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Review article

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 at 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 the 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 met inclusion criteria for review. Three studies showed 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 supports ongoing restrictions on freedom to smoke in public areas, including the workplace, and has implications for those exposed in the home environment.

1. 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 climb

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ischaemia (CLI) have the highest mortality as lower limb amputation has a 5-year survival rate of 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 the 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.

2. 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.

In the initial search, studies (n = 105) were excluded based on the 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 focussing 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 (Fig. 1 for the 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.

2.1. 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.

3. 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) (Tables 2–4). The cross-sectional and cohort study subjects 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 participants' self-reporting of ETS exposure by using specifically designed questionnaires. Five studies [18,21–24] classified participants according to the amount of exposure in min/h 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] (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 to side stream smoke, non-tobacco smoke and normal air for 1 h, while Heiss et al. [27] exposed participants to ETS and/or smoke free air for 30 min.

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 with standardised tools.

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

In a cross-sectional study, Lu et al. [30] found that a 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 of 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 h per week associated with high-sensitivity C-reactive protein (hsCRP) elevated >2 mg/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) equal to or greater than 2.7 μg/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 0.7 μg/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