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

Samantha Huo Yung Kai1*, Jean Ferrières2, Camille Carles3, Marion Turpin4, François-Xavier Lapébie5, Frederic Dutheil6, Alessandra Bura-Riviere7, Yolande Esquirol8

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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\textsuperscript{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 28\textsuperscript{th} 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, 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\textsuperscript{11}, and 2005\textsuperscript{12} which provided only prevalence and incidence data were excluded. An article\textsuperscript{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>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Study design, country, follow-up or recruitment period</th>
<th>Participants (gender, age)</th>
<th>Vascular Events</th>
<th>Occupational constraints and environmental exposures</th>
<th>Confounders</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stewart et al. 1955</strong></td>
<td>Cross-sectional England and Egypt Recruitment: 1964-1966</td>
<td>Three English regions 3,582♂&lt;45 yo</td>
<td>Varicose veins (Civilian Medical Board records)</td>
<td>Occupational status standardized on age and region</td>
<td></td>
<td>Standardized prevalence ratios in occupational groups: Boot and Shoe: 116 (p&lt;0.001) Clerical: 69 (p&lt;0.001) Professional and administrative: 81 (p&lt;0.01)</td>
<td>Strobe: 13/22 NOS: 4/10</td>
</tr>
<tr>
<td><strong>Abramson 1981</strong></td>
<td>Cross-sectional Israel Recruitment: 1969-1971</td>
<td>Western Jerusalem 2,245♂92,557♀</td>
<td>Varicose veins (clinical examination)</td>
<td>Time spent sitting, standing, and walking during working hours; lifting or carrying of heavy weights, physical exertion (interview at home) age, gender</td>
<td></td>
<td>Much standing (ref: Little standing): OR= 1.6 (p&lt;0.01) Lifting or carrying of heavy weights, physical exertion at work: no significant associations</td>
<td>Strobe: 17/22 NOS: 7/10</td>
</tr>
<tr>
<td><strong>Labropoulos 1995</strong></td>
<td>Cross-sectional Recruitment: 1991-1994</td>
<td>28 vascular surgeons 25 normal volunteers men, 29-45 yo</td>
<td>Venous reflux in the lower extremities (colour-flow duplex imaging)</td>
<td>Prolonged standing age</td>
<td></td>
<td>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)</td>
<td>Strobe: 10/22 NOS: 4/10</td>
</tr>
<tr>
<td><strong>Tomei et al. 1999</strong></td>
<td>Cross-sectional Italy</td>
<td>Industrial workers, stoneworkers, office workers 308♂</td>
<td>Chronic venous disorders (clinical examination by a trained physician)</td>
<td>Standing, sitting, walking during working time (questionnaire) job classification</td>
<td></td>
<td>Prevalence: industrial workers (39.28%), stoneworkers (24.16%) and office workers (22.11%) Standing for 50% of the work shift (ref: &lt;50%): OR= 1.07, p&lt;0.001</td>
<td>Strobe: 13/22 NOS: 5/10</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Location</td>
<td>Subjects</td>
<td>Mean Age</td>
<td>Diagnosis</td>
<td>Occupational Status</td>
<td>Exposure Factors</td>
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<tr>
<td>Kontosic et al. 2000</td>
<td>Cross-sectional</td>
<td>Rijeka Community, Croatia</td>
<td>♂530♀794</td>
<td>36-39</td>
<td>Varicose veins</td>
<td>Standing, moving, lifting, high temperature</td>
<td>Gender, age, BMI, flat feet, duration of fertile period/pregnancies/deliveries, family history of varicose veins</td>
</tr>
<tr>
<td>Fowkes et al. 2001</td>
<td>Cross-sectional</td>
<td>Registers of 12 general practices</td>
<td>♂609♀739</td>
<td>18-64</td>
<td>Varicose vein</td>
<td>Visual analogue scales of time spent sitting, standing, walking, and heavy lifting (never to all the time) (self-administered questionnaire)</td>
<td>Stratified on gender; age, gastrointestinal habits, smoking, BMI</td>
</tr>
<tr>
<td>Lee et al. 2003</td>
<td>Cross-sectional</td>
<td>Registers of 12 general practices</td>
<td>♂699♀867</td>
<td>18-64</td>
<td>Varicose vein</td>
<td>Visual analogue scales of time spent sitting, standing, walking, and heavy lifting (never to all the time) (self-administered questionnaire)</td>
<td>Stratified on gender; age, diet intake, BMI, smoking</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Country</th>
<th>Recruitment/Age</th>
<th>Diagnosis/Examination</th>
<th>Occupation</th>
<th>Risk Factors/Stratification</th>
<th>Results</th>
<th>Strobe:</th>
<th>NOS:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ziegler et al 2003</td>
<td>Cross-sectional</td>
<td>Austria</td>
<td>Vienna’s general hospital, employees</td>
<td>Chronic venous disease (CEAP classification)</td>
<td>Group 1: medical doctors and nurses Group 2: medical technician assistants, secretaries and scientific staff Group 3: cleaners and utility workers (self-questionnaire)</td>
<td>none</td>
<td>Occurrence of CVD according to groups, p&lt;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&lt;0.02: ♂ 4.4 / 2.7 ♀ 3.9 / 3.2</td>
<td>13/22</td>
<td>2/10</td>
</tr>
<tr>
<td>Criqui et al 2007</td>
<td>Cross-sectional</td>
<td>USA</td>
<td>Current and retired employees of the University of California, San Diego</td>
<td>Varicose veins (doppler examination, CEAP classification)</td>
<td>Occupational status (laborers, no laborers)</td>
<td>age, ethnicity</td>
<td>Laborers, men (ref: no laborer): OR= 3.24 (1.21, 8.67)</td>
<td>15/22</td>
<td>6/10</td>
</tr>
<tr>
<td>Basic et al. 2014</td>
<td>Cross-sectional</td>
<td>Croatia</td>
<td>60 dentists (median 42 yo) 60 other occupation (median 38 yo) Gender unknown</td>
<td>Lower limb varicose veins (questionnaire, ultrasonograph y)</td>
<td>Being a dentist</td>
<td>none</td>
<td>No statistically significant difference between-group according to the presence of varicose leg veins (p=0.835)</td>
<td>7/22</td>
<td>2/10</td>
</tr>
<tr>
<td>Chen et al. 2014</td>
<td>Cross-sectional</td>
<td>Southern Taiwan</td>
<td>♂15 ♀166 average age 45.8 yo</td>
<td>Lower limb varicose veins (self-administered questionnaire)</td>
<td>Hairdressers Prolonged standing at work (self-administered questionnaire)</td>
<td>stratified on age (≤45 yo, &gt;45 yo)</td>
<td>Monthly standing work hours (ref &lt;120 hours; OR for ≤ 45 yo and &gt; 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)</td>
<td>14/22</td>
<td>6/10</td>
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<tr>
<td>Kohno et al 2014</td>
<td>Cross-sectional</td>
<td>Japan</td>
<td>♂113 ♀205 ≥45 yo</td>
<td>Varicose veins (doppler examination, CEAP classification)</td>
<td>Occupation, duration of standing per day</td>
<td>BMI, gender, age, family history, physical activity, lumber corset, history of</td>
<td>Standing at work (ref: No or &lt;5 h a day): With substantial movement: OR= 0.89 (0.40, 1.98) Upright posture: OR= 1.98 (1.04, 3.77)</td>
<td>16/22</td>
<td>6/10</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Recruitment Year</td>
<td>Gender</td>
<td>Mean Age</td>
<td>Varicose Veins (diagnostic methods)</td>
<td>Number of Working Hours in Static &amp; Siting Positions</td>
<td>Number of Consecutive Service Years</td>
<td>Duration of Standing per Day</td>
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<tr>
<td>Ebrahimi et al. 2015</td>
<td>Cross-sectional</td>
<td>Iran</td>
<td>2012</td>
<td></td>
<td>18-68 yo</td>
<td>Varicose veins (questionnaire + standard physical examination, severity score)</td>
<td>Duration of standing per day</td>
<td>age, BMI, pregnancy, family history, high blood pressure, oral contraceptive, constipation</td>
<td>Duration of Standing per day (ref: ≤3 hours):</td>
</tr>
<tr>
<td>Sharif et al. 2015</td>
<td>Cross-sectional</td>
<td>Iran</td>
<td>2010</td>
<td></td>
<td></td>
<td>Varicose veins (CEAP classification: clinical degrees, C0 to C6)</td>
<td>Time sitting, standing, walking posture, and overtime (self-questionnaire)</td>
<td>gender, age, BMI, education level, family history</td>
<td>Leg varicose intensity (C0-C6) and standing (ref: &lt;2 h):</td>
</tr>
<tr>
<td>Yun et al. 2018</td>
<td>Cross-sectional</td>
<td>Korea</td>
<td>2014</td>
<td></td>
<td>Mean age 30 yo</td>
<td>Varicose veins (doppler ultrasound)</td>
<td>Number of daily working hours in a static standing, walking, and sitting position number of consecutive service years (questionnaire)</td>
<td>age, pregnancy, compression stocking period</td>
<td>Work posture (ref: &lt;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)</td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Country</td>
<td>Follow-up Period</td>
<td>Data Source</td>
<td>Exposure Factors</td>
<td>Outcome</td>
<td>Results</td>
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</tbody>
</table>
| Tuchsen et al. 2000| Prospective       | Denmark       | 1991-1993        | Central population register♂727 145 9878 756 20-59 yo (random sample of 5,940 participants) | Varicose veins (ICD-8: 454) from hospital register | 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       | 1991-2002        | Central population register♂2,939 92,708 20-59 yo                          | Varicose veins (ICD-8: 454, ICD-10:183) from hospital register | 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      | 1991-2002        | Registers of 12 general practices♂390 9490 18-64 yo                      | Varicose vein (clinical examination, Basle Study classification), Venous reflux (Duplex scan) | 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       | 1980-2011        | Musculoskeletal Research Database (MRD) at the Danish Ramazzini Centre♂16,259 921,777 18-65 yo mean 42-45 yo | Varicose veins surgery (ICD-8: 454, ICD-10:183) hospital register | 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 |
<table>
<thead>
<tr>
<th>Huang et al. 2017</th>
<th>Retrospective cohort Taiwan Period: 2007-2011</th>
<th>National Health Insurance Research Database: Physician $#24,802/#4,042$ Non-physician $#7,984/#18,115$ General population (matched 1:1)</th>
<th>Varicose veins (ICD-9)</th>
<th>Occupation: physician, non-physician health care providers</th>
<th>age, gender, deep venous thrombosis</th>
<th>Ref: general population Being a physician: OR=0.86 (0.53, 1.40) Being a non-physician: OR=1.43 (0.82, 2.50)</th>
<th>Strobe: 18/22 NOS: 6/9</th>
</tr>
</thead>
</table>

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, 1 retrospective study, with 54,943 physicians and non-physicians, and 4 prospective studies including two conducted in the same population, 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 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. 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\textsuperscript{17, 21, 33, 35} but not for Yun et al. study\textsuperscript{18} and Edinburgh studies\textsuperscript{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\textsuperscript{17}.

In population in age to be employed, Tuchsen 2000 at al.\textsuperscript{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\textsuperscript{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\textsuperscript{17, 18} and from the Edinburgh study, sitting time at work appeared to be protective on vein reflux only in women\textsuperscript{28, 29}

Only one study investigated the exposition to high temperatures at work with no significant association\textsuperscript{24}.

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

17
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\textsuperscript{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\textsuperscript{40,41} including respectively 97 and 192 cases, one among insured bank staff \textsuperscript{42}, and one from clinic services\textsuperscript{43} and five case-reports\textsuperscript{44-48}. 
<table>
<thead>
<tr>
<th>Authors, year of publication</th>
<th>Study design, country, follow-up or recruitment period</th>
<th>Participants (gender, age)</th>
<th>Vascular Events</th>
<th>Occupational constraints and environmental exposures</th>
<th>Confounders</th>
<th>Results</th>
<th>Quality assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beasley et al. 2003</td>
<td>Case report</td>
<td>♂ 32 yo</td>
<td>PE (pulmonary angiography)</td>
<td>Sitting for long periods at a computer (at work and at home)</td>
<td>NA</td>
<td>Regularly 12 h per day (up to 18 h) spent sitting at his computer</td>
<td>Care: 18/29</td>
</tr>
<tr>
<td>Aldington 2008</td>
<td>Case series</td>
<td>♂ 38 ♀ 23 17-64 yo</td>
<td>Lower limb DVT (imaging)</td>
<td>Prolonged seated immobility at work in the 4 weeks before VTE event</td>
<td>NA</td>
<td>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%)</td>
<td>Care: 9/29</td>
</tr>
<tr>
<td>Patel et al. 2011</td>
<td>Case reports USA</td>
<td>Case 1: ♂ 38 yo Case 2: ♂ 39 yo</td>
<td>Case 1: lower limb DVT (doppler ultrasound) Case 2: Bilateral PE (CT scan)</td>
<td>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</td>
<td>NA</td>
<td>Prolonged sitting period at work, with no other known risk factors</td>
<td>Care: 13/29</td>
</tr>
<tr>
<td>Van Beeck et al. 2014</td>
<td>Case report South Africa</td>
<td>♂ 41 yo</td>
<td>Lower limb DVT (ultrasound)</td>
<td>Mould maker, tooling department, boat building company Prolonged kneeling</td>
<td>NA</td>
<td>Lower limb deep vein thrombosis Have worked during about 6 weeks, in a kneeling position, 8 hours/day</td>
<td>Care: 9/29</td>
</tr>
<tr>
<td>Doctor and Seth 2018</td>
<td>Case reports</td>
<td>Case 1: ♂ 50 yo Case 2: ♂ 18 yo</td>
<td>DVT (ultrasound duplex imaging)</td>
<td>Case 1: software professional Case 2: student</td>
<td>NA</td>
<td>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</td>
<td>Care: 16/29</td>
</tr>
<tr>
<td>Study</td>
<td>Study Design</td>
<td>Recruitment Period</td>
<td>Recruitment Location</td>
<td>Cases and Controls</td>
<td>Case Definition</td>
<td>Control Definition</td>
<td>Number of Missions and Travel Days</td>
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<tr>
<td>Dimberg et al 2001</td>
<td>Case-control</td>
<td>USA</td>
<td>Washington, DC</td>
<td>World Bank staff employed and insured</td>
<td>111 cases (81♂, 30♀)</td>
<td>Phlebitis, thrombophlebitis or thromboembolism (definition 1); lower limb DVT (definition 2) (filed medical insurance claims, ICD-9)</td>
<td>Number of missions and travel days, Days since last mission</td>
</tr>
<tr>
<td>WEST et al. 2008</td>
<td>Case-control</td>
<td>New Zealand</td>
<td>Wellington Hospital</td>
<td>97 cases (VTE clinic, 58.8%), mean age=44.9 yo (SD 13.1)</td>
<td>106 controls (Coronary Care Unit, 54.6%), mean age=52.4 yo (SD 9.7)</td>
<td>VTE (DVT, PE) (Doppler ultrasound, pulmonary angiography, scan)</td>
<td>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)</td>
</tr>
<tr>
<td>HEALY et al. 2010</td>
<td>Case-control</td>
<td>New Zealand</td>
<td>Wellington Hospital</td>
<td>192 cases (VTE clinic, 48.7%), 195 controls (Coronary Care Unit, 26.9%)</td>
<td>lower limb DVT, PE (Doppler ultrasound, pulmonary angiography, scan)</td>
<td>Prolonged work- and computer at home-related seated immobility (interviewer administered questionnaire)</td>
<td>age, gender, family history of VTE, medical risk factors, personal history of VTE</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Recruitment/ Follow-up</td>
<td>Cases/Controls</td>
<td>Exposure</td>
<td>Outcome</td>
<td>Confounders</td>
<td>Results</td>
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<tr>
<td>Braithwaite et al. 2016</td>
<td>Case-control</td>
<td>New Zealand</td>
<td>200 cases (Venous thromboembolism service) 200 controls (Orthopaedic service) 18-65 yo</td>
<td>Seated at work, and/or on the computer at home in a 24-h period (interviewer-administered questionnaire)</td>
<td>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)</td>
<td>Mean work/computer seated (per hour) OR= 1.08 (1.01, 1.6)</td>
<td>200 cases (Venous thromboembolism service) 200 controls (Orthopaedic service) 18-65 yo</td>
</tr>
<tr>
<td>Kuipers et al. 2007</td>
<td>Prospective</td>
<td>Follow-up: 2000-2005</td>
<td>International companies and organisations: 8,755♂ 44%♀ 56%</td>
<td>DVT (compression ultrasonography or venography), PE (CT scanning)</td>
<td>Number of flights per employee per year (internet-based questionnaire)</td>
<td>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)</td>
<td>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)</td>
</tr>
<tr>
<td>Rosengren et al. 2008</td>
<td>Prospective</td>
<td>Sweden</td>
<td>Mean follow-up: 22.9 years</td>
<td>Lower limb DVT, PE (ICD 8-10)</td>
<td>Stress (using a single question about working conditions and at home), Socio-economic index</td>
<td>Age, diabetes, BMI, and height, treatment for hypertension, alcohol</td>
<td>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)</td>
</tr>
<tr>
<td>SUADICANI et al. 2012</td>
<td>Prospective Denmark Follow-up: 1997-2006</td>
<td>Danish Occupational Hospitalisation Register 105,564 sedentary workers (♀ 5.4%) 283,966 dynamic workers (♀ 5.5%) 20-59 yo</td>
<td>Death, lower limb DVT, PE (ICD 10)</td>
<td>Jobs encompassing prolonged sitting, drivers vs. construction workers (Statistics Denmark’s Standard Classification of Occupations)</td>
<td>age, gender</td>
<td>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)</td>
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<tr>
<td>Zoller 2012</td>
<td>Prospective Sweden Follow-up: 1990-2007</td>
<td>Total Population Register and the Swedish Hospital Discharge Register σ 23,464 Η 19,599</td>
<td>Lower limb DVT, PE (ICD 9-10)</td>
<td>Socio-economic status and occupations (n=53) (Statistics Denmark’s Standard Classification of Occupations)</td>
<td>age, time period, region of residence, immigrant status, and comorbidity stratified by gender</td>
<td>White-collars: - σ SIR=0.96 (0.94, 0.99) - Η SIR=0.93 (0.91, 0.95) Blue-collars: - σSIR=1.03 (1.01, 1.05) - Η SIR=1.05 (1.03, 1.08)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 footnote:
- σ, men
- Η, 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\textsuperscript{38, 40, 41} \textsuperscript{43} and case reports\textsuperscript{44, 45, 47, 48} with contrasted results. Only the studies undertaken from the Wellington Hospital register\textsuperscript{40, 41} and clinical services\textsuperscript{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\textsuperscript{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\textsuperscript{46}. A 41-year-old man presented with DVT in the left lower limb without no thrombosis risk factors. The involvement of kneeling 8
24 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\textsuperscript{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.\textsuperscript{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\textsuperscript{39}.

Air travel is a known risk factor of DVT (2 to 4 fold risk increase)\textsuperscript{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.\textsuperscript{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\textsuperscript{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

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

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.\textsuperscript{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.

\textbf{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.\textsuperscript{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\textsuperscript{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\textsuperscript{14 18 19 21 22 24 28 31-34}, walking\textsuperscript{18 28 33 34}, sitting\textsuperscript{17 18 26 28}, working overtime\textsuperscript{17}, and heavy lifting\textsuperscript{24 28 29 31}.  

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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\textsuperscript{33} and for nurses\textsuperscript{17} studies, >3 hours for hairdressers\textsuperscript{21}, 5 hours only for people who have upright standing posture without some movements in the same time for Kohno study\textsuperscript{22}. Moreover, this link was not confirmed by Yun\textsuperscript{18}, Kontosis\textsuperscript{24} and Edinburgh\textsuperscript{34} studies, using dichotomized variables: > 4hours/day vs <4 hours/day or exposed vs unexposed people. Chen et al.\textsuperscript{14} found only significant results in hairdressers aged more than 45 years old (with large confidence intervals) and Tuchsen et al.\textsuperscript{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\textsuperscript{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\textsuperscript{53} leads to venous stasis inducing a high risk of varicose veins and thrombosis. Using ultrasound Doppler, Labropoulos et al.\textsuperscript{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. 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, 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 found an increased risk with extended sitting-time, while the only prospective study 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, 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. The 2014 literature review of Austin et al. 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. Mitsuya et al. 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{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.

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DISCLOSURE

The authors have no conflict of interest.

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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


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.

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<thead>
<tr>
<th>Lower limb varicose veins</th>
<th>Deep vein thrombosis and pulmonary embolism</th>
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<td>- Varicose AND occupation OR occupational</td>
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<td>- Chronic venous insufficiency AND occupation OR occupational</td>
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<td>Intermittent claudication</td>
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### Supplementary table 2: Newcastle Ottawa Score

#### Varicose veins

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<tr>
<th>Cross-sectional studies</th>
<th>Selection (max. 5★)</th>
<th>Comparability (max. 2★)</th>
<th>Outcome (max. 3★)</th>
<th>Max. 10★</th>
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<tr>
<td>Stewart et al. 1955</td>
<td>★</td>
<td>★★★★</td>
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<td>Mekky et al. 1969</td>
<td>★★</td>
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<tr>
<td>Abramson 1981</td>
<td>★★★★</td>
<td>★</td>
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<tr>
<td>Labropoulos 1995</td>
<td>★</td>
<td>★★</td>
<td>★★</td>
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<tr>
<td>Tomei et al. 1999</td>
<td>★</td>
<td>★</td>
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<td>★★</td>
<td>★★</td>
<td>★★★★</td>
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<tr>
<td>Fowkes et al. 2001</td>
<td>★★★★</td>
<td>★</td>
<td>★★</td>
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<td>Lee et al. 2003</td>
<td>★★★★</td>
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<td>★★★★</td>
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<tr>
<td>Ziegler et al. 2003</td>
<td></td>
<td></td>
<td>★★</td>
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<th>Max. 9★</th>
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<td>Huang et al. 2017</td>
<td>★★</td>
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#### Venous Thromboembolism

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<th>Case-Control studies</th>
<th>Selection (max. 4★)</th>
<th>Comparability (max. 3★)</th>
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<td>Dimberg et al. 2001</td>
<td>★★</td>
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<td>West et al. 2008</td>
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<td>Healy et al. 2010</td>
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<td>Braithwaite et al. 2016</td>
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<td>★★</td>
<td>★★</td>
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<table>
<thead>
<tr>
<th>Prospective studies</th>
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<th>Comparability (max. 3★)</th>
<th>Outcome (max. 3★)</th>
<th>Max. 9★</th>
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<td>Kuipers et al 2007</td>
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<td>Rosengreen et al. 2008</td>
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<td>★★</td>
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<td>Suadiciani et al. 2012</td>
<td>★★</td>
<td>★</td>
<td>★★★★</td>
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<td>Zoller 2012</td>
<td>★★★★</td>
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#### Arterial diseases
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<th>Outcome (max. 3★)</th>
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<td>Case-Control (dissection)</td>
<td>★★★★</td>
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<td>★</td>
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<td>Owada et al.</td>
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<td>Cross-sectional study</td>
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<td>Max. 10★</td>
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<tr>
<td>(aneurism)</td>
<td>★</td>
<td>★</td>
<td>★★★★</td>
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<tr>
<td>Aparci et al. 2013</td>
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Supplementary figure 1: Varicose vein, flow chart for study selection, according to the PRISMA guidelines.

Identification
Records identified through PubMed searching (n = 186)
Additional records identified through other sources (Web of Science) (n = 245)
Additional records identified through other sources (ClinicalTrials.gov, OpenGrey.eu, references) (n = 26)

Eligibility
Language and species
Articles retrieved (n = 457)
Written in English, French, and Humans (n = 319)
Records excluded on language and species (n = 138)
Duplicates excluded (n = 94)

Screening
Records screened (n = 225)
Records excluded
- Title (n = 142)
- Abstract (n = 31)

Eligibility
Full-text
Full-text articles assessed for eligibility (n = 52)
Full-text articles excluded (n = 31)
- Not available (n = 14)
- Occupational constraint not described (n = 3)
- Only descriptive data (n = 10)
- Review (n = 4)

Included
Studies included in qualitative synthesis (n = 21)
Supplementary figure 2: Venous thromboembolism (deep vein thrombosis and pulmonary embolism), flow chart for study selection, according to the PRISMA guidelines

Records identified through Pubmed searching (n = 263)

Additional records identified through other sources (Web of Science) (n = 269)

Additional records identified through other sources (ClinicalTrials.gov, OpenGrey.eu, references) (n = 3)

Articles retrieved (n = 535)

Records excluded on language and species (n = 133)

Written in English, French, and Humans (n = 402)

Duplicates excluded (n = 103)

Records screened (n = 299)

Records excluded - Title (n = 231)
- Abstract (n = 23)

Full-text articles assessed for eligibility (n = 45)

Full-text articles excluded (n = 32)
- Not available (n = 12)
- Occupational constraint not described (n = 10)
- Only descriptive data (n = 3)
- Not relevant (n = 4)
- Upper limbs (n = 2)
- Poster (n = 1)

Studies included in qualitative synthesis (n = 13)
Supplementary figure 3: Aortic dissection, flow chart for study selection, according to the PRISMA guidelines.

- Records identified through Pubmed searching (n = 30)
- Additional records identified through other sources (Web of Science) (n = 14)
- Additional records identified through other sources (ClinicalTrials.gov, OpenGrey.eu, references) (n = 0)

- Articles retrieved (n = 44)
  - Records excluded on language and species (n = 13)
  - Duplicates excluded (n = 8)

- Written in English, French, and Humans (n = 31)

- Records screened (n = 23)
  - Records excluded
    - Title (n = 19)
    - Abstract (n = 1)

- Full-text articles assessed for eligibility (n = 3)

- Studies included in qualitative synthesis (n = 1)
  - Full-text articles excluded
    - Aortic dissection not described (n = 2)
    - Occupational constraint not described (n = 1)
Supplementary figure 4: Aortic aneurysm, flow chart for study selection, according to the PRISMA guidelines.

Identification
- Records identified through Pubmed searching (n = 132)
- Additional records identified through other sources (Web of Science) (n = 35)
- Additional records identified through other sources (ClinicalTrials.gov, OpenGrey.eu, references) (n = 0)

Eligibility
Language and species
- Articles retrieved (n = 167)
- Written in English, French, and Humans (n = 138)
- Records excluded on language and species (n = 29)
- Duplicates excluded (n = 23)
- Records excluded
  - Title (n = 105)
  - Abstract (n = 6)

Screening
- Records screened (n = 115)

Eligibility
Full-text
- Full-text articles assessed for eligibility (n = 4)
- Full-text articles excluded (n = 2)
  - Occupational constraint not described (n = 1)
  - Not relevant to the topic (n = 1)

Included
- Studies included in qualitative synthesis (n = 2)
Supplementary figure 5: Intermittent claudication, flow chart for study selection, according to the PRISMA guidelines.

Identification
- Records identified through Pubmed searching (n = 61)
- Additional records identified through other sources (Web of Science) (n = 23)
- Additional records identified through other sources [ClinicalTrials.gov, OpenGrey.eu, references] (n = 0)

Eligibility
- Articles retrieved (n = 84)
- Written in English, French, and Humans (n = 70)

Screening
- Records screened (n = 58)
- Duplicates excluded (n = 12)
- Records excluded: Title (n = 40), Abstract (n = 14)

Eligibility Full-text
- Full-text articles assessed for eligibility (n = 4)
- Full-text articles excluded (n = 4): Occupational constraint not described (n = 1), Intermittent claudication not identified (n = 3)

Included
- Studies included in qualitative synthesis (n = 0)