hopp C, Epstein LM. The epidemiology of varicose veins. A survey in western Jerusalem. *J Epidemiol Community Health* 1981;35:213-7.
28 Fowkes FG, Lee AJ, Evans CJ, Allan PL, Bradbury AW, Ruckley CV. Lifestyle risk factors for lower limb venous reflux in the general population: Edinburgh Vein Study. *Int J Epidemiol* 2001;30:846-52.
29 Lee AJ, Evans CJ, Allan PL, Ruckley CV, Fowkes FG. Lifestyle factors and the risk of varicose veins: Edinburgh Vein Study. *J Clin Epidemiol* 2003;56:171-9.
30 Huang HK, Weng SF, Su SB et al. Standing Posture at Work Does Not Increase the Risk of Varicose Veins among Health Care Providers in Taiwan. *Med Princ Pract* 2017;26:266-272.
31 Tuchsen F, Hannerz H, Burr H, Krause N. Prolonged standing at work and hospitalisation due to varicose veins: a 12 year prospective study of the Danish population. *Occup Environ Med* 2005;62:847-50.

32 Tuchsen F, Krause N, Hannerz H, Burr H, Kristensen TS. Standing at work and varicose veins. *Scand J Work Environ Health* 2000;26:414-20.
33 Tabatabaeifar S, Frost P, Andersen JH, Jensen LD, Thomsen JF, Svendsen SW. Varicose veins in the lower extremities in relation to occupational mechanical exposures: a longitudinal study. *Occup Environ Med* 2015;72:330-7.
34 Robertson LA, Evans CJ, Lee AJ, Allan PL, Ruckley CV, Fowkes FG. Incidence and risk factors for venous reflux in the general population: Edinburgh Vein Study. *Eur J Vasc Endovasc Surg* 2014;48:208-14.
35 Chen MY, Langan S, Benchimol EI. Routinely collected electronic health data and STI research: RECORD extension to the STROBE guidelines. *Sex Transm Infect* 2016;92:2-3.
36 Kuipers S, Cannegieter SC, Middeldorp S, Robyn L, Buller HR, Rosendaal FR. The absolute risk of venous thrombosis after air travel: a cohort study of 8,755 employees of international organisations. *PLoS Med* 2007;4:e290.
37 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;6:558-64.
38 Suadicani P, Hannerz H, Bach E, Gyntelberg F. Jobs encompassing prolonged sitting in cramped positions and risk of venous thromboembolism: cohort study. *JRSM Short Rep* 2012;3:8.
39 Zoller B, Li X, Sundquist J, Sundquist K. Socioeconomic and occupational risk factors for venous thromboembolism in Sweden: a nationwide epidemiological study. *Thromb Res* 2012;129:577-82.
40 Healy B, Levin E, Perrin K, Weatherall M, Beasley R. Prolonged work- and computer-related seated immobility and risk of venous thromboembolism. *J R Soc Med* 2010;103:447-54.
41 West J, Perrin K, Aldington S, Weatherall M, Beasley R. A case-control study of seated immobility at work as a risk factor for venous thromboembolism. *J R Soc Med* 2008;101:237-43.
42 Dimberg LA, Mundt KA, Sulsky SI, Liese BH. Deep venous thrombosis associated with corporate air travel. *J Travel Med* 2001;8:127-32.
43 Braithwaite I, Healy B, Cameron L, Weatherall M, Beasley R. Venous thromboembolism risk associated with protracted work- and computer-related seated immobility: A case-control study. *JRSM Open* 2016;7:2054270416632670.
44 Aldington S, Pritchard A, Perrin K, James K, Wijesinghe M, Beasley R. Prolonged seated immobility at work is a common risk factor for venous thromboembolism leading to hospital admission. *Intern Med J* 2008;38:133-5.
45 Patel T, Cohen D. Work ergonomics and e-thrombosis: a grievous yet preventable combination. *Am J Med* 2011;124:e3-4.
46 van Beeck JL, Versfeld K, Ehrlich R. Deep vein thrombosis following prolonged kneeling: a case report. *Occup Med (Lond)* 2014;64:305-7.
47 Beasley R, Raymond N, Hill S, Nowitz M, Hughes R. eThrombosis: the 21st century variant of venous thromboembolism associated with immobility. *Eur Respir J* 2003;21:374-6.
48 Doctor N, Seth P. When Computers Can Kill—Two Unusual Cases of "E-Thrombosis" *International Journal of Clinical Medicine* 2018;9:335-340.

49 Kuipers S, Schreijer AJ, Cannegieter SC, Buller HR, Rosendaal FR, Middeldorp S. Travel and venous thrombosis: a systematic review. *J Intern Med* 2007;262:615-34.
50 Owada M, Aizawa Y, Kurihara K, Tanabe N, Aizaki T, Izumi T. Risk factors and triggers of sudden death in the working generation: an autopsy proven case-control study. *Tohoku J Exp Med* 1999;189:245-58.
51 Aparci M, Erdal M, Isilak Z et al. Enlargement of the aorta: An occupational disease? *Exp Clin Cardiol* 2013;18:93-7.
52 Cohn R. Rupture of dissecting aneurysm of the aorta. The relationship of effort to onset. *Calif Med* 1960;92:13-5.
53 Meissner MH, Moneta G, Burnand K et al. The hemodynamics and diagnosis of venous disease. *J Vasc Surg* 2007;46 Suppl S:4S-24S.
54 Lippi G, Mattiuzzi C, Favaloro EJ. e-thrombosis: epidemiology, physiopathology and rationale for preventing computer-related thrombosis. *Ann Transl Med* 2018;6:344.
55 Gavish I, Brenner B. Air travel and the risk of thromboembolism. *Intern Emerg Med* 2011;6:113-6.
56 Austin AW, Wissmann T, von Kanel R. Stress and hemostasis: an update. *Semin Thromb Hemost* 2013;39:902-12.
57 Mitsuya R, Ebine Y, Nozaki M, Noro K. Prevention of deep vein thrombosis in VDU work. *Int J Occup Saf Ergon* 2003;9:393-403.
58 Montani D, Lau EM, Descatha A et al. Occupational exposure to organic solvents: a risk factor for pulmonary veno-occlusive disease. *Eur Respir J* 2015;46:1721-31.
59 Munzel T, Schmidt FP, Steven S, Herzog J, Daiber A, Sorensen M. Environmental Noise and the Cardiovascular System. *J Am Coll Cardiol* 2018;71:688-697.
60 Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol* 2010;25:603-5.

SUPPLEMENTARY FILES

Supplementary table 1: Search terms.

Supplementary table 2: Newcastle Ottawa Score.

Supplementary figure 1: Varicose vein, flow chart for study selection, according to the PRISMA guidelines.

Supplementary figure 2: Venous thromboembolism (deep vein thrombosis and pulmonary embolism), flow chart for study selection, according to the PRISMA guidelines.

Supplementary figure 3: Aortic dissection, flow chart for study selection, according to the PRISMA guidelines.

Supplementary figure 4: Aortic aneurysm, flow chart for study selection, according to the PRISMA guidelines.

Supplementary figure 5: Intermittent claudication, flow chart for study selection, according to the PRISMA guidelines.

Supplementary table 1: Search terms.

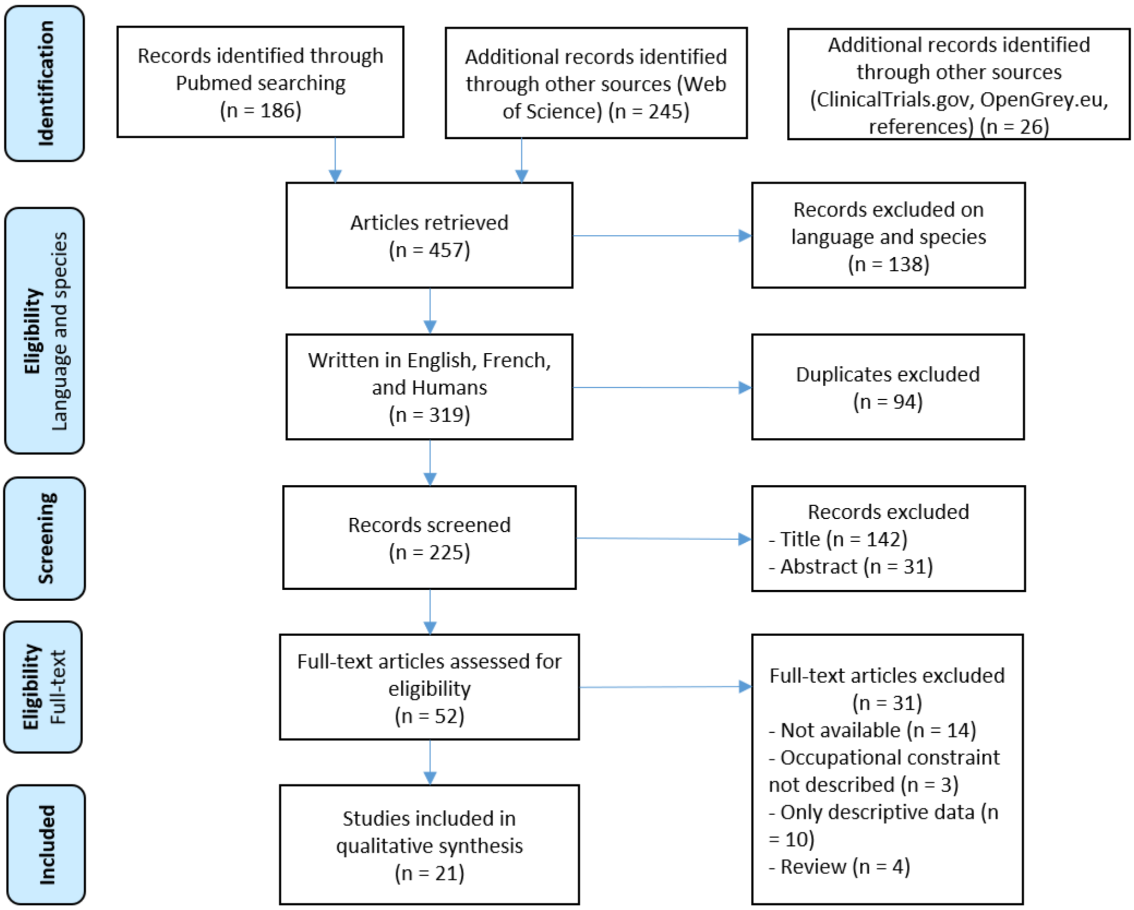
Lower limb varicose veins	**Deep vein thrombosis and pulmonary embolism**
- Varicose AND occupation OR occupational - Chronic venous insufficiency AND occupation OR occupational - Varicose AND job - Chronic venous insufficiency AND job - Varicose AND employment - Chronic venous insufficiency AND employment	- Deep vein thrombosis AND occupation OR occupational - Phlebitis AND occupation OR occupational - Pulmonary embolism AND occupation OR occupational - Venous thromboembolism AND occupation OR occupational - Deep vein thrombosis AND job - Phlebitis AND job - Pulmonary embolism AND job - Venous thromboembolism AND job - Deep vein thrombosis AND employment - Phlebitis AND employment - Pulmonary embolism AND employment - Venous thromboembolism AND employment
Intermittent claudication	**Aortic dissection**
- Claudication of the lower limb AND occupation OR occupational - Arteriopathy of the lower limb AND occupation OR occupational - Obliterating arteriopathy of the lower limb AND employment - Obliterating arteriopathy of the lower limb AND occupation OR occupational - Claudication of the lower limb AND job - Arteriopathy of the lower limb AND job - Intermittent claudication AND job - Obliterating arteriopathy of the lower limb AND job	- Aortic dissection AND occupation OR occupational - Aortic dissection AND job - Aortic dissection AND employment **Aortic aneurysm** - Aortic aneurysm AND occupation OR occupational - Aortic aneurysm AND job - Aortic aneurysm AND employment

Supplementary table 2: Newcastle Ottawa Score

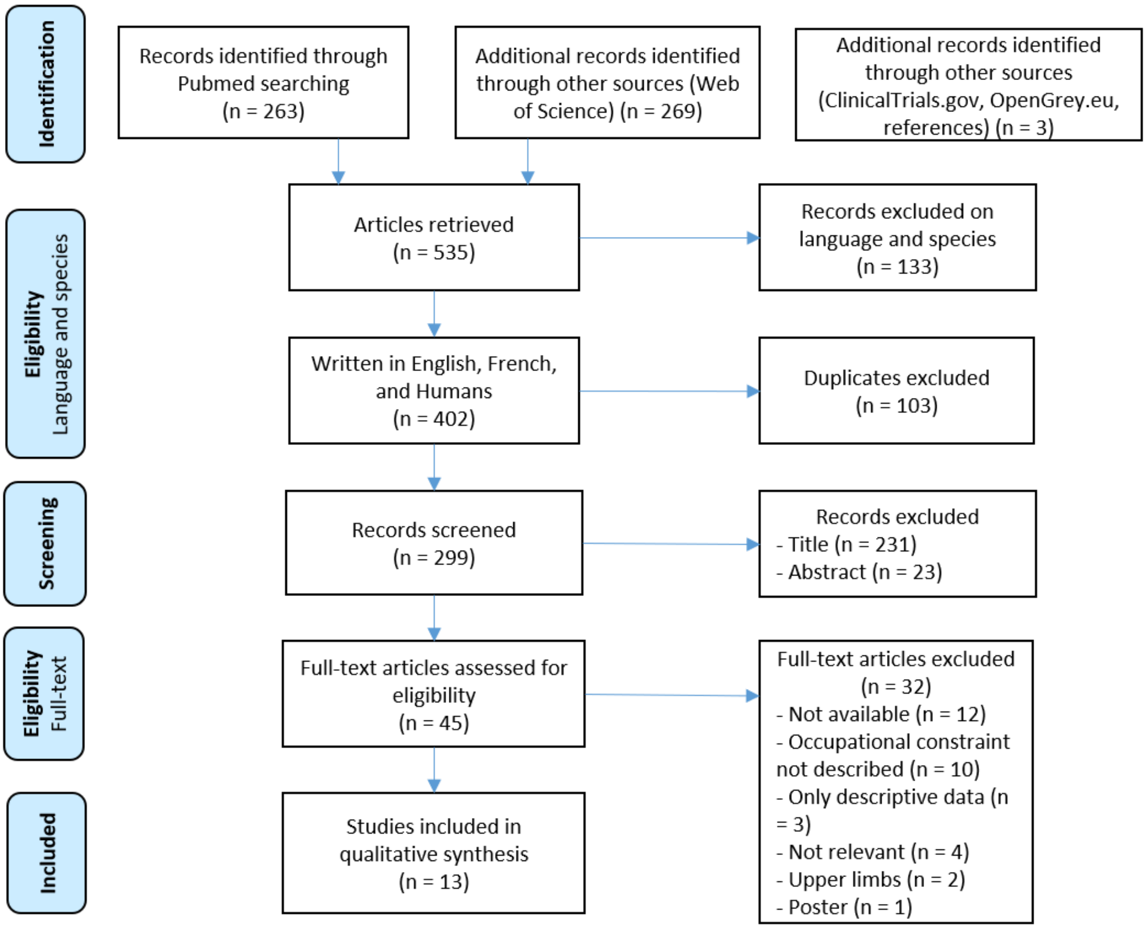
Varicose veins				
Cross-sectional studies	**Selection (max. 5★)**	**Comparability (max. 2★)**	**Outcome (max. 3★)**	**Max. 10★**
Stewart et al. 1955	★		★★★	4
Mekky et al. 1969			★★	2
Abramson 1981	★★★	★	★★★	7
Labropoulos 1995	★	★	★★	4
Tomei et al. 1999	★	★	★★★	5
Kontosic et al. 2000	★★	★★	★★★	7
Fowkes et al 2001	★★★★	★	★★	7
Lee et al 2003	★★★★	★	★★★	8
Ziegler et al 2003			★★	2
Criqui et al 2007	★	★★	★★★	6
Basic et al. 2014	★	★		2
Chen et al. 2014	★★	★★	★★	6
Kohno et al 2014	★	★★	★★★	6
Ebrahimi et al 2015		★	★★★	4
Sharif et al. 2015	★★	★★	★★	6
Yun et al. 2018	★★		★★★	5
Prospective studies	**Selection (max. 4★)**	**Comparability (max. 2★)**	**Outcome (max. 3★)**	**Max. 9★**
Tuchsen et al. 2000	★★★★	★★	★★	8
Tuchsen et al. 2005	★	★★	★★	5
Robertson et al. 2014	★★★★	★	★★★	8
Tabatabaeifar et al. 2015	★★★★	★★	★★	8
Retrospective study	**Selection (max. 4★)**	**Comparability (max. 3★)**	**Outcome (max. 3★)**	**Max. 9★**
Huang et al. 2017	★★	★★	★★	6
Venous Thromboembolism				
Case-Control studies	**Selection (max. 4★)**	**Comparability (max. 3★)**	**Outcome (max. 3★)**	**Max. 9★**
Dimberg et al. 2001	★★	★★	★★	6
West et al. 2008	★★	★★	★	5
Healy et al. 2010	★★	★★	★	5
Braithwaite et al. 2016	★★★	★★	★	6
Prospective studies	**Selection (max. 4★)**	**Comparability (max. 3★)**	**Outcome (max. 3★)**	**Max. 9★**
Kuipers et al 2007	★★★★	★	★★	7
Rosengreen et al. 2008	★★	★★	★★	6
Suadiciani et al. 2012	★★★	★	★★★	7
Zoller 2012	★★★	★★	★★★	8
Arterial diseases				

Case-Control (dissection)	**Selection (max. 4★)**	**Comparability (max. 2★)**	**Outcome (max. 3★)**	**Max. 9★**
Owada et al.	★★★★	★★	★	7
Cross-sectional study (aneurism)	**Selection (max. 5★)**	**Comparability (max. 2★)**	**Outcome (max. 3★)**	**Max. 10★**
Aparci et al. 2013	★	★	★★★	5

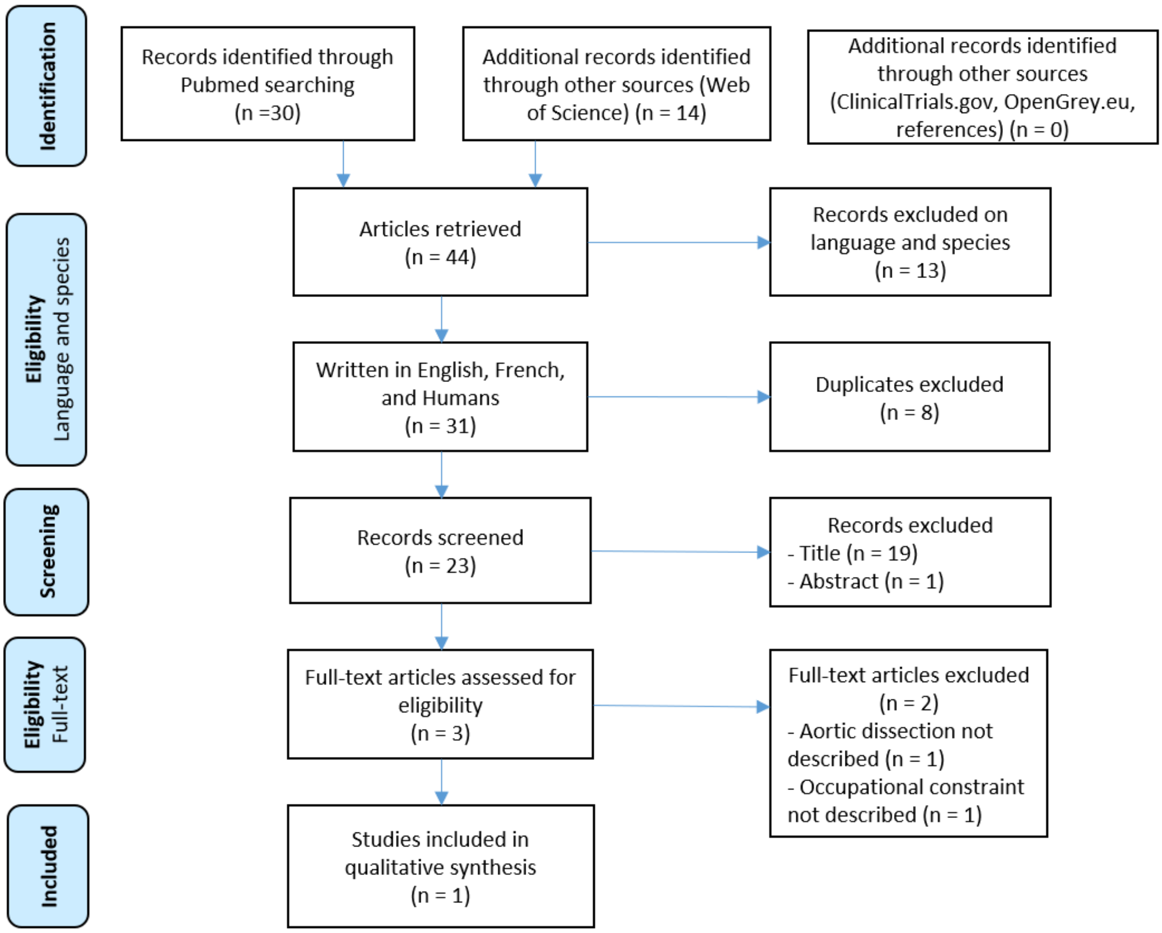
Supplementary figure 1: Varicose vein, flow chart for study selection, according to the PRISMA guidelines.



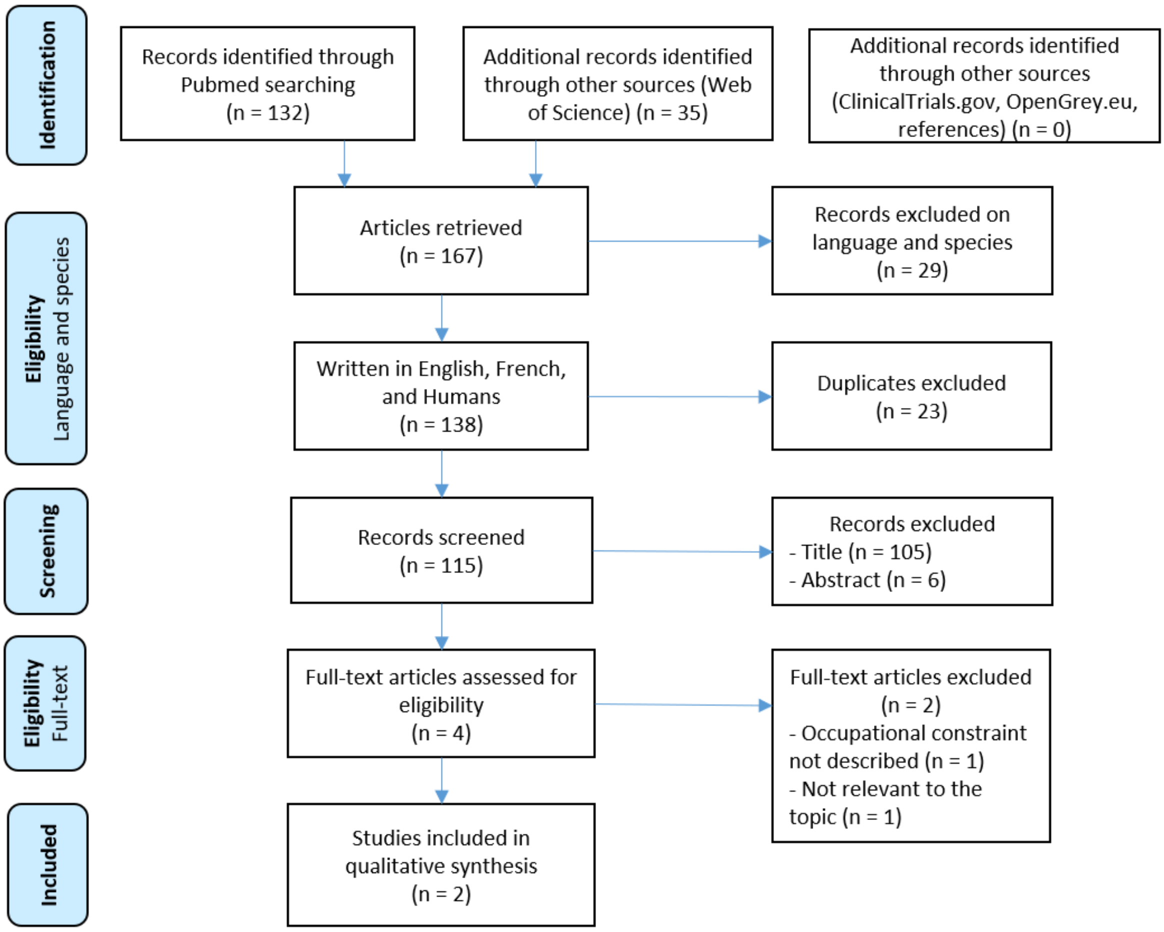
Supplementary figure 2: Venous thromboembolism (deep vein thrombosis and pulmonary embolism), flow chart for study selection, according to the PRISMA guidelines



Supplementary figure 3: Aortic dissection, flow chart for study selection, according to the PRISMA guidelines.



Supplementary figure 4: Aortic aneurysm, flow chart for study selection, according to the PRISMA guidelines.



Supplementary figure 5: Intermittent claudication, flow chart for study selection, according to the PRISMA guidelines.