Prevention – Passive smoking and pregnancy

Tim S. Nawrot [*], *Bianca Cox*, *Bram G. Janssen*, *Michelle Plusquin*

Centre for Environmental Sciences, Hasselt University, Belgium
Leuven University, Department of Public Health & Primary Care, Belgium

1. Introduction

Epidemiological studies have demonstrated that tobacco smoke is a major cause of both cancer and vascular diseases. More than 3800 chemicals are present in tobacco smoke, which may cause oxidative stress via biotransformation or by macrophage activation. In 1954, Richard Doll and Bradford Hill published the first prospective evidence on cigarette smoking and lung cancer [1,2]. In 1962, Framingham investigators published data showing that smoking increased the risk of heart disease [3]. Nevertheless, despite the strong evidence, uncertainty was manufactured and enlarged. This strategy is a common practice to reduce the public health implications from epidemiological findings and was used not only by tobacco companies but also by other industrial arms, including asbestos and lead factories [4]. For almost half a century, the tobacco companies hired scientists to dispute first that smokers were at greater risk of dying of lung cancer; second, the role of tobacco use in heart disease; and finally, the evidence that environmental tobacco smoke increased disease risk in non-smokers [5,6].

The effect of in-utero exposures on health in childhood and later in life is a growing area of research interest, with major public health implications. Children are vulnerable to the adverse effects of environmental tobacco smoke as their lungs and immune system are undergoing further development. The first publications of detrimental health effects of parental smoking on children's respiratory health were published in the early 1970s [7]. Exposure to environmental tobacco smoke in the first 2 years of life has been estimated in some European countries by Pattenden et al. [8] and ranged from 19% in Germany to 70% in Bulgaria.

2. Meta-analytical evidence of early-life effects

There is pooled evidence that constituents of cigarette smoke cross the placenta, induce pregnancy complications, reduce intrauterine foetal growth and increase the risk of preterm delivery (Table 1) [9,10]. Meta-analytical evidence has also shown increased risk of respiratory and ear infections [11–13], overweight [14]and an increase in blood pressure [15] in early life and/or childhood, suggesting that maternal smoking in pregnancy influences the foetal development of different organ systems. Indeed, low birth weight and preterm delivery are also determinants of health risks later in life, including childhood asthma [16,17]. A cross-sectional study of 11,500 participants of 8–11-year-old children showed that prenatal exposure to cigarette smoke has a stronger effect on childhood asthma compared with postnatal smoke [18]. Prenatal exposure to maternal smoking without subsequent postnatal exposure to environmental tobacco smoke was related to the presence of asthma at school age with an odds ratio (OR) of 1.8 (95%CI: 1.1–2.9) [18].

Parental smoking increases the risk of acute lower respiratory tract diseases in children [12,13]. The pooled estimates showed a higher risk in association with smoking by the mother (OR: 1.56, 95%CI: 1.51–1.62) than with smoking by the father (OR: 1.31, 95%CI: 1.20–1.42) [12]. The higher risk related to the mother's smoking could be explained by the fact that young children usually spend more time with their mother or by the interplay with maternal smoking during pregnancy. In addition to lower respiratory tract infections (OR: 1.51 95%CI: 1.44–1.52), exposure to environmental tobacco smoke has been associated with an increased risk of otitis media (OR: 1.32, 95%CI: 1.14–1.52) [12].

Exposure to prenatal tobacco increases the level of genetic damage in newborns and children. A meta-analysis performed in children exposed to environmental tobacco smoke showed that children and newborns had, respectively, 1.3 and 6.7 times higher levels of haemoglobin adducts compared with non-exposed newborns [19]. Available meta-analytical evidence of an association between in-utero exposure to tobacco smoke from the parents and childhood cancer seems weak. Maternal smoking was estimated as an increased risk

* Corresponding author. Address: Centre for Environmental Sciences, Hasselt University, Agoralaan building D, 3590 Diepenbeek, Belgium (T.S. Nawrot). Tel.: +32 11 268382; fax: +32 11 268299.
E-mail address: tim.nawrot@uhasselt.be (T.S. Nawrot).
1359-6349/$ - see front matter
http://dx.doi.org/10.1016/j.ejcsup.2013.07.003

Table 1 – Meta-analytical evidence of early-life exposure to cigarette smoke.

Disease	Author/Year (population)	Design	N articles	N	Pooled Estimate
Placenta previa	Castles et al. [9] (North America, Western Europe)	Case–control Cohort	6	50.695 Patients	1.58 (1.04–2.12)[a]
Abruptio placenta			8	57.302	1.62 (1.46–1.77)[a]
Ectopic pregnancy			9	10.632	1.77 (1.31–2.22)[a]
Preterm PROM[c]			6	34.668	1.7 (1.18–2.25)[a]
Pre-eclampsia			5	4.451	0.51 (0.38–0.64)[a]
Preterm delivery (>32 weeks but <37 weeks of gestation)	Shah et al. [10] (Europe, North America)	Case–control	20	Cases: >100.000	1.27 (1.21–1.33)[a] 0-10 Cig/Day: 1.25 (1.12–1.38)[a] 11-20 Cig/Day: 1.38 (1.23–1.55)[a] >1 Pack/Day: 1.31 (1.19–1.45)[a]
Acute lymphoblastic Leukaemia (Childhood)	Boffeta et al. [20] (Europe, North America)	Case–control	4	Primary Not Given	Paternal smoking during pregnancy1.17 (0.96–1.42)[b]
	Milne et al. [23] (Europe, North America, Australia)		11	Cases: 1994	Paternal smoking around the time of conception1.15 (1.06–1.24)[a]
Acute otitis media	Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)		3	Primary Not Given	Smoking by Either Parent0.99 (0.70–1.40)[a]
Asthma	Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)		31	Primary Not Given	Asthma Smoking by Either Parent: 1.23 (1.14–1.33)[a] Smoking by Both Parents: 1.42 (1.30–1.56)[a] Maternal Smoking: 1.33 (1.24–1.43)[a] Paternal Smoking: 1.07 (0.97–1.18)[a]
Bladder cancer	Van Hemelrijck et al. [51] (Asia, Europe, North America)	Case–controlCohort	8	~223.000 Participants	Childhood Exposure1.19 (0.88–1.62)[b]
Blood pressure	Brion et al. [15] (Primary not given)	Cohort	9	16.690 Participants	Maternal Smoking During Pregnancy Systolic Blood Pressure:0.67 mmHg (0.31 to 1.04)
Breast cancer	Pirie et al. [52] (Asia, Europe, North America)	Case–controlCohort	25	~220.000 Participants	Childhood Exposure: 0.98 (0.88–1.08)[b]
Childhood cancer (overall)	Boffeta et al. [20] (Europe, North America)	Case–control Cohort	12	900 participants 6351 cases 6253 controls	Maternal smoking during pregnancy1.10 (1.03–1.19)[b]
Cough	Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)		39	Primary not given	Cough Smoking by either parent: 1.35 (1.27–1.43)[a] Smoking by both parents: 1.64 (1.48–1.81)[b] Maternal smoking: 1.34 (1.17–1.54)[a] Paternal smoking: 1.22 (1.12–1.32)[a]
Cancer of the nervous system (childhood)	Boffeta et al. [20] (Europe, North America)	Case–control	12	Primary not given	Maternal smoking during the pregnancy 1.04 (0.92–1.18)[b]
		Case–control	10	1627 cases 2974 controls	Paternal smoking during pregnancy 1.22 (1.05–140)[b]
Genetic damage in children	Neri et al. [19] (Australia, Europe, USA, South America)	Case–control Cohort	6	Primary not given	HB adducts Children exposed to environmental tobacco smoke: 1.38 (0.98–1.96)
			5		Prenatal Exposure: 6.67 (2.56–17.24) SCE[e]:prenatal exposure: 1.02 (0.94–1.10)[d]

Lower respiratory illnesses	Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)	Case–control Cohort	38	Primary not given	Lower respiratory illnesses Smoking by either parent: 1.51 (1.44–1.59)[a] Maternal smoking: 1.56 (1.51–1.62)[a] Paternal smoking: 1.31 (1.20–1.42)[a]
Lower respiratory tract infection	Li et al. [11] (Asia, Europe, North America)	Case–control Cohort	13	32,945 cases	Hospitalisation for respiratory illness 1.93 (1.66–2.25)[a] Serious infections0–2 years: 1.71 (1.33–2.20)[a] 3-6 years: 1.25 (0.88–1.78)[a]
Lymphatic and haematopoietic Neoplasm (childhood)	Boffeta et al. [20] (Europe, North America)	Case–control	9	Cases: 3610 Controls: 5054	Maternal smoking during pregnancy 1.03 (0.90–1.17)
Kidney cancer (childhood)	Boffeta et a. [20] (Europe, North America)	Case–control	5	Cases: 442 Controls: 2536	Maternal smoking during pregnancy 0.95 (0.76–1.19)
Middle ear effusion	Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)		6	Primary not given	Middle ear effusion Smoking by either parent: 1.20 (0.90–1.60)[a] Maternal smoking: 1.84 (1.54–2.20)[a] Paternal smoking: 1.49 (1.13–1.96)[a]
Non-Hodgkin lymphoma (childhood)	Boffeta et al. [20] (Europe, North America)	Case–control	4	Primary not given	Paternal smoking during the pregnancy 2.08 (1.08–3.98)[b]
Overweight[f]	Oken et al. [32] (Australia, Europe, North America)	Cohort	14	84,563 Participants	Maternal smoking during pregnancy 1.50 (1.36–1.65)[a]
Recurrent otitis media	Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)		9	Primary not given	Recurrent otitis media Smoking by either parent: 1.32 (1.14–1.52)[a] Maternal smoking: 1.37 (1.19–1.59)[a] Paternal smoking: 0.90 (0.70–1.15)[a]
Respiratory tract infections	Peat et al. [13] (Asia, Australia, Chili, Europe, New Zealand, USA)	Case–control Cohort	14	Primary not given	Parental smoking Hospitalisation for respiratory illness: 2[a] Lower respiratory tract infection: 1.7[a] Early respiratory illness: 1.6[a]
Sudden infant death syndrome (after prone-sleep-position intervention programs)	Mitchell et al. [24] (Europe, New Zealand, US)	Case–control Cohort	24	Cases: 15,694 Controls: 3,592,021 Cases: 719 Controls: 4885	Maternal smoking during pregnancy 3.93 (3.78–4.08)[b] Paternal smoking, mother does not smoke 1.49 (1.25–1.77)[b]
Wheeze	Moritsugu et al. [12] (Europe, North America, Australia, Asia, Africa)		45		Wheeze Smoking by either parent: 1.26 (1.20–1.33)[a] Smoking by both parents: 1.41 (1.23–1.63)[a] Maternal smoking: 1.28 (1.21–1.35)[a] Paternal smoking: 1.22 (1.12–1.32)[a]

[a] Odds ratio.

[b] Relative risk.

[c] PROM, premature rupture of membranes is a rupture (breaking open) of the membranes (amniotic sac) before labour begins. If PROM occurs before 37 weeks of pregnancy, it is called preterm premature rupture of membranes (PPROM).

[d] MR is a point estimate of the relative effect of the exposure on biomarker level detected in each study taking the value 1 when there is no effect, values >1 when exposure is associated with a decreased level of the investigated biomarker.

[e] SCE: sister chromatid exchange is the exchange of genetic material between two identical sister chromatids. The reason for the SCE is not known but it is required and used for mutagenic testing of many products. Four to five sister chromatid exchanges are in the normal distribution, 14–100 exchanges are not normal and present a danger to the organism.

[f] Primary analysis of overweight has been chosen, defined as BMI ⩾85th percentile or ⩾90th percentile for age and sex.

of 10% (95%CI: 1.03–1.19) for childhood cancer, yet no significant elevated risk was found for lymphomatic and haematopoietic neoplasm, or for cancer of the central nervous system or kidney cancer (Table 1) [20]. When considering maternal and paternal in-utero exposure to genotoxic compounds, a difference in the mode of action is implied in the direct transplacental effects versus the preconception alterations. Carcinogens in tobacco can induce DNA damage in sperm: male smokers have higher levels of 8-oxo-2-deoxyguanosine in their semen than non-smokers, which may result in oxidative damage to sperm DNA [21,22]. Paternal smoking during conception and acute lymphoblastic leukaemia are related with a pooled odds of 1.15 (CI: 1.06–1.24), paternal exposure during pregnancy is not [20,23]. Furthermore, meta-analytical work suggests an increased risk after paternal exposure to tobacco smoke with childhood non-Hodgkin lymphoma and tumors in the central nervous system [20].

Based on pooled evidence of 25 studies [24], maternal smoking was associated with almost a 4-fold time increase in risk of sudden infant death syndrome. The corresponding risk of paternal smoking with absence of maternal smoking was 1.49 (Table 1). While the effect of smoke exposure in utero seems to be stronger, postnatal environmental tobacco smoke has been found to increase the risk of sudden infant death syndrome even after controlling for prenatal exposure. However, in most cases this is difficult to distinguish as most children that have been exposed in utero are also exposed during their first months of life.

3. Smoking ban and health gains

The positive effect of smoking cessation suggests a causal association between active smoking and cardiovascular disease [25]. Evidence from observational studies shows a decrease in cardiovascular events in progression of atherosclerosis in those who quit smoking compared with those continuing to smoke cigarettes. Along with this, evidence from cohort studies and ecological evidence on recent smoking bans (introduced by law) consistently shows a rapid decrease in hospitalisation for myocardial infarction (MI). The pooled aggregated data showed that the rate of acute MI hospitalisation in countries that implemented a smoking ban law, decreased 12 months after its implementation, on average by 17% (95%CI: 20–13%) [26]. The rapid decrease in MI after introduction of bans suggests an interplay between chronic and acute processes, including triggers. A trigger can be defined as an external stimulus that produces acute physiological or pathophysiological changes. The idea of the pathophysiological relevance of triggers leading to the onset of acute myocardial infarction (MI) has been proposed [27]. In general, ageing leads to functional and structural abnormalities of the arterial wall, which are amplified by hypertension and atherosclerosis [28]. A vulnerable atherosclerotic plaque might lead to an occlusive thrombus which is more likely to be formed if other factors come into play to narrow homoeostasis and increase vasoconstriction. The role of triggers such as alcohol [29], anger [30,31], physical exertion [31,32]and use of marijuana [33] in the onset of MI is recognised [34].

Recently gained evidence supports the notion that premature birth is also a syndrome which might have trigger components, including ambient temperature and smoking [35,36]. Recent Scottish [36] and Belgian [35] data support reductions in the rate of preterm births after the implementation of smoking bans, whereas no such decrease was evident in the years or months before these bans.

In Belgium, smoke-free legislation was implemented in different phases (in public places and most workplaces in January 2006, in restaurants January 2007, and in bars serving food January 2010). We were able to demonstrate a consistent pattern of changes in preterm delivery with stepwise reductions over the different enforcements. In an analysis using a birth register comprising 606,877 live-births, we observed an immediate change in the risk of spontaneous preterm delivery of −3.13% (95%CI: −4.37% to −1.87%; $P < 0.01$) on 1st January 2007 (ban on smoking in restaurants), and an annual slope change of −2.65% (−5.11% to −0.13%; $P = 0.04$) after 1st January 2010 (ban on smoking in bars serving food). In 716,941 Scottish newborns, the risk was decreased by 11.72% (95% CI: –15.87 to –7.35) 3 months prior to the introduction of the comprehensive smoking ban in 2006. Similarly to Belgian findings, a study on the impact of the Irish workplace smoking ban on birth weight and preterm birth found a protective effect only on the latter outcome [37]. Although their analysis was limited to a comparison of rates 1 year before and after the ban, they even found an increase in the risk of low birth weight.

The smoking ban studies must be viewed as an investigation of the possible impact of a ‘population intervention’ rather than an investigation of changes in individual behaviour. It is possible that unmeasured confounders were responsible for the observed changes. Nevertheless, it is hard to conceive of a factor that could change the population risk of preterm births after the introduction of the different successive smoking bans. It is unlikely that our observations could be explained by abrupt changes in therapeutic strategies coinciding with the smoking bans. Nevertheless, the Belgian study collected data on the prescription of atosiban and on cervical cerclage treatment from a social security organisation covering 42% of the population. Atosiban is an inhibitor of oxytocin and vasopressin and is specifically used to halt premature labour. Cervical cerclage is used for the treatment of cervical incompetence, a condition where the cervix has opened slightly and there is a risk of miscarriage.

Given that even a mild reduction in gestational age has been linked to adverse health outcomes in early and later life, these population interventions have important public health implications. Indeed, a Swedish study found that, even among those born late preterm (34–36 weeks), preterm birth was associated with a 31% (13–50%) increase in mortality in young adulthood [38].

4. Molecular epidemiological aspects

The human placenta forms the interface between foetal and maternal circulation, and by controlling nutrient supply plays a critical role in the regulation of foetal growth and development. Maternal smoking causes perturbations in this uteroplacental exchange as it increases the risk of low birth weight [39,40] and preterm delivery [35,41]. The mechanisms underlying these observed effects remain unclear, but emerging data suggest that biochemical, genetic and epigenetic activi-

ties respond to and are modified by in-utero tobacco exposure. Nutrients and potential pollutants are metabolised, making the placenta a molecular 'footprint' to which the foetus has been exposed in utero.

Mitochondria are abundant in placental cells, they provide energy for the functioning of this metabolically active organ. Each cell contains approximately 200–2000 mitochondria, carrying between two and ten copies of mitochondrial DNA (mtDNA). Recently, by assessing the relative mtDNA content (a marker of mitochondrial damage and dysfunction), its functioning has been linked to various disease mechanisms [42,43]. The placental mtDNA content has been shown to be very adaptive to environmental insults, including maternal smoking [44] and air pollution [45]. The relative mtDNA content is decreased by 37% ($P < 0.02$) in placentas of mothers who smoke [44] compared with a decrease of 17.4% ($P = 0.05$) for each 10-$\mu g/m^3$ increase in PM_{10} exposure during the third trimester of pregnancy [45].

Important questions remain concerning how mitochondrial biogenesis and maintenance are regulated as a response to tobacco exposures, and how these relate to placental functioning. An attractive link between adverse insults and altered foetal development is gene regulation. Maternal smoking during pregnancy can lead to changed placental gene expression levels, which is epigenetically regulated by DNA methylation, histone modifications or non-coding RNAs. Epigenetic changes can occur throughout the course of life as a result of environmental conditions. Much of the epigenome is already established in germ cells and embryos as it appears to be particularly important for the regulation of embryonic growth and placental development [46]. Recently, studies investigating cord blood and placental tissue showed that the epigenetic system is sensitive to tobacco exposure in utero. Global DNA methylation levels in cord blood is lower among newborns with smoking mothers (mean = 15.04%; 95%CI: 8.4–21.7) compared with second-hand smokers (21.1%; 95%CI: 16.6, –25.5) and their non-smoking counterparts (mean = 29.2%; 95%CI: 20.1–38.1) [47]. An epigenome-wide methylation study in cord blood of newborns exposed to tobacco smoke during pregnancy showed that genes that play an important role in detoxifying components of tobacco smoke (*AHRR* and *CYP1A1*) are differentially methylated [48]. Accordingly, Suter and colleagues reported site-specific changes in DNA methylation of the *CYP1A1* promoter, and this hypomethylation correlated with an increase in *CYP1A1* gene expression in the placenta [49]. They showed in an epigenome-wide methylation study on placental tissue that methylation levels of 623 genes are deregulated in a CpG site-specific manner [50].

Despite a limited number of (epi)genomic studies in cord blood and placental tissue, we are getting a better picture of how maternal tobacco smoke can alter placental functioning and contribute to adverse pregnancy outcomes. Therefore the potential health consequences of changes in mitochondrial functioning, gene expression and epigenetics in early life should be further elucidated.

Conflict of interest statement

None declared.

REFERENCES

[1] Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
[2] Doll R, Hill AB. The mortality of doctors in relation to their smoking habits: a preliminary report. 1954. BMJ 2004;328:1529–33 [discussion 33].
[3] Doyle JT, Dawber TR, Kannel WB, Heslin AS, Kahn HA. Cigarette smoking and coronary heart disease. Combined experience of the Albany and Framingham studies. N Engl J Med 1962;26:796–801.
[4] Michaels D, Monforton C. Manufacturing uncertainty: contested science and the protection of the public's health and environment. Am J Public Health 2005;95(Suppl. 1):S39–48.
[5] Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. JAMA 1998;279:1566–70.
[6] Francis JA, Shea AK, Samet JM. Challenging the epidemiologic evidence on passive smoking: tactics of tobacco industry expert witnesses. Tob Control 2006;15(Suppl. 4):iv68–76.
[7] Harlap S, Davies AM. Infant admissions to hospital and maternal smoking. Lancet 1974;1(7857):529–32.
[8] Pattenden S, Antova T, Neuberger M, et al. Parental smoking and children's respiratory health: independent effects of prenatal and postnatal exposure. Tob Control 2006;15:294–301.
[9] Castles A, Adams EK, Melvin CL, Kelsch C, Boulton ML. Effects of smoking during pregnancy. Five meta-analyses. Am J Prev Med 1999;16:208–15.
[10] Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. Am J Obstet Gynecol 2000;182:465–72.
[11] Li JS, Peat JK, Xuan W, Berry G. Meta-analysis on the association between environmental tobacco smoke (ETS) exposure and the prevalence of lower respiratory tract infection in early childhood. Pediatr Pulmonol 1999;27:5–13.
[12] Moritsugu KP. The 2006 report of the surgeon general: the health consequences of involuntary exposure to tobacco smoke. Am J Prev Med 2007;32:542–3.
[13] Peat JK, Keena V, Harakeh Z, Marks G. Parental smoking and respiratory tract infections in children. Paediatr Respir Rev 2001;2:207–13.
[14] Oken E, Levitan EB, Gillman MW. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. Int J Obes (Lond) 2008;32:201–10.
[15] Brion MJ, Leary SD, Lawlor DA, Smith GD, Ness AR. Modifiable maternal exposures and offspring blood pressure: a review of epidemiological studies of maternal age, diet, and smoking. Pediatr Res 2008;63:593–8.
[16] Jaakkola JJ, Ahmed P, Ieromnimon A, et al. Preterm delivery and asthma: a systematic review and meta-analysis. J Allergy Clin Immunol 2006;118:823–30.
[17] Jaakkola JJ, Gissler M. Maternal smoking in pregnancy, fetal development, and childhood asthma. Am J Public Health 2004;94:136–40.
[18] Cunningham J, O'Connor GT, Dockery DW, Speizer FE. Environmental tobacco smoke, wheezing, and asthma in children in 24 communities. Am J Respir Crit Care Med 1996;153:218–24.
[19] Neri M, Ugolini D, Bonassi S, et al. Children's exposure to environmental pollutants and biomarkers of genetic damage. II. Results of a comprehensive literature search and meta-analysis. Mutat Res 2006;612:14–39.
[20] Boffetta P, Tredaniel J, Greco A. Risk of childhood cancer and adult lung cancer after childhood exposure to passive

smoke: A meta-analysis. Environ Health Perspect 2000;108:73–82.
[21] Fraga CG, Motchnik PA, Wyrobek AJ, Rempel DM, Ames BN. Smoking and low antioxidant levels increase oxidative damage to sperm DNA. Mutat Res 1996;351:199–203.
[22] Shen HM, Chia SE, Ni ZY, New AL, Lee BL, Ong CN. Detection of oxidative DNA damage in human sperm and the association with cigarette smoking. Reprod Toxicol 1997;11:675–80.
[23] Milne E, Greenop KR, Scott RJ, et al. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. Am J Epidemiol 2012;175:43–53.
[24] Mitchell EA, Milerad J. Smoking and the sudden infant death syndrome. Rev Environ Health 2006;21:81–103.
[25] Critchley J, Capewell S. Smoking cessation for the secondary prevention of coronary heart disease. Cochrane Database Syst Rev; 2004(1): CD003041.
[26] Meyers DG, Neuberger JS, He J. Cardiovascular effect of bans on smoking in public places: a systematic review and meta-analysis. J Am Coll Cardiol 2009;54:1249–55.
[27] Tofler GH, Muller JE. Triggering of acute cardiovascular disease and potential preventive strategies. Circulation 2006;114:1863–72.
[28] Nawrot T, Den HE, Thijs L, Staessen JA. Isolated systolic hypertension and the risk of vascular disease. Curr Hypertens Rep 2003;5:372–9.
[29] Kauhanen J, Kaplan GA, Goldberg DE, Salonen JT. Beer binging and mortality: results from the Kuopio ischaemic heart disease risk factor study, a prospective population based study. BMJ 1997;315:846–51.
[30] Mittleman MA, Maclure M, Sherwood JB, et al. Triggering of acute myocardial infarction onset by episodes of anger. Determinants of myocardial infarction onset study investigators. Circulation 1995;92:1720–5.
[31] Strike PC, Perkins-Porras L, Whitehead DL, McEwan J, Steptoe A. Triggering of acute coronary syndromes by physical exertion and anger: clinical and sociodemographic characteristics. Heart 2006;92:1035–40.
[32] Mittleman MA, Maclure M, Tofler GH, et al. Triggering of acute myocardial infarction by heavy physical exertion. Protection against triggering by regular exertion. Determinants of myocardial infarction onset study investigators. N Engl J Med 1993;329:1677–83.
[33] Mittleman MA, Lewis RA, Maclure M, Sherwood JB, Muller JE. Triggering myocardial infarction by marijuana. Circulation 2001;103:2805–9.
[34] Nawrot TS, Perez L, Kunzli N, Munters E, Nemery B. Public health importance of triggers of myocardial infarction: a comparative risk assessment. Lancet 2011;377:732–40.
[35] Cox B, Martens E, Nemery B, Vangronsveld J, Nawrot TS. Impact of a stepwise introduction of smoke-free legislation on the rate of preterm births: analysis of routinely collected birth data. BMJ 2013;346:f441.
[36] Mackay DF, Nelson SM, Haw SJ, Pell JP. Impact of Scotland's smoke-free legislation on pregnancy complications: retrospective cohort study. PLoS Med 2012;9:e1001175.
[37] Kabir Z, Clarke V, Conroy R, McNamee E, Daly S, Clancy L. Low birthweight and preterm birth rates 1 year before and after the Irish workplace smoking ban. BJOG 2009;116:1782–7.
[38] Crump CSKSJWMA. Gestational age at birth and mortality in young adulthood. JAMA 2011;306:1233–40.
[39] Jaddoe VWV, Troe E-JWM, Hofman A, et al. Active and passive maternal smoking during pregnancy and the risks of low birthweight and preterm birth: the Generation R Study. Paediatr Perinat Epidemiol 2008;22:162–71.
[40] Windham GC, Hopkins B, Fenster L, Swan SH. Prenatal active or passive tobacco smoke exposure and the risk of preterm delivery or low birth weight. Epidemiology 2000;11:427–33.
[41] Fantuzzi G, Aggazzotti G, Righi E, et al. Preterm delivery and exposure to active and passive smoking during pregnancy: a case-control study from Italy. Paediatr Perinat Epidemiol 2007;21:194–200.
[42] Sahin E, Colla S, Liesa M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature 2011;470:359–65.
[43] Lee HC, Wei YH. Mitochondrial biogenesis and mitochondrial DNA maintenance of mammalian cells under oxidative stress. Int J Biochem Cell Biol 2005;37:822–34.
[44] Bouhours-Nouet N, May-Panloup P, Coutant R, et al. Maternal smoking is associated with mitochondrial DNA depletion and respiratory chain complex III deficiency in placenta. Am J Physiol Endocrinol Metab 2005;288:E171–7.
[45] Janssen BG, Munters E, Pieters N, et al. Placental mitochondrial dna content and particulate air pollution during *in utero* life. Environ Health Perspect 2012; 120:1346–52.
[46] Constancia M, Hemberger M, Hughes J, et al. Placental-specific IGF-II is a major modulator of placental and fetal growth. Nature 2002;417:945–8.
[47] Guerrero-Preston R, Goldman LR, Brebi-Mieville P, et al. Global DNA hypomethylation is associated with in utero exposure to cotinine and perfluorinated alkyl compounds. Epigenetics 2010;5:539–46.
[48] Joubert BR, Haberg SE, Nilsen RM, et al. 450 K Epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. Environ Health Perspect 2012;120:1425–31.
[49] Suter M, Abramovici A, Showalter L, et al. In utero tobacco exposure epigenetically modifies placental CYP1A1 expression. Metabolism 2010;59:1481–90.
[50] Suter M, Ma J, Harris AS, Patterson L, et al. Maternal tobacco use modestly alters correlated epigenome-wide placental DNA methylation and gene expression. Epigenetics 2011;6:1284–94.
[51] Van Hemelrijck MJ, Michaud DS, Connolly GN, Kabir Z. Secondhand smoking, 4-aminobiphenyl, and bladder cancer: two meta-analyses. Cancer Epidemiol Biomarkers Prev 2009;18:1312–20.
[52] Pirie K, Beral V, Peto R, Roddam A, Reeves G, Green J. Passive smoking and breast cancer in never smokers: prospective study and meta-analysis. Int J Epidemiol 2008;37:1069–79.