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Cardiovascular Consequences of Childhood Second Hand Tobacco Smoke Exposure:

Prevailing Evidence, Burden, Racial and Socioeconomic Disparities

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Abstract

Background—Although public health programs have led to a substantial decrease in the prevalence of tobacco smoking, the adverse health effects of tobacco smoking is by no means a thing of the past. In the U.S, four out of 10 school aged children and 1 out of 3 adolescents are involuntarily exposed to second-hand tobacco smoke (SHS) with children of minority ethnic backgrounds and those living in low socioeconomic status households being disproportionately affected (68% and 43% respectively). Children are particularly vulnerable with little control over home and social environment and lack the understanding, agency, and ability to avoid SHS exposure on their own volition; they also have physiological or behavioral characteristics that render them especially susceptible to effects of SHS.

Side stream smoke (the smoke burned directly off the end of the cigarette), a major component of SHS, contains a higher concentration of some toxins than mainstream smoke (inhaled by the smoker directly), making SHS potentially more dangerous than direct smoking. Compelling animal and human evidence shows that SHS exposure during childhood is detrimental to arterial function and structure resulting in premature atherosclerosis and its cardiovascular consequences. Childhood SHS exposure is also related to impaired cardiac autonomic function and changes in heart rate variability. In addition, childhood SHS exposure is associated with clustering of cardiometabolic risk factors such as obesity, dyslipidemia, and insulin resistance. Individualized interventions to reduce childhood exposure to SHS are shown to be at least modestly effective, so are broader based policy initiatives such as community smoking bans and increased taxation.

Purpose—The purpose of this statement is to summarize the available evidence on the cardiovascular health consequences of childhood SHS exposure which will support ongoing efforts to reduce and eliminate SHS exposure in this vulnerable population. This statement reviews relevant data from epidemiologic studies; laboratory based experiments, and controlled behavioral trials, concerning SHS and cardiovascular disease risk in children. Information regarding the effects of SHS exposure on the cardiovascular system in animal and pediatric studies, including vascular disruption and platelet activation, oxidation and inflammation, endothelial dysfunction, increased vascular stiffness, changes in vascular structure, and autonomic dysfunction are examined.

Conclusion—The epidemiological, observational and experimental evidence accumulated to date, demonstrates the detrimental long-term cardiovascular consequences of SHS exposure in children.

Implications—Increased awareness of these adverse effects will facilitate the development of targeted individual, family-centered and community public health interventions to reduce and ideally eliminate SHS exposure in the vulnerable pediatric population. This evidence calls for a robust public health policy that embraces “zero tolerance” to childhood SHS exposure.

Keywords

Second hand tobacco smoke; children; vasculature; side-stream smoke; atherosclerosis

Introduction

Over the past 50 years, health care providers and public health professionals in the United States have increased awareness of the health risks associated with smoking tobacco. In 1964, approximately 40% of adults in the United States (US) were smokers, including one-third of women[1]. Although the percentage of US adults who smoke has decreased to an estimated 18.1%, over 45 million US adults still smoke cigarettes[2], with approximately 500,000 dying each year from tobacco smoke-related illnesses, and millions of children are involuntarily exposed to second hand tobacco smoke (SHS) in the household or during transportation[3]. Recent reports from the Centers for Disease Control and Prevention (CDC) show disparities in SHS between children and adults of different socio-economic statuses (SES)[3]. Children, 3–11 years old, have the highest exposure to SHS, particularly children of minority ethnic backgrounds. Additionally, youth and adults of a lower SES have more SHS exposure than youth and adults of higher SES[3]. Direct tobacco smoking in the US has been estimated to cost $97 billion in medical costs annually,[4] while SHS exposure is associated with $5.6 billion in lost productivity each year[5]. Cigarette smoke is a potent atherosclerosis promoting risk factor, atherosclerosis can begin as early as the first decade of life and is often mediated by risk factors such as obesity, dyslipidemia, hypertension, insulin resistance, and tobacco use [6, 7]. Several studies have linked SHS exposure to accelerated atherosclerosis as well [8–13].

SHS is a mixture of gases and fine particles that emit from a burning tobacco product (such as a cigarette, cigar, or pipe), or from smoke that has been exhaled by an individual actively smoking tobacco[14, 15]. The scope of SHS exposure can span the life cycle, beginning *in utero* with exposure to maternal direct smoking or maternal SHS. SHS consists of many noxious chemicals including nicotine, carbon dioxide, carbon monoxide, carbonyls, hydrocarbons, polycyclic aromatic hydrocarbons, nitrosamines, and particulates collectively referred to as ‘tar’[16]. Exposure to SHS is associated with increased prevalence of respiratory infections, increased frequency and severity of asthma exacerbations, and a greater risk of sudden infant death syndrome (SIDS)[14, 17]. While the pulmonary consequences of SHS exposure are clinically apparent in childhood, the cardiovascular effects of SHS exposure are occult but substantial. Existing evidence suggests that SHS exposure in children and youth is detrimental to their cardiovascular health and that consequences attributable to SHS exposure may persist into adult life[18]. Furthermore, some studies speculate that, SHS

exposure may be equally or even more harmful to cardiovascular health than direct cigarette use due to increasing concentrations of some chemicals than can promote inflammation and oxidation as SHS ages[8, 19–21]. Furthermore, there is substantial evidence that SHS has adverse cardiovascular consequences as early as the first decade of life including when the fetus is exposed to maternal smoking or maternal SHS *in utero* and in children who have no other atherosclerosis promoting risk factors[22–24].

Children of smoking parents are significantly more likely to be exposed to SHS[25], and are also more likely to smoke later in life. This may be associated with many interrelated factors, including SHS exposure itself [3, 26, 27], parental modeling[28, 29], or physical sensitivities to SHS[30]. However, recent studies suggest that SHS in childhood is an independent factor in susceptibility to smoking initiation[31]; that home smoking bans may delay or prevent smoking initiation among children of smokers[32]; and, conversely, that SHS exposure may be a mediating factor making adolescent quitting less likely within the context of a smoking family[25]. Thus, childhood SHS exposure may also have indirect impacts on lifetime cardiovascular health by increasing the likelihood that these children will choose to smoke in adolescence and adulthood.

In the past 2 decades since the last publication of an American Heart Association Statement concerning the health of children exposed to SHS[33], there has been substantial evolution of epidemiological and clinical research related to SHS. The current statement updates previous statements with recent data concerning SHS and cardiovascular disease (CVD) risk in children. Emphasis is placed on the adverse effects of SHS on cardiovascular health in children and includes discussions on mechanisms of vascular disruption and platelet activation, oxidation and inflammation as noted in animal studies, human endothelial dysfunction, increased vascular stiffness, changes in vascular structure and autonomic dysfunction. The effectiveness of currently available behavior modification techniques and smoking bans to reduce SHS exposure in children are also addressed. The purpose of this statement is to increase awareness amongst providers and policy makers regarding the substantial SHS exposure that continues to be prevalent in children and its lifelong, adverse cardiovascular consequence.

Epidemiology of SHS Exposure

Prevalence of SHS exposure in children

Approximately 24 million non-smoking children and adolescents in the US are currently exposed to SHS[3]. Nationally-representative data from 2011–2012 National Health and Nutrition Examination Survey (NHANES) shows that 40.6% of children aged 3–11 years and 33.8% of adolescents aged 12–19 years had detectable serum cotinine levels (>0.05 ng/mL), which is consistent with exposure to SHS[3]. Cotinine is a metabolite of nicotine found in biologic fluids and is a commonly used marker of tobacco smoke exposure[34]. These SHS exposure estimates represent a substantial reduction in prevalence since the NHANES III survey from 1988–1994[35] (Figure 1). The majority of this decline in SHS exposure in children appears to have occurred by the early 2000's[35–37], with a relative leveling off in the past decade[36]. However, a national sample of non-smoking middle- and high-school-aged adolescents who self-reported exposure to SHS revealed declines in SHS from 58.9% to

34.0% between 2000 and 2009 as well[38]. Despite these significant declines in children and adolescents exposed to SHS over the past 30 years, the prevalence remains substantial with approximately 1 in 3 children in the US still exposed to SHS.

These declining trends in SHS exposure among children in the US are not, however, consistent worldwide. A study of SHS exposure in rural areas of China identified that 68% of children were exposed to SHS at home, and that exposure prevalence was further amplified in households with low income or low educational status of the head of household [39]. Prevalence of adult SHS exposure is approximately 35% in Shanghai, but was surprisingly higher in households with children under age 18 years[40]. A 43-country report "World Health Organization's Global Youth Tobacco Survey of children aged 13–15 years" was released in 2002[41]. Home SHS exposure in this age group exceeded 70% in six sites in India, was 69% in Indonesia, and was a median of 49% across all surveys [41]. Updated nationwide representative data from India in 2009 showed lower prevalence at 22%, but remained high in Indonesia in 2014 (57%) [42, 43]. Although public smoke-free bans were instituted in 2007 in Hong Kong and in 2011 in China, evidence from Hong Kong indicates that smoking bans have displaced smoking from public to private spaces, including the home, increasing home SHS exposure in children [44]. Thus, childhood exposure to SHS both at home and in public places remains significant in many countries worldwide, particularly in southeast and east Asia and the Indian subcontinent. Results from a recent systematic review of SHS exposure and CVD reaffirm these findings with evidence indicating high prevalence of SHS exposure in both low- and middle-income countries [45]. Taken together, available evidence supports the global need for public and provider education about childhood SHS.

Smoking inside the home

It has long been recognized that parental smoking is a major source of SHS exposure for non-smoking children and adolescents[46]. Children have less control over home and social environments leading to an increased likelihood of involuntary confined exposure to SHS. These developmental/behavioral barriers, in combination with physiological differences from adults discussed later[47], reflect that non-smoking children have significantly higher objectively measurable exposure to SHS than non-smoking adults[37].

The proportion of children aged 3–11 years living with someone who smokes inside the home declined from 38.2% in 1994–1998 to 23.8% in 1999–2004[35] to 18.2% in 2007–2008[48], with similar declines seen among non-smoking adolescents (35.4%, 19.5% and 17.1%, respectively). This is consistent with the secular decline in overall adult smoking prevalence, as well as an increase in voluntary smoke-free home rules[49]. These reductions in smoking inside the home contribute substantially to the overall decline in childhood SHS exposure. However, youth who remain in smoking home environments still face near-certain SHS exposure.

Epidemiological studies report that over 98% of children and adolescents *living* with someone who smokes at-home has detectable SHS exposure[48], a proportion that has not appreciably declined since 1988[50]. However, when the data of at-home SHS exposure[35, 48, 50] with data on overall prevalence of SHS exposure among children[35, 48] is

combined, we estimate that only 1 in 3 SHS-exposed youth has exposure within the home environment (Figure 2A and 2B), suggesting that the majority of children and adolescents with detectable SHS exposure are exposed outside their home or in an automobile. This is consistent with a study of inner-city youth, where 95% reported SHS exposure outside the home, often in relatives' or friends' homes, or in cars[51]. Although both in-home and in-car smoking bans are associated with less SHS exposure in children[52], 71% of smoking parents did not report having a smoke-free car policy, and only a third of parents who enforced a strict in-home smoking ban also strictly enforced a smoking ban in the car[53]. This is especially important, as SHS in a car can be significant, even with the windows open[54, 55].

SHS exposure trends, demographics and socioeconomics

Although there has been reduction in overall SHS exposure, racial disparities persist[3]. There is some indication that SHS metabolism differs by race, for a given amount of exposure, cotinine levels may be higher in African-Americans[56]. NHANES data suggest that, 31.3 million non-Hispanic, white, non-smokers aged ≥3 years were SHS exposed in 2011–2012, including 7.2 million children aged 3–11 years. Additionally, 12.4 million, non-Hispanic, black non-smokers were SHS exposed including 3.4 million children and; 6.2 million Hispanic non-smokers aged ≥3 years were exposed to SHS, including 1.9 million children during the same time period. Specifically, the prevalence of SHS exposure declined comparably from 1999–2000 to 2011–2012 among non-Hispanic white children (−41.2%) and Hispanic children (−39.0%)[3]. The decline observed among non-Hispanic black children, however, was substantially less (−19.8%) (Figure 3). During 2011–2012, SHS exposure in 3–11 year old children was significantly higher among non-Hispanic blacks (67.9%) than non-Hispanic whites (37.2%) and Hispanics (29.9%) $p< 0.05$. Prevalence of SHS exposure in adolescents aged 12–19 years, was also significantly higher among non-Hispanic blacks (54.6%) than non-Hispanic whites (35.8%) and Hispanics (16.9%) $p< 0.05$ (Figure 4)[3]. So while cotinine metabolism differs by race, higher cotinine levels in African Americans may be due to increased exposure to SHS as well.

In addition to differences in SHS exposure by race/ethnicity, there are significant differences by SES. NHANES data from 2011–2012 indicate that individuals living below the poverty level have greater exposure to SHS (43.2%) than those living above the poverty level (21.2%)[3]. By education, SHS exposure was highest among individuals with grade 11 or less education (27.6%) and lowest among those with a college diploma or graduate education (11.8%). Exposure to SHS was higher among individuals who rented their housing (36.8%) than individuals who owned housing (19.1%). Importantly, the prevalence of voluntary home smoking bans was also significantly lower for households with low income, single parent or lower educational attainment[57], which may exacerbate the disparities in SHS exposure in these groups. Many individuals with low SES live in multi-unit housing, where SHS exposure can infiltrate smoke-free units and areas shared by others who smoke. Recent estimates indicate that 80 million individuals in the US live in multiunit housing and approximately 25% of these individuals are below the poverty level[58]. The living environment is recognized as a setting where substantial exposure to SHS occurs for children and youth[59]. There is substantial scientific evidence to support efforts designed to

prohibit smoking in commonly shared areas in subsidized housing as summarized above [57, 58].

A recent systematic review generated from 41 studies across 21 countries adds to the NHANES findings indicating that parental smoking, low SES, and being less educated are frequently and consistently associated with SHS exposure in children and youth[60]. The significance of socio-demographic factors are also supported by data from Denmark[61], the UK[62], and Australia[63]. More recently, longitudinal studies have focused on the effects of *in utero* SHS exposure on developmental and health outcomes in childhood, adolescence, and young adulthood[64–66] with these adversities also being disproportionately prevalent in minorities and lower SES groups. Taken together, these findings continue to underscore the importance of socio-demographic factors including household SES, educational levels of parents/guardians, and the home environment, in increasing the likelihood of childhood SHS exposure.

Influence of SHS exposure on childhood obesity, dyslipidemia and metabolic syndrome

Another area of emphasis has been the deleterious effect of *in utero* SHS exposure on weight status. The overall pattern appears to be one of lower weight at birth, larger postnatal weight gain, which is recognized to be a pattern that predicts future obesity. Supporting this theoretical pattern, data shows that *in utero,* exposure to tobacco smoke has obesogenic effects[67]. Results from the longitudinal Healthy Start Study, suggest that *in utero* exposure to SHS is associated with intrauterine growth retardation and rapid postnatal compensatory growth[64]. Specifically, at birth, those exposed to *in utero* SHS had reduced fat mass ($p=0.007$) and fat free mass ($p=0.02$). At 5 months of life, exposed and unexposed offspring were phenotypically similar in overall weight, length and body composition. However, after adjustment for birth weight, offspring exposed to *in utero* SHS had significantly greater fat free mass ($p=0.04$) and sum of skin folds ($p=0.04$) suggesting postnatal compensatory growth[64].

Data from the National Institute of Child Health and Human Development Study, a longitudinal study that followed a cohort of children from birth, suggested a long-term combined effect of *in utero* SHS due to maternal smoking and exposure of the non smoking pregnant mother to SHS from a partner or other household member, on obesity among offspring at adolescence, independent of birth weight[66]. After adjustment for maternal and child factors, the odds of adolescent obesity increased both with *in utero* SHS exposure (OR=1.57; 95% CI=1.03–2.39) and exposure of the pregnant mother to SHS (OR=1.53; 95% CI= 1.04–2.27). Furthermore, the odds for obesity in adolescence increased two-fold among adolescents exposed to any *in utero* SHS (OR=2.10; 95% CI= 1.24–3.56) compared with those without any SHS exposure[66].

The Southern California Children's Health Study collected data on current SHS exposure and maternal smoking during pregnancy on 3,318 children who were around 10 years of age at study entry. Both *in utero* and current SHS exposure were associated with greater subsequent body mass index (BMI) over an 8-year period spanning adolescence through young adulthood[68.] In another study, maternal smoking during pregnancy was associated with a 60% greater chance of the child being overweight at age 4 years[69]. A Swedish cohort

study of 5–15 year-old children has suggested that parental smoking is also associated with a 3–4% increase in BMI in children, compared with controls[70]. In a large study of German children, SHS exposure after birth was significantly associated with overweight status at age 6 years[65]. The mechanisms behind this association are not well understood. Taken together, results of cross-sectional and longitudinal studies suggest adverse effects of SHS exposure including *in utero* exposure on BMI in childhood and adolescence.

It appears that SHS exposure in early childhood, even *in utero*, can cause persistent lipoprotein changes later in life. Ayer et al have documented that *in utero* SHS exposure was associated with lower high-density lipoprotein cholesterol (HDL C) levels in 8 year-old children, even after adjusting for postnatal SHS exposure[71]. Neufeld et al[72] documented a similar effect of SHS exposure and decreased HDL C level in SHS-exposed children, after adjusting for potential confounding atherosclerosis promoting risk factors. Abnormalities have been documented in low-density lipoprotein cholesterol (LDL C) as well. Yang et al, in their study of Tibetan adolescents, documented that Apolipoprotein-B values were significantly lower in SHS exposed teenagers compared with controls[73]. Furthermore, in an ex-vivo study performed in healthy non-smokers exposed to SHS for 5.5 hours, Valkonen and Kuusi noted that exposure of non-smoking subjects to SHS leads to accelerated lipid peroxidation, LDL C modification, and accumulation of LDL C in human macrophages[74].

The effects of SHS exposure on blood pressure are less well studied but Simonetti et al[22] have found that childhood exposure to SHS is associated with a significant (albeit modest) effect on blood pressure in 6 year-old children. Clustering of atherosclerosis promoting risk factors can result in metabolic syndrome and the association between SHS and metabolic syndrome has been examined in adolescents. Non SHS exposed children had a 5.6% incidence of metabolic syndrome whereas those exposed to SHS had a 19.6% incidence of metabolic syndrome, with SHS exposure being assessed by cotinine levels and this effect persisted after adjustment for confounders[75].

Summary Table - Epidemiology of childhood SHS exposure

- Up to 4 of 10 children have detectable cotinine
- Parental smoking is a major source of SHS exposure
- Nearly all children living with someone who smokes is SHS exposed
- SHS exposure is highest in African Americans
- SHS exposure is inversely linked to socio-economic status
- *In utero*/post natal SHS exposure is associated with cardiovascular risk factors

Economic impact of SHS exposure

Tobacco smoke (from both smoking and SHS exposure) has a significant economic impact in direct health care costs and loss in productivity. Annual smoking-related economic costs in the US exceeded $289 billion, and exposure to SHS caused an estimated $5.6 billion yearly in lost productivity due to premature death over a 3-year period, between 2009 and

2012[14]. Among children, living with at least one smoker, is associated with a modest impact on emergency department expenditures[76] and inpatient use[77]. Some estimate that the additional cost associated with birth complications in pregnant women smoking, or being exposed to SHS, may be as high as $2 billion per year[78]. Lightwood et al. reported on health and economic benefits of smoking cessation during pregnancy, estimating savings of $572 million in direct pediatric medical expenses in 7 years[79].

There is a negative economic impact of SHS exposure on the education system. Children exposed to SHS have higher rates of adverse behavioral and cognitive effects, including Attention Deficit Hyperactivity Disorder[80]. Max *et al* estimated that the costs to the education system from SHS may be 4 times higher than the annual healthcare cost attributable to Attention Hyperactivity Deficit Disorder[80]. With school absenteeism used as a surrogate measure of child health[81–83], an article by Levy et al. showed, in a nationally representative sample of 6–11 year olds, that children living with two or more adults who smoke at home have 1.54 more days absent from school each year than children living with non smokers. Caregivers' time tending to children absent from school is estimated to cost $227 million each year. The authors concluded that household SHS exposure is significantly associated caregivers' loss of productivity and child school absenteeism[84].

Tobacco Cessation Programs/Efforts

Resources spent towards education, counseling and health promotion are highly efficient, resulting in substantial health care cost savings and public health improvements. In 2015, an estimated $25 billion in revenue from tobacco settlements and taxes will be collected by all 50 states, with less than 2 percent of the revenue being spent on programs that help prevent children from smoking and help smokers quit[85]. These prevention programs are known to reduce smoking, save lives, and reduce tobacco-related healthcare costs that are estimated to run into hundreds of billions of dollars annually[86].

Data from Washington State (2000–2009) indicated healthcare cost of tobacco prevention and cessation programs are not just a cost-effective healthcare intervention but actually have a savings multiplier effect, saving in excess of $5 for every dollar spent. Over the ten-year period, this program prevented almost 36,000 hospitalizations, a saving of $1.5 billion compared to $260 million spent on the program[87]. A 2013 study conducted in California, a leader in tobacco prevention, found that from 1989 to 2008, the state's tobacco control programs reduced healthcare costs by $134 billion, compared to the $2.4 billion spent administering these programs[88].

The economic impact of changing smoking locations is also substantial. For example, prohibiting smoking in all US subsidized and public housing is estimated to generate annual cost savings of approximately $500 million[89]. These figures likely underestimate true benefits as proper accounting of life course benefits cannot be modeled using currently available data. Thus, while the economic costs of smoking and SHS exposure are significant, well-designed and well-targeted programs can minimize these costs, at great benefit to society.

Summary Table - Childhood SHS exposure - Economic impacts

- ⇑ emergency room and inpatient use, and medical expenses
- ⇑ rates of cognitive disorders
- ⇑ rates of behavioral and cognitive adversities
- ⇑ school absenteeism

Cardiovascular dysfunction associated with SHS exposure in children

Chemical composition of second hand smoke and biochemical/mechanistic effects

The multiple gases and chemicals of SHS make the causal attribution to any single component challenging[16, 90, 91]. Effects of tobacco smoke depend on whether the exposure is from direct smoking or SHS[92, 93], the distance of those exposed from source, which is necessarily different between the direct smoking and SHS, length of time from when the constituents enter the environment and the individual is exposed (SHS aging)[94], and whether it is mainstream versus side stream smoke[95]. Mainstream smoke is the inhaled component, some of which is then exhaled, while side stream smoke (containing 75% of the smoke generated by a cigarette[96]) is burned off directly from the cigarette and not immediately inhaled (Figure 5). Mitigation of CVD risk from SHS critically depends on the chemicals present in the side stream smoke. The precise composition of SHS depends on fluctuating conditions including pH, ambient temperature, atmospheric gas composition, and degree of combustion[90, 95]. For example, some constituents such as carbon monoxide and nicotine dissipate quickly, while others persist, and still others such as acrolein and certain organic chemicals concentrate and increase over time. In addition, the changes in these determinants over time affect the composition of SHS. This complex milieu synergistically results in the adverse consequences of SHS[16, 90, 92]. While interested stakeholders make much ado about filtered versus unfiltered distinctions or ‘low tar’ varieties, emitted chemical compositions of side stream smoke actually differ little among the various cigarette subtypes (i.e. low vs. high tar, filtered vs. unfiltered etc). Specific chemical constituents present in SHS number into the thousands; a few of the most prominent chemicals are presented in Table 2. Side stream smoke, containing approximately 3 times more toxins than main stream smoke, is equally as or potentially more dangerous than directly smoking depending on intensity of exposure [97, 98]. Some studies suggest that the toxicity of some tobacco smoke constituents in side stream smoke actually increases over time due to ambient environmental reactions where certain compounds deposit onto surfaces resulting in continuing exposure and highly volatile gas constituents remain suspended in air[95, 98–100]. These compound specific features further obscure mechanisms of action since the degree of the exposure may vary based on the type of compound in question[97, 101]. While a panoply of noxious chemicals can result from SHS exposure, the precise degree of exposure varies from constituent to constituent and CVD relevant effects may vary accordingly. Regardless of mechanism, consensus has developed around quantifying the severity of smoke exposure by measuring nicotine and its metabolites in body fluids or hair, cotinine in body fluids, airborne nicotine and its metabolites, and particulate matter[16, 34, 90, 102].

Mechanisms of vascular disruption

Cigarette smoke both mainstream and side stream is understood by in vitro, in vivo, and epidemiological studies to have acute and sub acute effects leading to cardiovascular consequences. The specific mechanistic domains include acute effects on endothelial function, platelet function, vasoconstriction, autonomic function, heart rhythm, and inflammation[16, 90]. Sub acute effects can include inflammation via oxidative stress, dyslipidemia, thrombosis, insulin sensitivity, and endothelial dysfunction[16, 90]. While the sheer number of compounds precludes a full account of the mechanism of each compound here, a few key examples deserve mention. Nicotine alone is associated with hemodynamic alterations, dyslipidemia and insulin resistance[103–105]. Acrolein, a volatile organic chemical is highly reactive and causes oxidative stress, inflammation and is linked to hypertension, dyslipidemia, arrhythmia, and thrombosis while crotonaldehyde is an atherogenic compound that induces plaque instability, increases thrombosis, and may have direct negative inotropic effects[106–108]. Cadmium is documented to cause inflammation and facilitate atherosclerosis[109, 110]. Lead exposure may cause hypertension and predicts cardiovascular mortality[111, 112]. Various particulate matter is known to be arrythmogenic and precipitate CVD events[113–115]. Exposure to carbon monoxide and various metals is minimal in those exposed to SHS[16]. Nicotine exposures are also quite low, due in part to the fact that nicotine dissipates rapidly from SHS[16]. Conversely, acrolein and other organic chemicals do persist in SHS over time, are highly reactive, and are known to produce oxidative stress, inflammation, endothelial dysfunction, blood clotting[16]. Moreover, other substances can adhere to the smoking-elaborated particulate matter and enhance their toxicities[100].

With respect to children specifically, investigators have demonstrated that SHS exposure markers are elevated in a graded fashion in concert with higher SHS exposure. Cotinine levels are detectable in fetal and cord blood serum and appear to be higher in younger children (compared to adults) either due to higher exposure from faster respiratory rates or inadequate cotinine metabolism[47, 116–119]. After adjustment for degree of exposure, children of African-American descent appear to have higher levels of SHS markers compared to children of Hispanic descent, underscoring race/ethnicity and metabolic differences[50]. SHS is thus an intricately interactive vector for producing cardiovascular consequences.

Summary Table - Effects of SHS exposure dependant on

- Length of time exposed
- Intensity of exposure
- Aging of the SHS constituents in the environment
- Race and age

Summary Table – Cardiovascular effects of key SHS components

• Nicotine	Hemodynamic alterations
• Acrolein	Hypertension, arrhythmia
• Crotonaldehyde	Plaque instability, thrombosis
• Cadmium	Inflammation

• Lead	Hypertension
• Particulate matter	Arrhythmias

Animal studies linking SHS exposure to mechanistics of atherosclerosis

Although the specific physiologic mechanisms of SHS exposure on cardiovascular health in humans are mostly unknown, animal studies have helped to shed light on potential mechanistic effects. Although experimental animals have substantial differences from humans in many respects (lipoprotein profiles, blood pressures, patterns of breathing such as nose versus mouth, and other biological dissimilarities), there is a remarkably consistent body of evidence from a variety of animal species concerning the potentially proatherogenic effects of SHS. Although most of the early work was done with SHS exposure in adult animals, often in high doses, recent studies have examined environmentally plausible levels of SHS and its effects on vascular biology and atherosclerosis lesion development. It should be noted, however, that most such studies do not provide a biochemical assessment of post-exposure levels. Although the respiratory properties of animals are different than humans, animal studies are especially important in studying the life course effects of SHS exposure due to their shorter lifespan. Thus, these studies have given sophisticated mechanistic insights into the possible pathogenesis of SHS exposure-related vascular disease.

1. Mouse studies—In 2001, Gairola et al found that side stream cigarette smoke accelerates atherogenesis in apo-E knockout mice. When these mice were maintained on a western diet and exposed to relatively high dose of SHS, there was a duration-dependent increase in atherosclerosis lesion development[120]. In 2004, Tani et al[121] documented increased carotid-artery intima-media thickness (CIMT) in mice who were exposed to SHS compared to controls. This was associated with an excessive antibody response to oxidized LDL C, raising the possibility that SHS and high lipoprotein levels might have an additive proatherogenic effect. As human studies have linked SHS exposure to accelerated lipid peroxidation and LDL C modification, this additive effect could be relevant to children and young adults[74]. The mechanism of these effects has also been studied in mice. Zhang et al[122] documented high levels of pro-inflammatory cytokines such as Interleukin-6 in adult mice exposed to SHS. Knight-Lozano et al[123] studied the effect of SHS on normal or dyslipidemic mice and documented high levels of oxidative stress and increased mitochondrial DNA damage of aortic tissue in SHS exposed mice; this effect was maximal in mice with both dyslipidemia and SHS exposure.

Fetterman et al[124] examined the effects of *in utero* and neonatal SHS exposure on both atherosclerosis lesion development in later life, as well oxidative stress and mitochondrial DNA damage in aortic tissue. Animals were exposed to 1mg/m^3 of SHS (4–5 ppm carbon monoxide, and 200–300 μg/m^3 nicotine), a level frequently found in smoky entertainment areas for adults, both *in utero* and early life exposure significantly increased adult atherosclerosis lesion development and resulted in significant alterations to the aortic tissue, mitochondria, and their genome. Oxidative stress levels were also markedly increased in the SHS exposed animals.

2. Rat studies—Mullick et al[125] used quantitative fluorescent microscopy to study endothelial cell injury after SHS exposure. In rats, SHS exposure increased carotid artery LDL C accumulation more than 4 fold compared with filtered air exposure and was associated with marked ultra structural damage to the carotid artery endothelial cells. Biochemical studies implicated a potentially damaging role from highly reactive carbonyl components[125].

Hutchison et al[126] examined the effects of SHS on vascular reactivity in newborn rats. *In utero* or neonatal exposure to SHS resulted in enhanced constrictor sensitivity, reduced endothelium-dependent dilatation, and decreased sensitivity to nitroglycerin, suggesting that exposure to SHS might have detrimental effects on vascular endothelial and smooth muscle function in very young animals. Mechanistic studies in rats have also linked SHS exposure to increased LDL C accumulation in ex vivo perfused arteries[127].

3. Rabbit studies—Zhu et al[128] exposed cholesterol fed rabbits to low or high dose SHS compared with filtered air, finding a dose-dependent increase in percent aortic involvement with atherosclerosis-like lesions. An increase in bleeding time was also seen, suggesting an acquired platelet dysfunction in these animals. Hutchison et al[129] later examined the effects of high cholesterol diet with or without SHS exposure in rabbits, finding both endothelial dysfunction and increased atherogenesis, with greater impairment of endothelial function in the combined high cholesterol and SHS-exposed animals, compared to those with high cholesterol only.

4. Cockerel studies—In 1993, Penn and Snyder[130] exposed 6 week-old cockerels to side stream smoke or filtered air, finding markedly increased atherosclerotic plaque in the abdominal aorta. In a subsequent study, Penn et al then decreased the exposure of SHS to a level often observed in a smoky bars and again found enhanced atherosclerosis in the cockerels exposed to even this lower dose of SHS[131].

Taken together, the data from these animal studies suggest that exposure to environmentally plausible levels of SHS in early life (including *in utero*) can conceivably increase atherosclerosis lesions later in life. Inferred mechanisms include increased oxidative stress, pro-inflammatory effects, mitochondrial damage, and impaired endothelial function.

Human Studies - Changes in vascular endothelial function

The vascular endothelium plays a central role in cardiovascular homeostasis, making or modifying a large number of chemicals that regulate arterial tone, thrombogenesis, cell proliferation, leukocyte adhesion, and platelet interaction, amongst others. A healthy endothelium maintains a normal dilator state and antithrombotic surface whereas endothelial dysfunction predisposes to vasoconstriction, thrombosis, cell proliferation, and leukocyte adhesion. These processes are thought to play a key role in early atherogenesis. Furthermore, in the presence of plaques, the loss of normal endothelium-dependent dilator function can predispose to vasoconstriction, plaque rupture and acute coronary events. Normal endothelial function and the consequences of endothelial dysfunction has been summarized in detail elsewhere[132, 133]. Endothelial dysfunction has been associated with a variety of common cardiovascular risk factors[134] and predicts future cardiovascular events.

One method for assessing endothelial function in humans non-invasively is the measurement of arterial flow-mediated dilatation (FMD) by ultrasound. This vasodilator response to shear stress is due to the endothelial release of nitric oxide, a chemical entity, which is responsible for vasodilatation, inhibition of leukocyte adhesion, platelet aggregation, and smooth muscle cell proliferation. The measurement of FMD was first described in 1992 in children and young adults at high risk of atherosclerosis[135] and has recently been shown to predict cardiovascular events in high risk patients[136].

1. Acute arterial endothelial dysfunction with SHS exposure—Although the evidence on acute arterial endothelial dysfunction in children and adolescents is limited, adult studies suggest potential mechanistic changes. In 2001, Otsuka et al[137] examined the acute effects of SHS on the coronary circulation, in healthy young adults. The authors measured coronary flow velocity reserve in response to Adenosine in young adult male non-smokers versus active smokers (mean age 27 years) before and after a 30-minute exposure to environmental tobacco smoke. They found that coronary flow velocity reserve was significantly impaired by exposure to SHS, in both the non-smokers and active smokers. This acute effect of SHS on coronary physiology has also been examined in women. Sumida et al[138] examined the effects of SHS on endothelium-dependent coronary artery dilatation in 38 women aged 40–60 years, finding that acetylcholine caused coronary vasoconstriction in passive and active smokers whereas it led to a normal dilator response in non-smokers.

At a mechanistic level, the effects of cigarette smoke on endothelial function ex-vivo have been examined in a number of studies. Cigarette smoke increases adhesion molecule expression on human endothelial cells[139], increases human monocyte adhesion to endothelial cells, an effect reversible by the nitric oxide precursor L-arginine[140]. Cigarette smokers have also been shown to have increased tissue factor expression in atherosclerotic plaques[141].

Hausberg et al[142] provided more insight when they studied the effect of acute short-term SHS exposure on muscle sympathetic nerve activity in 17 healthy young non-smokers (aged 28±6 years). One smoke inhalation session increased resting muscle sympathetic nerve activity by approximately 20% in the SHS exposed but not in the control group. This could underscore (in part) the association between SHS exposure in children and higher blood pressure[22].

2. Effects of chronic SHS exposure on arterial endothelial function—In 1996, Celermajer et al studied 78 healthy teenagers and young adults (aged 15–30 years) comprising 26 active smokers, 26 who had never smoked but had been exposed to SHS for at least one hour daily for 3 or more years, and 26 controls who were not SHS exposed or actively smoking[8]. Arterial FMD showed profound impairment in the passive as well as active smoking teenagers. Arterial dilatation induced by nitroglycerin was similar in all groups, localizing the defect in vascular reactivity to the endothelium.

This finding was later confirmed by Kallio et al in younger subjects[9]. As part of a longitudinal study in Finland, children had annual serum cotinine concentrations measured between ages of 8 and 11 years to assess environmental tobacco smoke exposure, and at age

11 years, had FMD assessed. Exposure to SHS, documented by cotinine concentrations were associated with impaired endothelial function in a dose-dependent manner in pre-teenage children (Figure 6). This effect was also observed in a Chinese population of adolescents. Yang et al studied FMD in 16 year-old Tibetan school students and documented impaired endothelial function in those exposed to SHS[73].

Juonala et al examined the effects of parental smoking in childhood on endothelial function in adult life, 19–27 years following the period of SHS exposure in the home[143]. Two populations were studied, one from Finland and one from Australia, and both groups saw reduced FMD in participants whose parents had smoked compared to those whose parents had not smoked. These findings suggested that SHS exposure in childhood could cause impairment in endothelial function, observable many years later. However, the authors noted that arterial endothelial dysfunction related to passive smoking might be at least partially reversible in healthy young adults[143]. This reversibility was documented by Raitakari et al[144] who examined endothelium-dependent dilatation in those formerly exposed to SHS compared with those currently exposed to SHS, aged 15–39 years of age. FMD was 2% in those currently exposed, 5% in those formerly exposed and 9% in controls, suggesting at least partial reversibility of SHS-related endothelial dysfunction, in those who were removed from SHS-containing environments.

In summary, there is compelling evidence that regular exposure to SHS in children and young adults is associated with arterial endothelial dysfunction, a likely predisposing factor to atherosclerosis and increased CVD risk in later life.

Mechanisms—A number of potential cellular mechanisms related to endothelial dysfunction have been documented in association with SHS. Studies have documented markers of oxidative stress in SHS and non-smoker, non SHS exposed groups, including increased levels of glutathione peroxidase and catalase in SHS exposed[145]. Inflammatory markers such as C-reactive protein and oxidized LDL C are also higher in those who are SHS exposed[146]. The presence of such reactive oxygen species and inflammatory markers are known to reduce the production and/or activity of endothelial nitric oxide synthase[147]. Following up on animal work implicating mitochondrial damage as a potential pathogenetic mechanism in SHS exposure, a recent review by Yang et al[148] concerning fetal, childhood, and adult exposure to SHS and mitochondrial damage and dysfunction, concluded a potentially important role of mitochondrial abnormalities in mediating CVD susceptibility.

3. Changes in vascular tone/stiffness and structural vascular changes—

Adequate arterial function includes the transmission of blood flow to downstream tissue capillary beds with minimal energy loss, and regulation of blood flow in those tissue beds with steady flow proportional to metabolic demand. These arterial actions are determined by the structure and function of large “conduit” and small “resistant” arteries. Assessment of structure includes, but is not limited, to measurement of CIMT, and arterial stiffness. SHS exposure appears to distort arterial structure. These distortions are of clinical relevance as recent reports indicate that peripheral artery disease is higher in those exposed to SHS in childhood adjusted for other adult predictors of peripheral artery disease[149].

CIMT is assessed by ultrasound imaging of the carotid artery near the bifurcation into external and internal carotids. CIMT captures the effect of accumulated cardiovascular risk factors to the arterial wall. With every 1mm increase in CIMT measurement in adults, the hazard ratio for CVD increases by 2.46[150]. CIMT also measures localized plaque formation which may have independent prognostic information[150]. The Atherosclerosis Risk in Communities study demonstrated in adults a clear association between SHS exposure and thickening of CIMT[151]. Other studies suggest that SHS exposure is dangerous in younger adults and in those with low levels of other CVD risk factors as well[152–154]. In children with *in utero* SHS exposure, CIMT was thicker, while postnatal SHS exposure appeared to be less predictive of a higher CIMT[10]. Some studies suggest a positive relationship between higher postnatal SHS exposure (Figure 7) and thicker CIMT, while other investigators did not find this relationship[71, 155, 156]. It should be noted that although this evidence is not conclusive of cardiovascular disease as a result of SHS exposure, a relationship that will take decades to observe, this is compelling medium-term proxy evidence that supports the deleterious effects of SHS on the vasculature.

Arterial stiffness is a measure of the material properties of the artery, and is associated with traditional CVD risk factors, predicts future CVD, and hypertension[157, 158]. Several methods can be used to measure arterial stiffness including carotid-femoral pulse wave velocity, the degree of pulse wave reflection called augmentation index, or arterial distensibility which is a change in diameter of the carotid artery from diastole to systole. In adults, chronic SHS exposure decreased carotid artery distensibility in persons already at risk of impaired distensibility including the obese, the elderly, and those with increased CIMT[159]. Moreover, experiments of acute SHS exposure in adults showed reduced aortic distensibility[160]. Children with *in utero* SHS exposure also appeared to have 15% less distensible arteries[10]. Adolescents from the Special Turku Coronary Risk Factor Intervention Project demonstrated associations between serum cotinine and decreased aortic elasticity (Figure 8)[11]. However, other population based studies do not show differences in childhood aortic stiffness on the basis of *in utero* smoking exposure[161]. So while SHS exposure appears to consistently induce acute and chronic alterations in endothelial function, the effects on arterial structure are not consistent and may depend on the nature and degree of exposure.

4. Arrhythmia and SHS exposure—The effects of SHS exposure on heart rate and rhythm in children are not well studied. Acute cardiovascular effects of SHS in the young include tachycardia[137] and an increase in blood pressure[22]. An important potential pathway for tobacco exposure in children is *in utero.* Interestingly; the effects of *in utero* and postnatal SHS exposure on autonomic function seem to be gender specific. Schuetz et al[162] examined the association between *in utero* SHS exposure and neonatal heart rate and heart rate variability assessed at 2–4 weeks of age. Neonates with *in utero* SHS exposure had higher heart rates and lower heart rate variation with breathing, than those in the non-exposed group. For unexplained reasons boys who were exposed to SHS either *in utero* or postnatally had higher heart rates and lower heart rate variation than SHS exposed girls at age 2–4 weeks[162]. A recent longitudinal study by Dixit and colleagues measured the effects of SHS exposure in childhood and *in utero* on arrhythmia development as an adult. The authors found that SHS exposure *in utero* and during childhood were associated with having

atrial fibrillation later in life. The findings of this study indicated that SHS in early life may be an important, potentially modifiable risk factor for the development of late arrhythmia [163].

The cardiac effects of direct smoking and SHS exposure in adults are well documented and could suggest hypotheses for studying children exposed to SHS. Smoking is associated with release of the sympathetic neurotransmitter norepinephrine, and the adrenomedullary hormone epinephrine[164]. In addition, nicotine has a direct effect on sympathetic nerve endings, favoring catecholamine release. Thus, cigarette smoking has a powerful sympathetic excitatory effect influencing sympathetic drive to blood vessels, skin, and to the heart[165].

Supporting these theoretical concerns, chronic adult smokers have a blunted heart rate response to exercise and decreased exercise tolerance compared to non-smokers, partially due to down-regulation of cardiac beta-adrenergic receptors[166, 167]. SHS exposure generates an autonomic system imbalance associated with increased cardiac vulnerability and may lead to arrhythmias such as atrial fibrillation, ventricular tachycardia, and ventricular fibrillation especially in those with other pre-existing CVD risks [163, 168–170]. There is a higher incidence of arrhythmias in adults with coronary artery disease and cardiomyopathy who have been exposed to SHS and specific components of SHS (carboxyhemoglobin), including an increased frequency of premature ventricular contractions during supine bicycle exercise testing and ventricular arrhythmias[168–170].

The pathophysiological mechanism of smoking-related arrhythmias is complex and influenced by several of the major components of tobacco smoke. It includes alteration in autonomic function and a pro-fibrotic effect of nicotine and carbon monoxide on myocardial tissue with consequent increased sensitivity to catecholamine[171]. As noted above, specific components of SHS such as carbon monoxide, may contribute to the generation of ventricular arrhythmias via endothelial dysfunction and coronary vasoconstriction[171–173]. Nicotine, carbon monoxide, and oxidative stress induce fibrosis at different cardiac sites, resulting in a structural remodeling that can predispose the patient to arrhythmias[171].

Autonomic dysfunction and SHS exposure

In utero or postnatal SHS exposure increases the risk of Sudden Infant Death Syndrome (SIDS), particularly if postnatal exposure is in proximity to the infant[1, 174–187]. Compared with infants who were not exposed to SHS either *in utero* or postnatally, the risk of SIDS is greater in infants exposed in both *in utero* and postnatal periods (3 fold increase), and in those with only postnatal exposure (2 fold increase)[176]. Furthermore, the risk of SIDS increases with increasing dose of SHS exposure[176]. In the Wales Perinatal Survey, over half of the infants known to have died suddenly lived in households with SHS[186]. Behm et al studied the association between a higher prevalence of smoke-free homes and decreasing rates of SIDS, controlling for an important risk factor for SIDS, supine sleep position. On a population basis, for every 1% absolute increases in the prevalence of smoke-free homes, SIDS rates decreased 0.4% from 1995–2006[188].

The mechanism behind SHS exposure and SIDS may include effects on the normal regulation of breathing. Experimental data from animal studies have shown that exposure to SHS can have adverse effects on brain cell development[189–191]. In addition, autonomic function is altered by *in utero* exposure to SHS. Newborns whose mother smoked during pregnancy have lower beat-to-beat, heart rate variability during quiet sleep[192]. Unexposed infants demonstrated increases in heart rate with head-up tilt and decreases in heart rate with head-down tilt, while infants exposed to SHS showed no such responses[192]. Maternal smoking induces changes in autonomic control and maturation in infants[193]. Cardiovascular stress reactivity is increased in newborn infants of active smokers[194]. The resting heart rate of a smoker's infant is lower than non-exposed control, most likely secondary to excessive vagal tone[23]. Vagal potentiation is considered a predisposing factor in SIDS[195–197]. Any smoking during pregnancy or during the first year of the infant's life increases the risk of SIDS[186].

Summary Table - Childhood SHS exposure results in

- Endothelial dysfunction
- ⇑ arterial stiffness
- ⇑ carotid artery intima-media thickness
- Autonomic dysfunction
- Late onset arrhythmia

Behavioral and community strategies to reduce/eliminate SHS exposure in children

Individual and population based approaches

Several controlled trials over the last 25 years have evaluated interventions aimed at reducing or eliminating SHS exposure in children. Intervention strategies fall into two broad groups, including those that (1) directly attempt to minimize SHS exposure to children, and (2) indirectly minimize children's SHS exposure by assisting parents or caretakers to quit or reduce smoking. The majority of studies have targeted parents, rather than non-parental caregivers. Interventions that directly minimized child harm from SHS used a variety of strategies including, counseling (face to face or by telephone) or provision of materials to encourage parents not to allow smoking in the home or car, not smoke around their children, or remove the child from rooms in the home or other locations when smoking is taking place (hygienic smoking). Other strategies include providing air cleaners or biochemical feedback (as in cotinine measurements in children) of child SHS exposure.

Cessation/smoking reduction interventions typically have used behavioral counseling and/or pharmacotherapy such as nicotine replacement. A variety of outcomes have been assessed, including self-reported behavior change related to child SHS exposure (e.g., enforcement of home smoking ban, restricting smoking to designated smoking areas), self-reported smoking cessation or reduction (with or without biochemical verification), biochemical measures of children's absorption of environmental tobacco smoke (typically cotinine assessed in urine,

blood, saliva, or hair), and biochemical measures of ambient environmental tobacco smoke (usually nicotine or particulate matter) from rooms or other spaces where children are exposed.

Several literature reviews on this topic have been conducted. These include non-systematic narrative[198–200]; systematic narrative[201, 202]; and systematic quantitative (i.e., meta-analytic) reviews [203–206]. The meta-analytic reviews include one originally published in the Cochrane Collaboration database in 2003[203] and updated in 2008[204] and 2014[206]. Arborelius et al. only included interventions that occurred in pediatric practices, but other reviews did not limit the setting of interventions[198].

Two most recent reviews (Rosen et al.[205] and Baxi et al.[206]), both published in 2014, included 57 and 30 trials, respectively. Rosen et al.'s systematic review[205] included fewer studies than Baxi et al[206], due to restricting eligibility to studies that delivered interventions to parents (not other family members, child care workers, and teachers), targeting children no older than 6 years of age (compared to 12 years of age in Baxi et al's review), and focusing on interventions to help parents decrease child SHS exposure (Baxi et al. also included smoking cessation programs that measured child SHS exposure as an outcome but did not have child SHS reduction as an explicit goal).

Rosen et al. combined and analyzed effects for three categories of outcomes: 1) parent-reported exposure to SHS of the child at follow-up and change from baseline to follow-up; 2) parent-reported number of cigarettes smoked around the child at follow-up; and 3) measured levels of cotinine or nicotine in urine, blood, saliva, or hair of the target child at follow-up[205]. Parent-reported SHS exposure to child *at follow-up* was collected by 17 studies and showed a small, statistically significant effect favoring intervention groups vs. controls (Relative risk [RR] = 1.12 [1.07–1.18]). The risk difference (RD) was 0.07 (0.05–0.09) indicating that 7% of intervention families benefited, on average. The effect for parent-reported exposure to SHS was positive but not statistically significant when analyzed *as change from baseline to follow-up* (RR 1.44 [0.90–2.29])[205].

Parent-reported number of cigarettes to which children were exposed, decreased in both intervention and control groups, but to a greater extent in intervention groups (RD= −0.24 [−0.46 −0.03], p=0.03). Among thirteen studies that used biomarkers of child SHS as the outcome, eight showed positive effects, but statistical significance was reached in only one. The overall RD was −0.05 (−0.13 − 0.20, p=0.20) showing a non-significant trend toward a small benefit of intervention. No clear benefit was demonstrated in sub-group analyses that compared studies based on whether biochemical feedback was provided as an intervention strategy, intensity of the experimental intervention, intensity of the control intervention, and treatment fidelity[205].

The authors concluded that interventions to reduce child SHS exposure showed "small benefits" when assessed by parent self-report, but this effect was not corroborated by objective, biochemical outcomes. It is unclear why an effect is observed for self-reported vs. objective outcomes, but may be related to greater statistical power for parent-reported outcomes (due to a greater number of studies), unreliability of parent reports due to lack of

knowledge of their children's exposure or intentional misreporting, or inadequate sensitivity of biomarkers to detect small changes in exposure levels[205].

It is also noteworthy that many studies reported positive outcomes in control groups, which may be related to generally high levels of motivation in trial participants regardless of treatment allocation, effects of monitoring (Hawthorne Effect), or that parents tend to reduce their smoking around their children regardless of intervention (e.g., due to social pressure or secular trends that make childhood SHS exposure less acceptable). Regardless, the overall conclusion is that available interventions produce, at best, small effects, and there is no empirical basis to recommend specific intervention strategies, intensities, or delivery formats.

Baxi et al. reached similar conclusions. Among the 57 studies included in this review, 16 focused directly on minimizing child harm from SHS by changing parent/caregiver behaviors or attitudes, 20 focused exclusively on helping parents/caregivers to quit smoking or not relapse, and 21 used a combination of these two intervention approaches. Effects were not quantitatively combined due to heterogeneity of study design and characteristics. The resulting narrative review did not find evidence that any particular intervention strategies were more effective than others[206]. Only 14 of the 57 studies found a significant intervention treatment effect, and of these, 12 were judged to have either unknown or high risk of bias. These studies used a wide range of interventions including intensive counseling or motivational interviewing, telephone counseling, school-based strategies, picture books, and educational home visits. Similar to Rosen et al., this review found reductions in SHS exposure for children regardless of assignment to intervention or control groups[205]. Further, there was no evidence of difference in effectiveness according to age of the target child or whether targeted children were healthy or had respiratory or other illnesses. The authors concluded that effectiveness of interventions to reduce child SHS exposure has not been clearly demonstrated.

Expert Panel Recommendations

The Task Force on Community Preventive Services reviewed evidence for the effectiveness of community education to reduce exposure to SHS in the home. Community education approaches included enhancing motivation or providing skills to quit or reduce smoking or implementing home policies, such as bans, to reduce exposure to SHS. The task force concluded[207] that there was insufficient evidence to make a recommendation about the effectiveness of community education to reduce SHS exposure in the home.

A more recent expert panel[208] concluded that interventions in pediatric care settings to reduce children's SHS exposure showed "mixed results." However, due to the serious public health implications of SHS, it recommended that pediatric healthcare providers routinely intervene. The expert panel encouraged providers to identify parents and other caregivers who smoke and explicitly recommend that children not be exposed to tobacco smoke in the home, in automobiles, and in any other space where exposure can occur. Further, the expert panel concluded that parents and caregivers who smoke should be educated about the health consequences of tobacco use to the adult, the child, and (where appropriate) fetus, encouraged to quit, and referred for smoking cessation assistance. Adding routine

biochemical screening to detect metabolites of SHS as part of health promotion may detect levels of exposure different than what is reported by parents. Such screening could be used by clinicians to identify high risk children for intervention.

Effect of smoking bans and taxes

Home smoking bans significantly reduce SHS exposure among children[209], and may also lower the likelihood that children of smokers will take up smoking[32]. Unfortunately, approximately 16% of smoking households did not have any restrictions against indoor smoking by 2006–2007[57], with a similar proportion in 2010–2011[49] and children in these households were still likely be exposed to SHS.

The effect of smoking bans in public places and its effect on children's exposure to SHS are less clear, with some suggesting that smoking bans could potentially increase SHS exposure in children, by displacing parental smoking from public places into their households. An observational study from England in 2007 by Jarvis et al using cotinine levels in children, found no evidence of increased household exposure following implementation of a legislative smoking ban. Adoption of smoke-free homes by smoking parents increased significantly after this ban, suggesting that it helped reinforce an emerging social norm favoring voluntary parental smoking restrictions[210]. Similar results have been seen in the US, where voluntary home-smoking bans in both smoking and non-smoking households were significantly more likely when community-wide 100% smoking bans were also in effect[211].

In 2010, over 20 experts in economics, epidemiology, public policy, and tobacco-control concurred on the favorable effectiveness of increased tobacco excise taxes and cigarette prices in reducing overall tobacco consumption and improvement of public health, including prevention of initiation and uptake among young people[212].

Summary Table - Interventional strategies to ⇓ childhood SHS

- Tobacco cessation programs ⇓ health care costs
- Home smoking bans and public smoking bans ⇓ childhood SHS exposure
- ⇑ taxes on tobacco products ⇓ tobacco consumption

Future directions

Children exposed to SHS experience both short and long-term adverse effects, including not only well-known respiratory complications but also cardiovascular consequences related to heart rate, blood pressure, autonomic effects and vascular dysfunction.

Questions remain about the mechanisms by which SHS exposure is related to adverse effects in childhood. For example, infants exposed to SHS are at higher risk for SIDS, but the mechanism by which SHS exposure increases risk of SIDS is not clear. Hypotheses include altered breathing patterns and diminished autonomic variability but more investigation is needed. Is the risk related to *in utero* or current SHS exposure, or are they both important? Similarly, epidemiological studies show increases in heart rate and blood pressure in

children exposed to SHS. What is their clinical implication, if any, for an individual child, and for the population? How do the findings of increased heart rate and blood pressure integrate with the literature on chronic exposure to childhood stress, which may be an additional exposure for these children? Exposure to SHS is related to dyslipidemia and metabolic syndrome. Does SHS exposure cause these changes or are there confounding factors that mediate these relationships? Do epigenetic changes play a role? What is the impact of concomitant lifestyle factors, which may also increase the risk of CVD? Adults with SHS exposure are at risk for ventricular arrhythmias, possibly related to the release of catecholamines. Does this phenomenon also occur in childhood? In all these processes, are there particular components of SHS exposure that are to blame? Can we further tease out which components of SHS cause child-specific toxicities, particularly long-lasting ones, with a goal of minimizing or eliminating those in tobacco products as a plausible intervention?

Questions also remain with regard to the timing and durability of adverse effects of SHS exposure. What is reversible and what is persistent? Is there a tipping point after which the cardiovascular effects persist despite elimination of SHS exposure? Are there vulnerable periods where the effects are more pronounced or long lasting, perhaps infancy or adolescence? What about a threshold effect? How many years of SHS exposure are needed before the vascular changes are irreversible? More information is needed with regard to mechanisms, severity of effects, whether there are vulnerable periods for exposure, and if so, when they are, and whether all effects can be reversed. Despite these knowledge gaps about mechanisms and durability by which SHS exposure in children impacts the cardiovasculature, the sum of existing evidence suggests that reduction or elimination of SHS exposure in childhood will improve their cardiovascular health.

Therefore, new and better methods are needed to promote behavior change to reduce and ultimately eliminate SHS exposure using federal, state and local policy efforts, strategies within the healthcare system and interventions at the level of the individual. The concept of “hygienic smoking” which is defined as being as far away as possible from the smoker has been proposed, and some studies suggest a benefit, mitigating long term adverse vascular effects of childhood SHS exposure[18]. How exactly is “hygienic smoking” implemented? This will be important while we are perfecting prevention and cessation efforts directed at smoking parents and close contacts of children. Does banning smoking in public places increase exposure to SHS in children at home? Adolescents report that an important component of their SHS exposure occurs outside the home. What additional interventions can be brought to bear to address this high-risk population? Interventions to reduce SHS exposure in childhood are effective when parental report is the measurement outcome[205, 206] but the effect is quite small and no significant benefit is seen when biochemical markers of SHS are used as the outcome (e.g. cotinine levels). How can we make a bigger impact? Future experimental research, such as SHS exposure reduction trials, should include specific cardiorespiratory outcomes or proxy outcomes in children.

Future directions for policy makers, health systems administrators, and providers should include systematic change methods to promote cessation such as electronic health records prompts, making cessation referral programs more easily available, training providers to be

knowledgeable about best practices, working with “Head Start” to access parents outside of the medical system, providing real time feedback to parents about progress by way of changes in their child’s cotinine levels, focusing efforts to target high-risk minority and lower SES children living in multi unit housing, routine biochemical screening for tobacco metabolites in high risk children, and continued public health campaigns to spread information about the prevailing health and economic effects of SHS exposure, particularly as they relate to children.

Conclusion

A half a century following the first US Surgeon General warning about the harmful effects of cigarette smoking, we have seen dramatic reductions in incidence and prevalence of smoking as well as significant reductions in childhood SHS exposure. However, exposure to SHS in childhood remains high, and children remain especially vulnerable and are involuntarily exposed to SHS. Investments have been made in enforcing ordinances and bans that prohibit smoking in certain locations; increasing taxes on tobacco products and in education and behavior modification. While these have had a favorable impact in reducing smoking prevalence and improving awareness of the consequences of cigarette smoking, young and minority children remain disadvantaged. Based on the epidemiological, observational, and experimental evidence that is presented here, we conclude that the long-term cardiovascular consequences of SHS exposure in children are detrimental. Health care providers need to emphasize and promote heart healthy behaviors in caretakers of children at every encounter and encourage parents and caretakers to cease smoking for their own and their child’s wellbeing. According to recent US Surgeon General recommendations, interventions that include mass media campaigns, cigarette price increases including those that result from tax increases, school-based policies and programs, and statewide or community-wide changes in smoke free policies and norms are effective in reducing the initiation, prevalence, and intensity of smoking among youth and young adults and will in turn substantially decrease SHS exposure. Public health providers and communities need to promote interventions to lower and ultimately eliminate childhood SHS exposure. The evidence presented in this statement calls for a robust public health policy that embraces “zero tolerance” to childhood SHS exposure.

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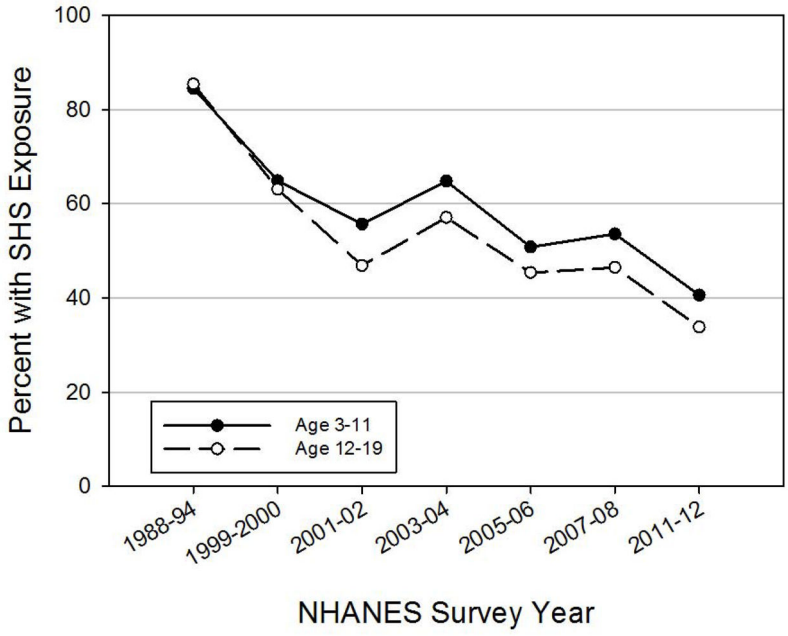

Figure 1.

Trends in SHS exposure among non-smoking children and adolescents in US. Data compiled from NHANES periodic survey data[3, 35, 48]

Solid line: children aged 3–11 years; Dashed line: adolescents aged 12–19 years

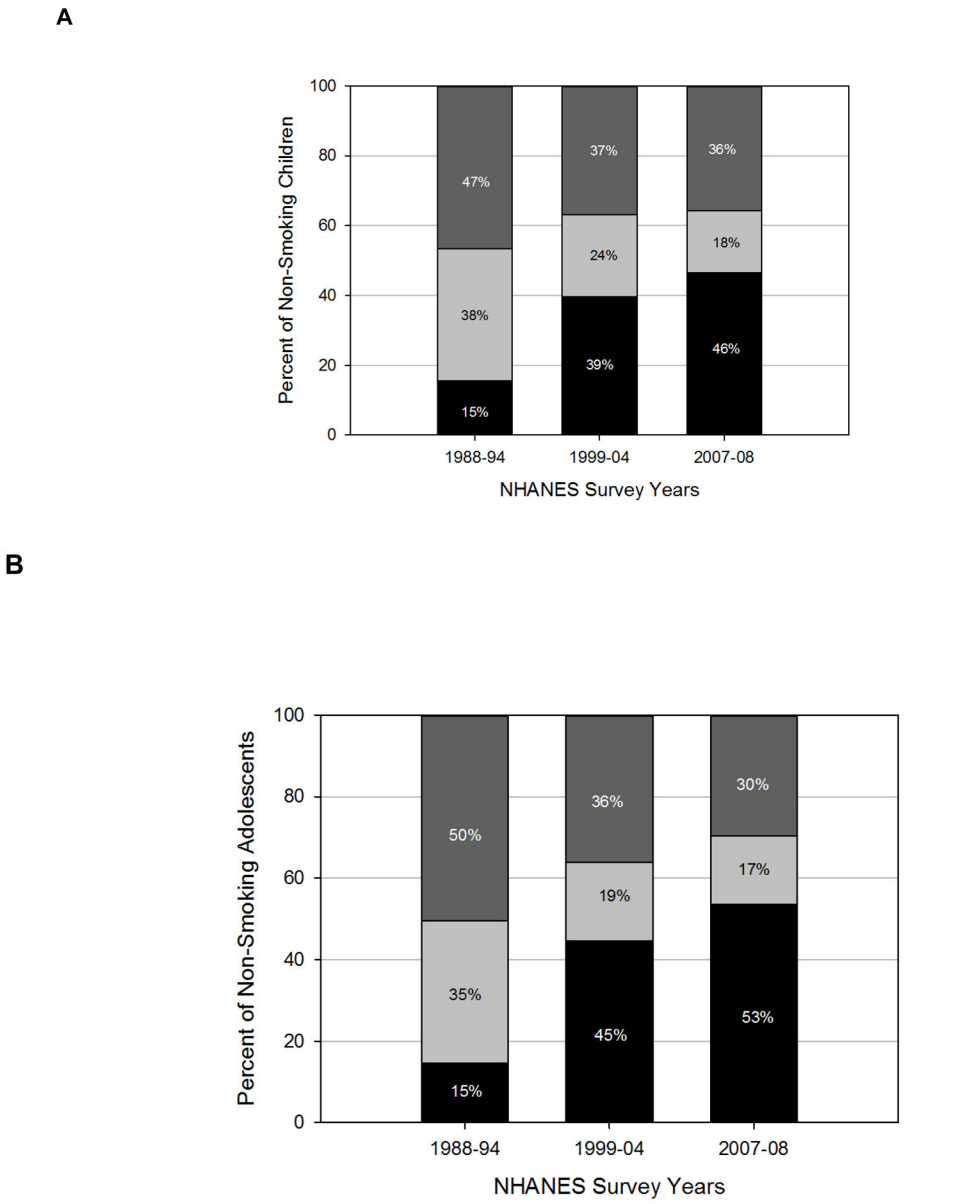

Figure 2.

Figure 2A and 2B. Prevalence and estimated source of SHS exposure in non-smoking A) children aged 3–11 years and B) adolescents aged 12–19 years by NHANES study years. Data for these figures were compiled using NHANES periodic survey data. Overall SHS exposure is presented as NHANES estimated prevalence of SHS exposure by age group [35, 48]. To then estimate home-specific exposure, the proportion of non-smoking children or adolescents living with a smoker at home[35, 48] was multiplied by the proportion of these children (98%) with detectable cotinine levels [48, 50]; the remainder of SHS exposure was assumed to be not in the home.

Black indicates no SHS exposure (inside or outside of the home), light gray indicates SHS exposure in the home, and dark gray indicates SHS exposure outside of the home.

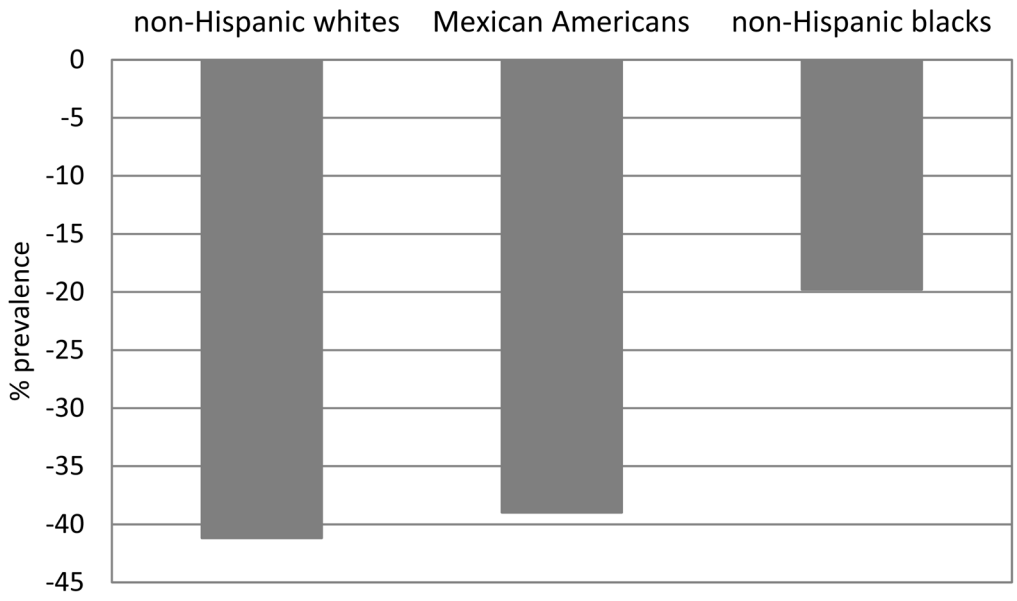

Figure 3.
Decline in SHS exposure prevalence from NHANES 1999–2000 to 2011–2012 by race

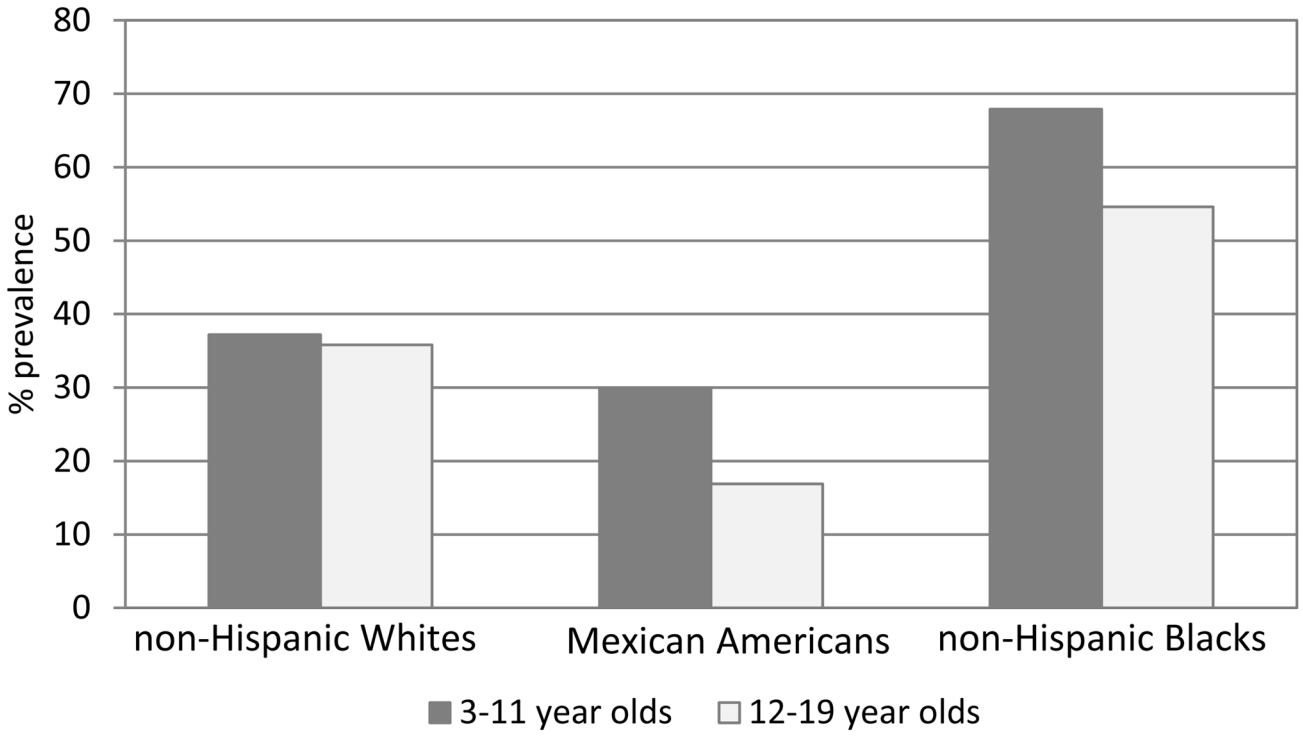

Figure 4.
NHANES 2011–2012 SHS exposure prevalence by age and race

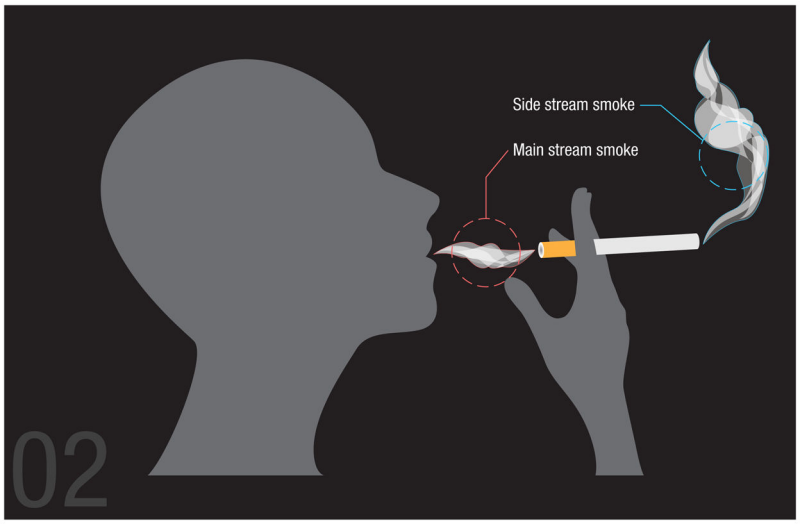

Figure 5.
Mainstream and side stream smoke

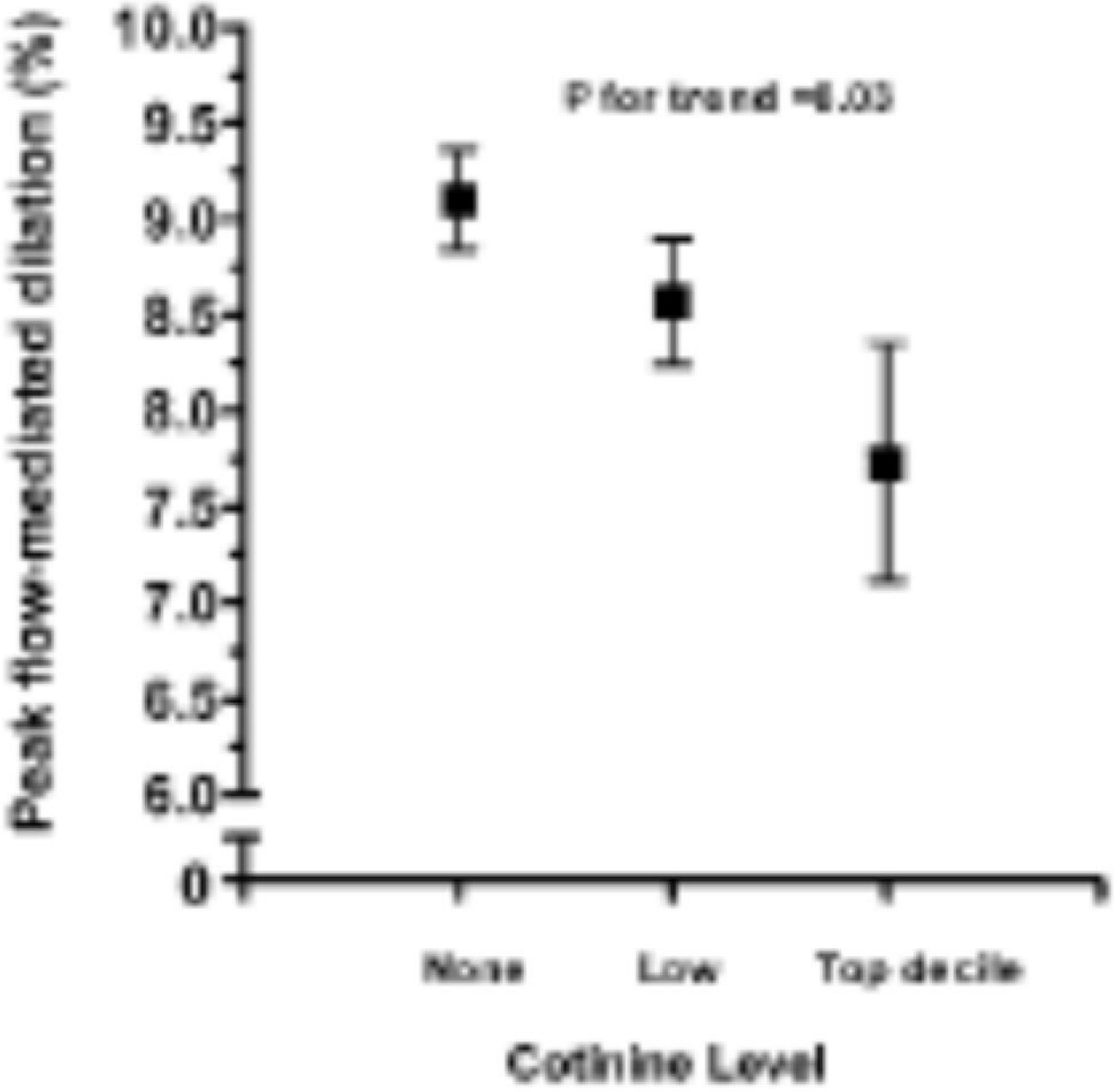

Figure 6.

Peak FMD of brachial artery in 11-year-old children according to cotinine group. Values are mean ± SEM.

Kallio K, Jokinen E, Raitakari OT, Hamalainen M, Siltala M, Volanen I, Kaitosaari T, Viikari J, Ronnemaa T, Simell O. Tobacco smoke exposure is associated with attenuated endothelial function in 11-year-old healthy children. *Circulation*. 2007;115:3205–3212

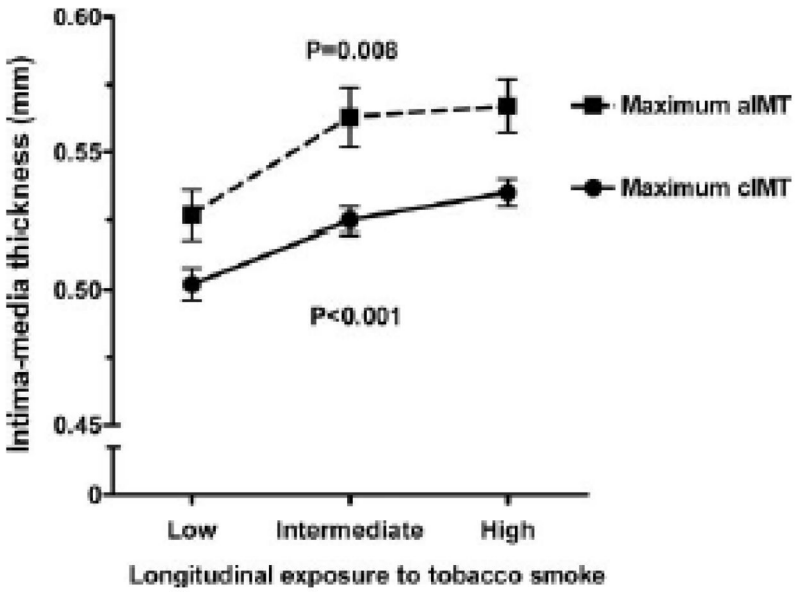

Figure 7.

Maximum cIMT (black circles) and maximum aIMT (black squares) in healthy 13-year-old adolescents according to longitudinal tobacco smoke exposure levels. Number of adolescents in exposure groups: cIMT: low (n=160), intermediate (n=171), high (n=163); aIMT: low (n=159), intermediate (n=167), high (n=161). Values are mean ± SEM

cIMT – carotid artery intima media thickness

aIMT – aortic intima media thickness

Kallio K, Jokinen E, Saarinen M, Hamalainen M, Volanen I, Kaitosaari T, Ronnemaa T, Viikari J, Raitakari OT, Simell O. Arterial intima-media thickness, endothelial function, and apolipoproteins in adolescents frequently exposed to tobacco smoke. *Circulation. Cardiovascular quality and outcomes*. 2010;3:196–203

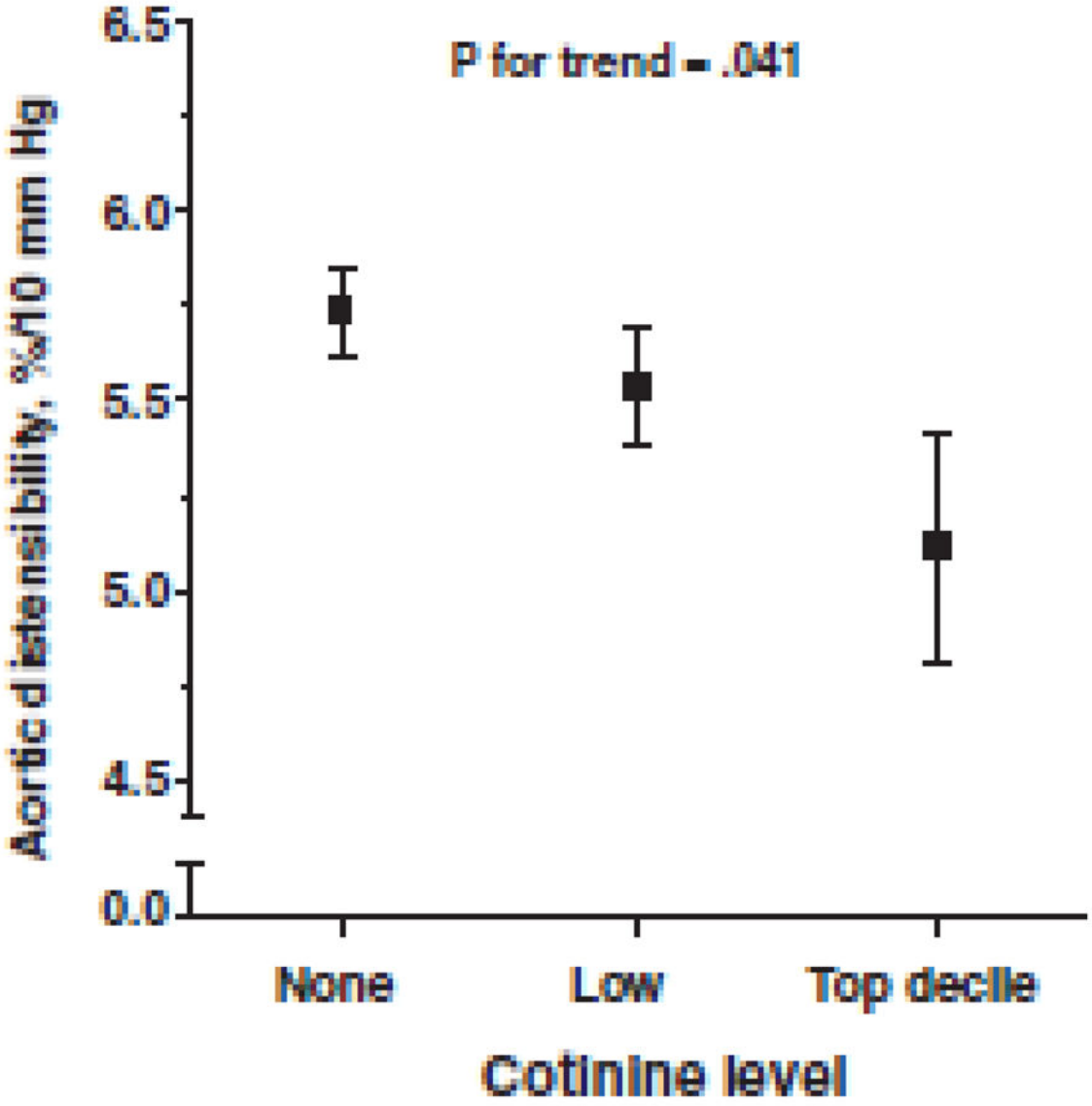

Figure 8.

Aortic distensibility in children exposed to second hand tobacco smoke

Kallio K, Jokinen E, Hamalainen M, Saarinen M, Volanen I, Kaitosaari T, Viikari J, Ronnemaa T, Simell O, Raitakari OT. Decreased aortic elasticity in healthy 11-year-old children exposed to tobacco smoke. *Pediatrics*. 2009;123:e267–273

Table 1

Abbreviations

	Abbreviation
Second-hand tobacco smoke	SHS
Centers for Disease Control and Prevention	CDC
Socio-economic status	SES
Sudden infant death syndrome	SIDS
Cardiovascular disease	CVD
National Health and Nutrition Examination Survey	NHANES
Body mass index	BMI
Carotid artery intima-media thickness	CIMT
Low-density lipoprotein cholesterol	LDL C
Flow mediated vasodilatation	FMD
High-density lipoprotein cholesterol	HDL C
Relative risk	RR
Confidence interval	CI
Risk difference	RD

Table 2

Selected chemicals present in SHS and their strength in side stream versus mainstream smoke

SHS* chemicals	Enrichment Ratio Side stream versus mainstream smoke
Carbon dioxide	8–11
Carbon monoxide	2.5–4.7
Nicotine	2.6–3.3
Carbonyls	
Acrolein	8–15
Formaldehyde	0.1–50
Hydrocarbons	
Toluene	5.6–8.3
Benzene	5–10
Pyridine	6.5–20
Ammonia	40–170
Nitrogen oxides	4–10
Hydrogen cyanide	0.1–0.25
Particulates: 'Tar'	
Larger PAH	1.3–1.9
Nitrosamines	0.6–100
Polonium	1–4
Nickel	13–30
Cadmium	7.2

*SHS – Secondhand tobacco smoke

Referenced from citation [213]