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Environmental tobacco smoke and peripheral arterial disease. A review.

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**Abstract**

**Background and aims:** Despite worldwide reductions in active smoking, non-smokers continue to be exposed to environmental tobacco smoke, especially in the home or workplace. There is a well-recognised association between active smoking and peripheral arterial disease however a relationship to environmental tobacco smoke exposure is less substantiated. The aims of this paper are to review the literature regarding the association between environmental tobacco smoke and peripheral arterial disease and identify the public health implications of findings.
Methods: Selected electronic databases (Medline, EMBASE, CINAHL, PsychINFO and Scopus) were searched for studies published up to August 2017. Key words and inclusion/exclusion criteria applied. A manual search of reference lists of studies selected for review was also performed.

Results: Of the initial 150 studies identified, 12 studies met inclusion criteria for review. Three studies demonstrated a positive association between environmental tobacco smoke exposure and definitive diagnosis of peripheral arterial disease, 6 studies demonstrated a positive association with features of vascular injury, and 3 studies found no significant positive or negative association.

Conclusions: An association between exposure to environmental tobacco smoke and development of peripheral arterial disease or clinically significant arterial injury in non-smokers is supported by moderate quality evidence in the literature. Larger, longitudinal observational studies addressing current limitations including sources of bias, inconsistency and imprecision, are needed to provide more robust and consistent evidence. Regardless, evidence of potential detrimental impacts support ongoing restrictions on freedom to smoke in public areas including the workplace and have implications for those exposed in the home environment.

Key words/ MeSH terms: Environmental tobacco smoke, tobacco smoke pollution, peripheral arterial disease, peripheral vascular disease
Introduction
The association between active smoking and peripheral arterial disease (PAD) has been established in a large number of studies[1-4], supported by a systematic review[5] with findings suggestive of a dose-response relationship. Although active smoking results in a 100-fold higher dose of inhaled smoke than passive smoking[6], environmental tobacco smoke (ETS) exposure is estimated to have contributed to 379,000 deaths from ischaemic heart disease and 21,400 from lung cancer and a total of 603,000 deaths worldwide in 2004[7]. The burden of disease may be underestimated in Australia, where an estimated 141 deaths in 2004-2005 were attributed to ETS exposure, however this does not include deaths from all related diseases[8].

A contributing factor to this mortality despite low dose of inhaled smoke is the higher toxicity of side stream smoke (SSS), emitted into the air between puffs[9]. It is estimated that ETS consists of 85% SSS and 15% exhaled main stream smoke,[9] thus many effects from passive smoking can occur even with low exposure[10]. Additionally, ETS exposure occurs without the somewhat protective factors of active smoking such as the filter and the more complete combustion that occurs at the higher temperature[9].

PAD is a manifestation of atherosclerosis associated with an annual mortality rate of 4-6% and the potential for disabling claudication symptoms.[11] Those
who develop critical limb ischaemia (CLI) have the highest mortality as lower limb amputation has a 5 year survival rate less than 30%.[11]

Prevalence increases with age, starting from childhood,[12] with overall rates thought to be 3-10%, increasing to 15-20% in those older than 70 years.[11] There is an estimated 202 million people with PAD globally, of which ~70% are living in low to middle income countries[13]. These figures however, may exclude many with asymptomatic disease, who are usually diagnosed with ankle-brachial systolic blood pressure index (ABI) or duplex ultrasound.[14] Due to the strong association with cardiovascular and cerebrovascular disease, the disease burden on both individual and societal levels is high. Risk factors are also similar and include smoking, obesity, diabetes mellitus and a sedentary lifestyle[11] There appears to be a dose-dependent relationship between smoking and PAD with heavy smokers having a four-fold greater risk of PAD compared to non-smokers[14].

The above-mentioned evidence of the contribution of both ETS exposure and PAD to the global burden of disease and lack of recent review of the literature, justifies further examination of existing research. The purpose of this article is to review the association between ETS exposure and PAD and to identify the public health implications of the findings.

**Materials and Methods**

A comprehensive search strategy was conducted to include peer-reviewed literature. MEDLINE (1946 to September 2016), EMBASE (1980 to
September 2016), PsychINFO (2002 to July 2016), Cochrane Central Register of Controlled Trials (to August 2016) CINAHL (1999 to September 2016) and Scopus (1960 to September 2016) were searched using combinations of the key words of ‘tobacco smoke pollution’, ‘passive smoking’, ‘peripheral arterial disease’, ‘peripheral vascular disease’ and other terms specified in Table 1.

Table 1. Search terms

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<tr>
<th>Term</th>
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<tr>
<td>Tobacco smoke pollution/ or</td>
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<td>Environmental tobacco smoke/ or</td>
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<td>Passive smok*/ or</td>
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<td>Secondhand smok*/ or</td>
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<td>Peripheral arterial disease/ or</td>
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<td>Peripheral vascular disease/ or</td>
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<td>Arterial disease, peripheral occlusive/ or</td>
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<td>Arterial obliteration/ or</td>
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<td>Arterial oblitative disease/ or</td>
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<td>Peripheral arterial obstructive disease/ or</td>
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<tr>
<td>Claudication/ or</td>
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<tr>
<td>Intermittent claudication/ or</td>
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<td>Vascular occlusive disease</td>
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In the initial search, studies (n=105) were excluded based on application of inclusion and exclusion criteria to titles. Studies were included if published in English language journals and reported on cohort studies, cross-sectional studies or randomised controlled trials of adult patients with a comparison group and which focussed on PAD. Exclusion criteria included participants who were active smokers, a focus on coronary artery disease, cerebrovascular disease or carotid artery disease, a focus on non-arterial disease, risk factors aside from ETS exposure, literature reviews, policy/guidelines or non-human studies. See Figure 1 for search flowchart.
The abstracts of forty-five articles were further evaluated and twenty-nine articles excluded, based on the same criteria. Reference lists were manually searched and five further relevant studies were identified. A further search using the same terms and criteria was conducted in August 2017 and another cohort study was identified. Twelve studies were included in the final review.

![Search strategy diagram]

**Figure 1. Search strategy**

**Quality assessment**

A quality assessment of included articles was conducted using Grading of Recommendations Assessment, Development and Evaluation (GRADE)[15] guidelines (Table 6). Factors considered were risk of bias, inconsistency, indirectness, imprecision and publication bias.

**Results**

Of the twelve studies included in this review the study designs were cross-sectional [16-21](n=6), cohort[22-25] (n=4) and controlled trials[26, 27] (n=2).
See Tables 2-4. The cross-sectional and cohort studies were recruited from the general population in the USA [17, 25, 28], China [29], Greece [21], England [23], Scotland [20, 30], Belgium [26] and Norway [19]; and casino workers in Macau [22]. The controlled trials involved assessment of clinical data following exposure of never-smokers to a discrete period of ETS [26, 27].

The age range for subjects varied, with all participants over 18 years of age. Approximately equal numbers of males and females were included, however some studies recruited only males [26] or females [29] and one did not record gender [20].

All twelve articles relied on self-reporting of ETS exposure by participants using specifically designed questionnaires. Five studies [18, 21-24] classified participants according to amount of exposure in minutes/hours per day, days per week and years exposed. Three studies attempted to quantify exposure using serum [27], salivary [20] or urinary [25] cotinine, a proximate metabolite of nicotine [31] (See definitions in Table 5). Participants in the two trials of never-smokers, were intentionally exposed to both smoke and smoke free air. Argacha et al [26] exposed participants for one hour to side stream smoke, non-tobacco smoke and normal air while Heiss et al [27] exposed participants for thirty minutes to ETS and/or smoke free air.

A cross-sectional study [18] and cohort study [24] found a positive association between exposure to ETS and definitive diagnosis of PAD using ABI<0.9, as did another cohort study [25] using ABI≤0.9 or ≥1.4. Six studies [20-23, 26, 27]
found a positive association between ETS exposure and features of arterial injury. Three cross-sectional studies found no association using the outcomes of ABI<0.9[16, 17] and IC[19] identified using standardised tools.

ETS and ankle-brachial index (ABI) or intermittent claudication (IC)

In a cross-sectional study, Lu et al[30] found that self-reported exposure to forty or more hours of ETS per week is associated with PAD (adjusted OR 5.56, 95% CI, 1.82 to 17.06, p=0.003), as determined by an ABI less than 0.9. Similarly, using a more robust prospective cohort design, He et al[29] found that exposure to ETS is associated with the presence of IC (adjusted OR 1.87, 95% CI, 1.30 to 2.68), ABI less than 0.9 (adjusted OR 1.47, 95% CI, 1.07 to 2.03) and either IC or ABI less than 0.9 (adjusted OR 1.67, 95% CI 1.23 to 2.16). The WHO/Rose questionnaire[32] was used for identification of IC.

A more recent cohort study[25] of 5032 self-reported non-smokers, found that diagnosis of PAD using ABI ≤0.9 or ≥1.4, is associated with ETS exposure defined by elevated urinary cotinine (OR 2.10, 95% CI 1.09-4.04, p<0.05), but not self-reported exposure. With regards to systemic inflammation, this study also found a dose-response with exposure for ≥12 hours per week associated with high-sensitivity C-reactive protein (hsCRP) elevated >2mg/L (OR 1.52, 95% CI 1.22-1.90, p<0.001).

In a separate subset of participants, Lu et al[20] examined the association between self-reported passive smoking, salivary cotinine concentration, as a marker of exposure to ETS, and features of IC based on the Edinburgh Claudication Questionnaire (ECQ)[32]. The study found that those with a
salivary cotinine concentration (SCC) of equal to or greater than 2.7µg/mL were significantly more likely to have IC (OR 1.76, 95% CI 1.04 to 3.00, p=0.036), compared to those with SCC less than 0.7µg/mL.

No association was found between ETS exposure and the prevalence of IC in a cross-sectional study of 19 748 participants.[19] The study found that non-smoking men with partners who smoked were more likely to have IC, as per the ECQ, than those whose partners did not smoke (OR 2.1, 95% CI 1.3 to 3.3) however this association was weaker among female participants (OR 1.4, 95% CI 0.9 to 2.1).

ETS and vascular abnormalities on ultrasound (US)

Two cohort studies[22, 23] using different subgroups from the same cohort, and a controlled trial[27] found an association between impaired FMD of the brachial artery and exposure to ETS. Celermajer et al[23] found that FMD was impaired in male passive smokers (3.2±2.5% compared to 7.3±1.9% in the controls, p<0.001) and also female passive smokers (3.0±2.9% compared to 9.1±3.9% in the controls, p<0.001). Further support for this association was provided by Woo et al who found that FMD is lower in casino workers regularly exposed to ETS compared with controls without regular exposure (6.6±3.4% ± 10.6±2.3%, p<0.0001). Heiss et al measured FMD using US and serum endothelial progenitor cell (EPC) levels following direct exposure to ETS for 30 minutes. The study found an immediate decrease in FMD, which resolved to baseline 2.5 hours following exposure, and a sustained increase in EPC, suggestive of vascular injury and impaired endothelial function[27].
In a controlled trial of thirty three healthy never-smokers, Argacha[26] et al assessed augmentation index (AI) of the aortic wave reflection[33] on ultrasound as a surrogate marker of peripheral arterial disease. The study found that AI increased both during (p=0.01) and after (p<0.01) one hour of exposure to ETS in never-smokers. This increase in AI was not apparent following exposure to non-tobacco smoke, suggesting that ETS exposure impairs microvascular function through a nicotine-dependent pathway.[26]

**ETS and deranged biomarkers**

A single cross-sectional study[21] used blood biomarkers including C-reactive protein (CRP), fibrinogen, homocysteine, oxidised low-density lipoprotein (oxLDL) and white blood cell count (WCC) as indirect makers of inflammation. Those reporting regular exposure to ETS for more than three days per week, had increased WCC (by 0.6x10^3 per µL, 95% CI 0.3 to 0.8, p<0.01), CRP (by 0.08 mg/dL, 95% CI 0.02 to 0.1, p<0.05), homocysteine (by 0.4 µmol/L, 95% CI 0.2 to 0.6, p<0.01), fibrinogen (by 5.2 mg/dL, 95% CI -1.2 to 12), and oxLDL (by 3.3 mg/dL, 95% CI 0.5 to 6, p<0.05).

**Discussion**

Nine of the twelve studies included in this review demonstrated a positive association between exposure to ETS and either diagnosis of PAD or increased surrogate markers of PAD. Despite the lack of association reported by the three largest cross-sectional studies [16, 17, 19], all four cohort studies[22-25] and the randomised controlled trial[26], which provide the
highest level of evidence, showed a detrimental effect of ETS on vascular injury or an association with a diagnosis of PAD itself.

There was a distinct difference in strength of association between exposure to ETS and diagnosis of PAD in the cohort study by He et al[29] (Adjusted OR 1.47, 95%CI, 1.07 to 2.03) and cross-sectional study by Lu et al[30] (adjusted OR 5.56, 95% CI, 1.82 to 17.06, p=0.003). He et al used definitive criteria to include those exposed at home or in the workplace for at least fifteen minutes daily, for more than one day per week for at least two years in the past ten years. This is contrasted with self-reporting used by Lu et al in which exposure was divided per the following categories: none, a little, some or a lot, while duration of exposure was: none, 1-19, 20-39 or ≥40 hours per week. This difference in OR is likely due to a dose relationship, more strongly demonstrated by Lu et al. A dose response was similarly identified by He et al[24] with increasing exposure (measured in number of cigarettes and minutes per day), associated with increasing prevalence of PAD, coronary artery disease and ischaemic stroke.

There appears to be conflicting data on an association between ETS exposure and IC, used as a common clinical criterion of PAD. Lu et al[20] found that never-smokers with a SCC less than that expected of smokers (15µg/mL) but greater than 2.7µg/mL were more likely to have IC than those with a negligible SCC. However, in the study by Jensen et al[19], using self-reported smoking status alone, no association was found between passive exposure and IC. Reasons for the disparity may include differing populations,
systematic error or inconsistent identification of IC. Although the ECQ was used in both, Jensen et al used a Norwegian translation, which may have altered validity of results. Given that ‘pseudoclaudication’ can occur due to spinal stenosis, arthritis, venous congestion or compartment syndrome[34], presence of IC on examination or following ECQ, should be correlated with other clinical findings prior to diagnosis of PAD.

The cross-sectional study of 995 never-smokers by Panagiotakos et al, found elevated WCC, CRP, fibrinogen, homocysteine and oxLDL in those regularly exposed to ETS. The association with PAD is supported by a study using cross-sectional data from a nationally representative sample of adults in the United States.[35] The study found a positive but statistically insignificant association between PAD diagnosed by ABI and levels of WBC (OR 1.67, 95% CI 0.84 to 3.31), CRP (OR 2.14, 95% CI 1.41 to 3.25) and fibrinogen (OR 2.49, 95% CI 1.27 to 4.85) in the top quartile compared to the bottom quartile. The association with homocysteine is supported by findings in a cross-sectional study of 6880 patients where the prevalence of PAD in patients with a homocysteine level in the highest quintile was increased by 11.3% (OR 2.1, 95% CI 1.7 to 2.6)[36]. Elevated LDL is a known risk factor for atherosclerosis[37] and its biomarker, lipoprotein(a) has been found to be associated with PAD in the elderly[38] and in those with Type 2 diabetes mellitus[39]. Serum inflammatory biomarkers are useful surrogate markers of PAD however have low specificity and are not diagnostic.
EPCs are a novel marker of vascular injury, with increasing potential for use in both diagnosis and treatment of arterial disease. Produced in the bone marrow, EPCs are activated by multiple factors in response to peripheral tissue hypoxia, as occurs in PAD[40]. As observed by Heiss et al[27], EPCs have been found to increase following an acute ischaemic event[41] such as that induced by exposure to ETS. Further observation with a longer follow-up period should be undertaken however, as patients with chronic, ischaemic vascular disease, have been found to have conversely low levels of EPC[42, 43]. The small populations in this study, as well as those by Celermajer[23] (n=78), Woo[22] (n=20) and Heiss[44] (n=10) necessitate future high-quality longitudinal research to investigate the potential association between ETS exposure and PAD, however these positive results may be sufficient to justify policies to minimise exposure in the interim and to acknowledge ETS exposure as a potential contributor to PAD.

There is a complex but well-described and causal association between tobacco smoke and cardiovascular disease[45, 46]. Key factors thought to contribute to atherothrombotic disease include vasomotor dysfunction, leukocyte and platelet activation, increased inflammatory molecules, smooth muscle proliferation and increased prothrombotic factors. These are mediated by the effects of inhaled mainstream and/or sidestream smoke on bioavailability of nitric oxide, increased oxidative stress and increased cytokines[45]. The contributions of other factors including genetic predisposition and insulin resistance need to also be considered as risk factors for cardiovascular disease.
The toxic metal cadmium, found in tobacco, many foods and as air-borne particles, has been implicated both directly and indirectly in the development of cardiovascular disease including PAD[47]. The greatest exposure in humans is from tobacco smoking and food, especially grains and root vegetables grown in soil exposed to fertilisers and industrial emissions[48]. Several studies have found a high level of cadmium in blood and/or urine is a risk factor for cardiovascular disease, independent of other risk factors[47-49].

A large, observational study of 2125 participants aged at least 40 years of age, found a dose-response association between blood cadmium levels and risk of PAD (OR 2.82 (95%CI 1.36 to 5.85) for the highest quartile and OR 1.07 (95% CI 0.44 to 2.60) for the lowest quartile, p=0.01 for trend)[50]. The same study demonstrated an OR of 4.13 when comparing current and never smokers, reduced to 1.84 when adjusting for cadmium. Thus cadmium is thought to partially mediate the effects of smoking on PAD. This is further supported by a systematic review on cadmium exposure and clinical cardiovascular disease, which found a relative risk of 1.49 (95% CI 1.15 to 1.92) for PAD. These findings suggest that the contribution of ETS to PAD is complex and multifactorial and highlight the need for investigation into several potential mechanisms and parameters of vascular injury.

The intentional exposure of participants to ETS in the clinical trial setting is controversial given the known adverse health effects of tobacco smoke constituents[51-53], however this can perhaps be justified by the short duration of exposure in healthy, young adults. Both trials reviewed found that
features of impaired vascular function were evident both during and after exposure[26, 27]. These studies do not provide insight into the effects of long-term exposure, as experienced by many never-smokers who live or work with smokers, but they do provide evidence that some degree of injury occurs with only a discrete period of exposure. Some reversibility is suggested by the return in FMD to baseline following cessation of exposure in the study by Heiss et al[27], however this would require further exploration using more ethically acceptable methods. Somewhat contrarily, Argacha et al found that the increase in central wave reflection and decrease in skin microvascular dilatation persisted for more than 20 minutes after cessation of exposure and no endpoint was defined. It is possible that the degree of reversibility of disease demonstrated with active smoking is also present with passive smoking, even if not completely back to the pre-morbid state. This hypothesis provides another solid basis for future observational studies of non-smokers exposed to ETS.

The WHO/Rose Questionnaire[54] has been shown to be only moderately sensitive (60-68%)[32] for the identification of IC and was used in one of the studies[29] examined, however the power of the study to identify cases is improved with the concurrent use of ABI measurement. The ECQ has been shown to be significantly more sensitive (91.3%, 95% CI, 88.1 to 94.5%)[32] and used as the sole diagnostic tool in two studies[19, 20], including one which found no association between ETS exposure and IC.[19]
The use of cotinine to quantify exposure to ETS is limited by its’ short half-life and ability to identify ETS exposure only up to the three days preceding collection[55], thus it is unable to accurately reflect the extent of exposure.

The studies are funded by varying combinations of for-profit (FP), not-for-profit (NFP) or government sources. No funding by tobacco companies or distributors is disclosed. The NFP sources are philanthropic, educational, medical or research based organisations. Argacha[26] discloses support from several FP sources in addition to government and NFP organisations. Of these Novartis[56] and Pfizer[57] have been involved in the development of anti-nicotine vaccinations. Both of these companies also produce nicotine replacement therapy[58, 59]. Therefore, a possible bias towards identifying a positive association between ETS exposure and PAD must be considered.

Overall, the quality of evidence was rated moderate with individual studies rated either ‘low’ or ‘moderate’ using GRADE criteria[15] (Table 6. Key areas limiting confidence in effect estimate are inclusion of observational studies (n=9), potential for recall bias in self-reported smoking status, inconsistency in conclusions or single study only and imprecision in results reported. Publication bias may cause reduced number of results obtained during literature search. Implicating factors may include outcome-reporting bias, industry sponsorship and language bias. Underestimation of a true association may also occur due to non-differential misclassification of ETS exposure. These limitations highlight the need for large, robust randomised
controlled trials, where ethically appropriate, to further evaluate the association between ETS exposure and PAD.

**Public Health Considerations**

These findings support the argument for increasing restrictions on smoking in public places or where there is the risk of exposing others to ETS. In Australia, smoking in enclosed public places is banned in every state and territory[60] however there is variability in regulating outdoor smoking. A similar trend can be seen in Europe, where Ireland, Greece, Bulgaria, Malta, Spain and Hungary[61] also ban smoking in enclosed public places, with ten other countries enacting comprehensive smoke free laws. Further restrictions designed to protect people from ETS exposure however, are continually impeded by groups arguing for freedom of choice to smoke[62]. These smokers’ rights groups are frequently financially supported by the tobacco industry[63], focus on autonomy and downplay evidence-based literature on the detrimental effects of ETS[64]. While these defences have historically focussed on coronary artery and lung disease[64-66], this review of the associations with PAD creates an additional counter-argument.

**Conclusion**

There is conflicting evidence of an association between exposure to ETS and PAD; however included studies with the highest levels of evidence did demonstrate a positive association. Several studies identified the increased risk of vascular injury or diagnosis of PAD through regular exposure, usually at home or in the workplace, however larger populations are needed to
provide more robust evidence for or against an association. Overall, these findings build upon previously demonstrated evidence on the health detriments of active smoking, challenging the argument that freedom to smoke is an individual choice alone.

**Conflict of Interest**

None.

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None.

**Author Contributions**

Both authors contributed to original concept and agreed on methodology. NN drafted the manuscript. Both authors read and approved the final manuscript.

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References

14. Norgren L, Hiatt,WR; Dormandy, JA; Nehler,MR; Harris,KA; Fowkes,FGR. Inter-society consensus for the management of peripheral arterial disease. J Vasc Surg. 2007;45(S1):S5A-S67A.


Smith EA, Malone RE. ‘We will speak as the smoker’: the tobacco industry’s smokers’ rights groups. European journal of public health. 2007;17(3):306-13.

