

Evaluation of the Association between Maternal Smoking, Childhood Obesity, and Metabolic Disorders: A National Toxicology Program Workshop Review

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BACKGROUND: An emerging literature suggests that environmental chemicals may play a role in the development of childhood obesity and metabolic disorders, especially when exposure occurs early in life.

OBJECTIVE: Here we assess the association between these health outcomes and exposure to maternal smoking during pregnancy as part of a broader effort to develop a research agenda to better understand the role of environmental chemicals as potential risk factors for obesity and metabolic disorders.

METHODS: PubMed was searched up to 8 March 2012 for epidemiological and experimental animal studies related to maternal smoking or nicotine exposure during pregnancy and childhood obesity or metabolic disorders at any age. A total of 101 studies—83 in humans and 18 in animals—were identified as the primary literature.

DISCUSSION: Current epidemiological data support a positive association between maternal smoking and increased risk of obesity or overweight in offspring. The data strongly suggest a causal relation, although the possibility that the association is attributable to unmeasured residual confounding cannot be completely ruled out. This conclusion is supported by findings from laboratory animals exposed to nicotine during development. The existing literature on human exposures does not support an association between maternal smoking during pregnancy and type 1 diabetes in offspring. Too few human studies have assessed outcomes related to type 2 diabetes or metabolic syndrome to reach conclusions based on patterns of findings. There may be a number of mechanistic pathways important for the development of aberrant metabolic outcomes following perinatal exposure to cigarette smoke, which remain largely unexplored.

CONCLUSIONS: From a toxicological perspective, the linkages between maternal smoking during pregnancy and childhood overweight/obesity provide proof-of-concept of how early-life exposure to an environmental toxicant can be a risk factor for childhood obesity.

KEY WORDS: animal, chemically induced/epidemiology, diabetes, environmental epidemiology, glucose, insulin, maternal smoking toxicity, metabolism, nicotine toxicity, obesity. *Environ Health Perspect* 121:170–180 (2013). <http://dx.doi.org/10.1289/ehp.1205404> [Online 11 December 2012]

Childhood obesity and diabetes are major threats to public health in the United States and abroad. In the United States, the prevalence of obesity among children and adolescents has almost tripled since 1980, with an estimated 16.9% of children and adolescents (i.e., approximately 12.5 million children and adolescents) considered obese (Ogden and Carroll 2010). This trend is also apparent in preschool children 2–5 years of age, where obesity was shown to have increased from 5% in 1976–1980 to 10.4% in 2007–2008 (Ogden and Carroll 2010). Kim et al. (2006) reported an almost doubling in the prevalence of overweight in infants 0–6 months of age from 1980 to 2001 (3.4% to 5.9%) based on information from well-child visits at a large HMO (health maintenance organization) in Massachusetts. Understanding the factors that contribute to the childhood obesity epidemic

in order to identify intervention strategies is a critical public health need, given that obesity is a known risk factor for diabetes and other chronic conditions such as heart disease (Reilly and Kelly 2011). Diabetes incidence, both type 1 (T1D) and type 2 (T2D), is also on the rise [DIAMOND Project Group 2006; Centers for Disease Control and Prevention (CDC) 2011; Dahlquist et al. 2011; Patterson et al. 2009]. Based on data from the period 2005–2008, 25.6 million (11.3%) of all people in the United States ≥ 20 years of age have diagnosed or undiagnosed diabetes (CDC 2011). Although it is estimated that 70% of T2D can be attributed to being overweight or obese (Eyre et al. 2004), 30% of cases are not attributable to obesity. Therefore, factors other than changes in physical activity or diet may be contributing to this rise in childhood obesity and metabolic disorders. Indeed, there

is growing concern that perinatal exposure to chemical insults may play a significant role in the increased incidence of obesity and metabolic disorders including diabetes, possibly through direct “diabetogenic” effects or by acting as “obesogens.”

Research addressing the role of environmental chemicals in childhood obesity and diabetes has rapidly expanded in the past several years. The White House Task Force on Childhood Obesity (2010), the National Institutes of Health (NIH) Obesity Research Task Force (2011), and the Diabetes Strategic

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Plan from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK 2011) all acknowledge the growing science base in this area and cite the need to understand more about the role of environmental exposures as part of future research and prevention strategies.

To help develop such a research strategy, the National Toxicology Program organized a state-of-the-science workshop in January 2011 titled "Role of Environmental Chemicals in the Development of Diabetes and Obesity" (National Toxicology Program 2011). This review derives from discussions that occurred during that workshop.

Identification of Relevant Studies

A PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) search strategy updated through 8 March 2012 was developed to identify human and animal studies related to maternal smoking or tobacco exposure during pregnancy and *a*) weight, growth, or adiposity after infancy (≥ 1 year of age in humans, after postnatal day 21 in rodents), or *b*) health outcomes in offspring at any age related to T1D or T2D, glycemic control, or metabolic syndrome. Studies assessing growth in infants < 1 year of age were excluded because maternal smoking during pregnancy is a known risk factor for low birth weight, whereas the primary question being addressed at the workshop was whether maternal smoking is a risk factor for childhood obesity. The literature search included both MeSH-based and key word strategies to identify articles not yet indexed in PubMed [see Supplemental Material for a complete list of search terms (<http://dx.doi.org/10.1289/ehp.1205404>)]. This search identified a total of 1,551 publications (see Supplemental Material, Figure S1). Of these, 99 studies presented original data that met our inclusion criteria and were considered relevant as the primary literature. Two additional epidemiological studies identified during the peer-review process were also included (Fasting et al. 2009; Mendez et al. 2008) for a total of 101 studies (83 human studies and 18 animal studies).

Maternal Smoking during Pregnancy

Offspring overweight or obesity. Smoking during pregnancy is a known risk factor for low birth weight and small-for-gestational-age infants (Lumley et al. 2008; Oken et al. 2008; Samper et al. 2011), but is increasingly accepted as a risk factor for childhood overweight and obesity based on the consistent positive associations reported among studies (Figure 1). Most studies (34 of 42) summarized in Figure 1 present results that support a causal link between maternal smoking and subsequent child overweight or obesity. Many

of these studies were evaluated in two recent meta-analyses (Ino 2010; Oken et al. 2008). Based on results reported in 14 observational studies, maternal smoking during pregnancy was associated with overweight at 3–33 years of age [pooled adjusted odds ratio (adjOR) = 1.50; 95% CI: 1.36, 1.65] (Oken et al. 2008). The pooled OR estimated by Ino (2010) for obesity [body mass index (BMI) > 95th percentile] was 1.64 (95% CI: 1.42, 1.90) based on 16 studies. Women who smoked during pregnancy tended to weigh more, and tended to have lower socioeconomic status, have less education, and were less likely to breastfeed (Ino 2010; Oken et al. 2008). Both meta-analyses used funnel plot methods to ascertain publication bias and concluded there was some evidence for publication bias, but not enough to negate the overall conclusion of increased risk.

Ethnicity may affect the association between maternal smoking and childhood obesity. A large retrospective study by Sharma et al. (2008) of the PedNSS (Pediatric Nutrition Surveillance System) cohort found significant associations between maternal smoking and childhood obesity only in white ($n = 66,191$) and black ($n = 28,230$) children; the associations were not apparent for Hispanic ($n = 34,378$), American Indian/Alaska native ($n = 2,228$), or Asian/Pacific Islander children ($n = 4,740$). The lack of association in children of Asian/Pacific Island descent is interesting because studies on Japanese children have reported findings consistent with a positive relationship (Ino et al. 2011; Mizutani et al. 2007; Suzuki et al. 2009, 2011). Too few studies are available on Native American and Hispanic children to interpret the findings of Sharma et al. (2008) in the context of other studies. One Brazilian study by Tome et al. (2007) did not find an association between maternal smoking and offspring overweight at 8–10 years of age (adjOR = 1.07; 95% CI: 0.84, 1.37); however, they did find that children of mothers who smoked were less likely to be underweight (adjOR = 0.56; 95% CI: 0.40, 0.78). It is worth noting that this study was conducted in the Ribeirao region of Brazil where 9.5% of the children were malnourished (BMI < 5th percentile).

Unmeasured confounding. Although the literature on the association between maternal smoking and obesity/overweight in children is fairly consistent when looking across studies, there are some indications that unmeasured familial or lifestyle factors may contribute to the association. One study conducted sibling-based analyses to evaluate the relationship between maternal smoking and BMI in 124,203 males born between 1983 and 1988, identified in the Swedish Medical Birth Registry with the intent of investigating the impact of familial factors on the association between maternal smoking and child obesity

(Iliadou et al. 2010). They reported an association between maternal smoking during the first trimester and overweight (BMI ≥ 25) for the cohort as a whole (adjOR = 1.56; 95% CI: 1.46, 1.66 for > 10 cigarettes/day compared with 0 cigarettes). However, the authors found smaller associations based on within-family analyses, suggesting partial confounding by familial factors. Gilman et al. (2008) also conducted a sibling-based analysis of children enrolled in the Collaborative Perinatal Project to address the issue of unmeasured confounding factors by fitting conditional fixed-effects models among siblings. This type of analysis capitalizes on variability in exposure to tobacco smoke that can occur among siblings when the mother's smoking pattern during gestation differed across pregnancies. Conceptually, the sibling analysis matches exposed and unexposed siblings on family background to identify evidence of unmeasured sources of confounding. Gilman et al. (2008) found significant positive associations in the full cohort for overweight at 7 years of age were still apparent in the conditional sibling fixed effects analysis.

Secondhand smoke exposure during pregnancy or childhood. Although the literature search strategy and inclusion criteria were constructed to identify studies assessing maternal smoking during pregnancy, several studies of paternal or "partner" smoking during pregnancy (Durmus et al. 2011b; Kwok et al. 2010; Leary et al. 2006; Matijasevich et al. 2011) or during childhood (von Kries et al. 2008) were identified. Some of these studies reported no association between parental/partner smoking and BMI or adiposity end points (Durmus et al. 2011b; Matijasevich et al. 2011) whereas others did (Kwok et al. 2010; Leary et al. 2006; von Kries et al. 2008), suggesting that paternal/partner smoking may be a contributing factor on its own, either by unmeasured familial factors, or as a contributor to maternal exposure from secondhand smoke. Another study by Steur et al. (2010) assessed predictors of obesity at 8 years of age in 1,687 children participating in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, a prospective study based in the Netherlands. Maternal smoking during pregnancy and "smoking in the parental house" were both included in the model selection, but only "smoking in the parental house" was selected as a significant independent predictor of childhood overweight.

Other measures of adiposity, BMI, and leptin. The findings discussed above focus on studies of associations between maternal smoking and overweight or obesity. Other studies have estimated associations between maternal smoking during pregnancy and continuous measures of BMI, standardized BMI (i.e.,

z-score or SD score), or body weight in the offspring [see Supplemental Material, Table S1 (<http://dx.doi.org/10.1289/ehp.1205404>)] (Beyerlein et al. 2010, 2011; Durmus et al. 2011a; Goldani et al. 2007; Hill et al. 2005; Iliadou et al. 2010; Kanellopoulos et al. 2007; Leary et al. 2006; Matijasevich et al. 2011; Ravnborg et al. 2011; Suzuki et al. 2011; Syme et al. 2010). Overall, these studies have reported positive associations with maternal

smoking during pregnancy and child BMI. There are also indications that the children of mothers who smoked during pregnancy display more rapid weight gain earlier in life (Griffiths et al. 2010; Karaolis-Danckert et al. 2008; Wen et al. 2011).

Studies in the literature often assess obesity based on BMI, which is not necessarily a direct measure of adiposity because it does not distinguish fat and lean mass (Freedman and Sherry

2009; Wells 2001). Associations between maternal smoking and indicators of adiposity (i.e., body fat, abdominal fat, skin fold thickness) [see Supplemental Material, Table S2 (<http://dx.doi.org/10.1289/ehp.1205404>); Durmus et al. 2011a; Leary et al. 2006; Silva et al. 2010; Syme et al. 2010; Vik et al. 1996; von Schnurbein et al. 2011] are less consistent than associations with overweight/obesity or continuous measures of BMI-related end

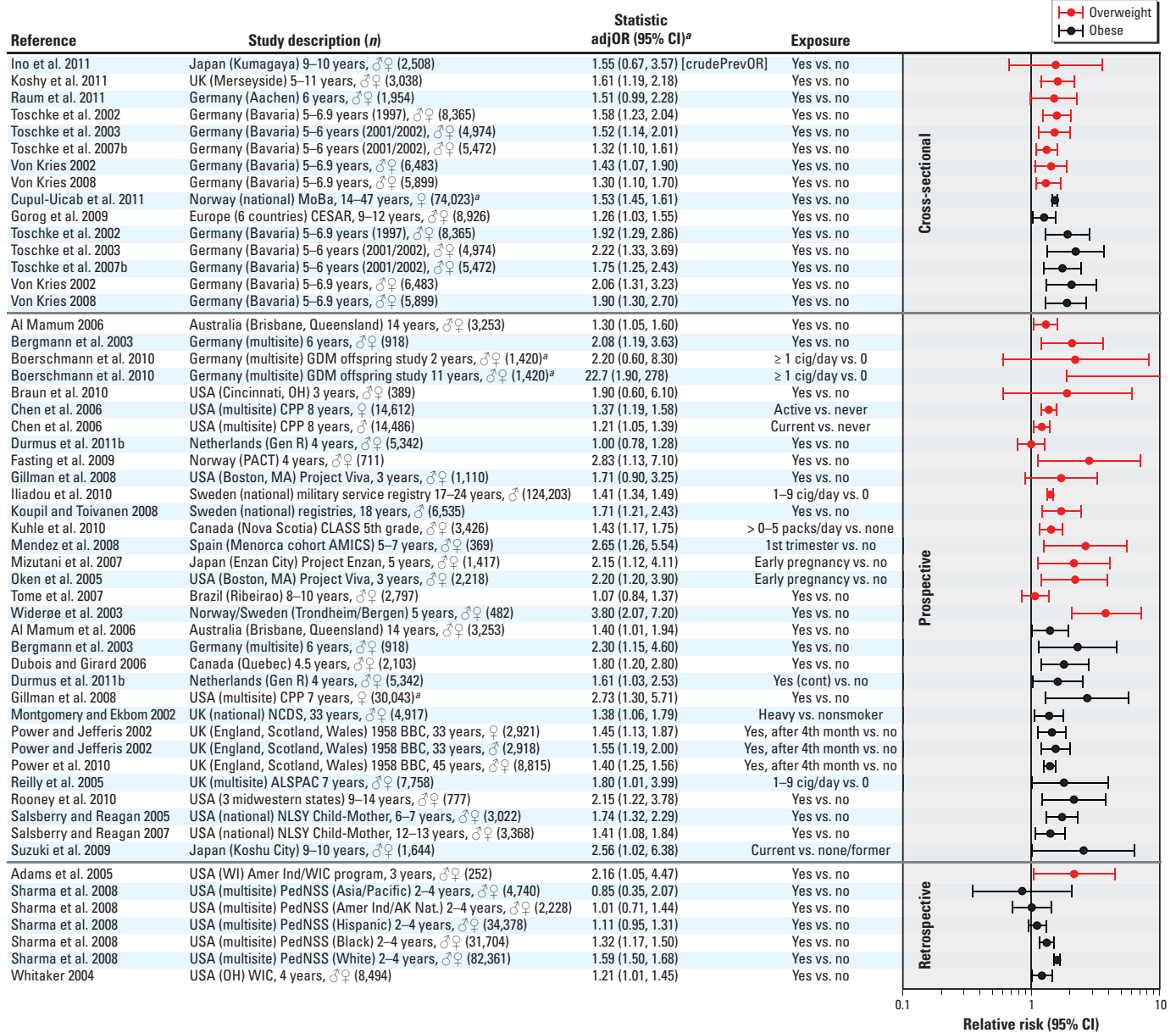


Figure 1. Human studies on maternal smoking during pregnancy and childhood overweight and obesity. The primary grouping of studies is based on study design [cross-sectional, prospective, or retrospective]. Within each study design, main findings are grouped by whether the outcome was overweight or obesity. Studies are then sorted alphabetically within these grouping categories. Abbreviations: AK Nat, Alaska Native; ALSPAC, Avon Longitudinal Study of Parents and Children; Amer Ind, American Indian; AMICS, Asthma Multicenter Infant Cohort Study; BBC, British Birth Cohort; CESAR, Central European Study on Air Pollution and Respiratory Health; cig, cigarettes; CLASS, Children’s Lifestyle and School Performance study; cont, continuous; CPP, Collaborative Perinatal Project; GDM, gestational diabetes mellitus; Gen R, Generation R Study; NCDS, National Child Development Study; NLSY, National Longitudinal Survey of Youth; PACT, Prevention of Allergy among Children of Trondheim study; PedNSS, Pediatric Nutrition Surveillance System; PrevOR, prevalence ratio; WIC, Women, Infants, and Children program.

^aRelative risk estimates for bracketed statistics, i.e., [crudePrevOR], calculated based on data presented in the paper using an open source epidemiology statistics programs, OpenEpi (<http://www.openepi.com/menu/openEpiMenu.htm>).

points (Figure 1). Given the limitations of BMI as a measure of adiposity, it is therefore important for future studies to consider other more direct measures of adiposity/fat mass to clarify the contribution of maternal smoking to childhood obesity.

Leptin, a protein produced by adipocytes and placental tissue, appears to function as a link between adiposity, satiety, and energy regulation (Lee and Fried 2009; Pellemounter et al. 1995; Woods and D'Alessio 2008). Leptin levels have been correlated with neonatal growth (Christou et al. 2001; Vatten et al. 2002), but very few studies have looked at leptin levels beyond the neonatal period, and it is unclear how informative the infant studies are for addressing issues related to childhood obesity, given the complex role that maternal smoking has on childhood growth (i.e., as a risk factor for low birth weight and for childhood obesity). Overall, the findings on leptin levels in cord blood or blood collected from infants in association with maternal smoking status are mixed, with some studies reporting positive associations (Helland et al. 2001), negative associations (Mantzoros et al. 1997; Ozkan et al. 2005), or no association (Coutant et al. 2001; Kayemba-Kay's et al. 2008; Pardo et al. 2004; Vatten et al. 2002).

T1D. The existing human studies do not provide support for an association between

maternal or paternal smoking during pregnancy and childhood T1D (Figure 2). Only 2 of the 13 studies assessing end points related to T1D following exposure during pregnancy reported findings consistent with an association (Sipetic et al. 2005; Wahlberg et al. 2011). In the study by Sipetic et al. (2005), the frequency of maternal smoking during pregnancy was higher in T1D cases compared with controls (37.2% vs. 24.8%, $p = 0.023$ or unadjusted OR = 1.79; 95% CI: 1.08, 2.97). Although the univariate finding was statistically significant, the authors did not include maternal smoking in the multivariate analysis conducted to identify risk factors for T1D. In the study by Wahlberg et al. (2011), a positive association was observed for one indicator of β -cell autoimmunity in T1D, tyrosine phosphatase (IA-2A) + antibody status (unadjusted OR = 1.6; 95% CI: 1.2, 2.2), and not for glutamic acid decarboxylase (GAD) + antibody status (data not shown). None of the five prospective studies reported a positive association between maternal or paternal smoking during pregnancy and T1D (Hummel et al. 2001; Johansson et al. 2008; Rosenbauer et al. 2007; Stene et al. 2004; Toschke et al. 2007a; Wadsworth et al. 1997), including two studies of children who were considered at high risk for developing the disease (Hummel et al. 2001; Stene et al. 2004). Several studies reported that T1D was less likely among children whose mothers smoked

during pregnancy than among the children of nonsmoking mothers (Dahlquist and Kallen 1992; Marshall et al. 2004; Svensson et al. 2005) for T1D. Hummel et al. (2001) reported a nonsignificant negative association between islet-cell antibodies (a marker of β -cell autoimmunity) and maternal smoking during pregnancy among children considered at high risk because one or both parents had T1D. However, the number of cases in this study was small (47 of 1,043 children). One hypothesis that may explain evidence of a protective effect of exposure to smoking relates to the hygiene theory of autoimmune disease; this suggests that the risk of autoimmune disease may be increased if the environment is "cleaner," which might be manifest in the households of nonsmokers (Johansson et al. 2008; Marshall et al. 2004). Alternatively, smoking may affect immune function, resulting in a reduced risk of developing autoimmune disorder (Prescott 2008).

Although the overall literature does not support an association between maternal smoking during pregnancy and T1D in offspring, associations with exposure to smoke during childhood should be investigated further. Three studies have assessed childhood exposure and T1D, and both reported findings supportive of an association (Hathout et al. 2006; Sipetic et al. 2005; Skrodeniene et al. 2008). In the study by Skrodeniene et al. (2008), Lithuanian

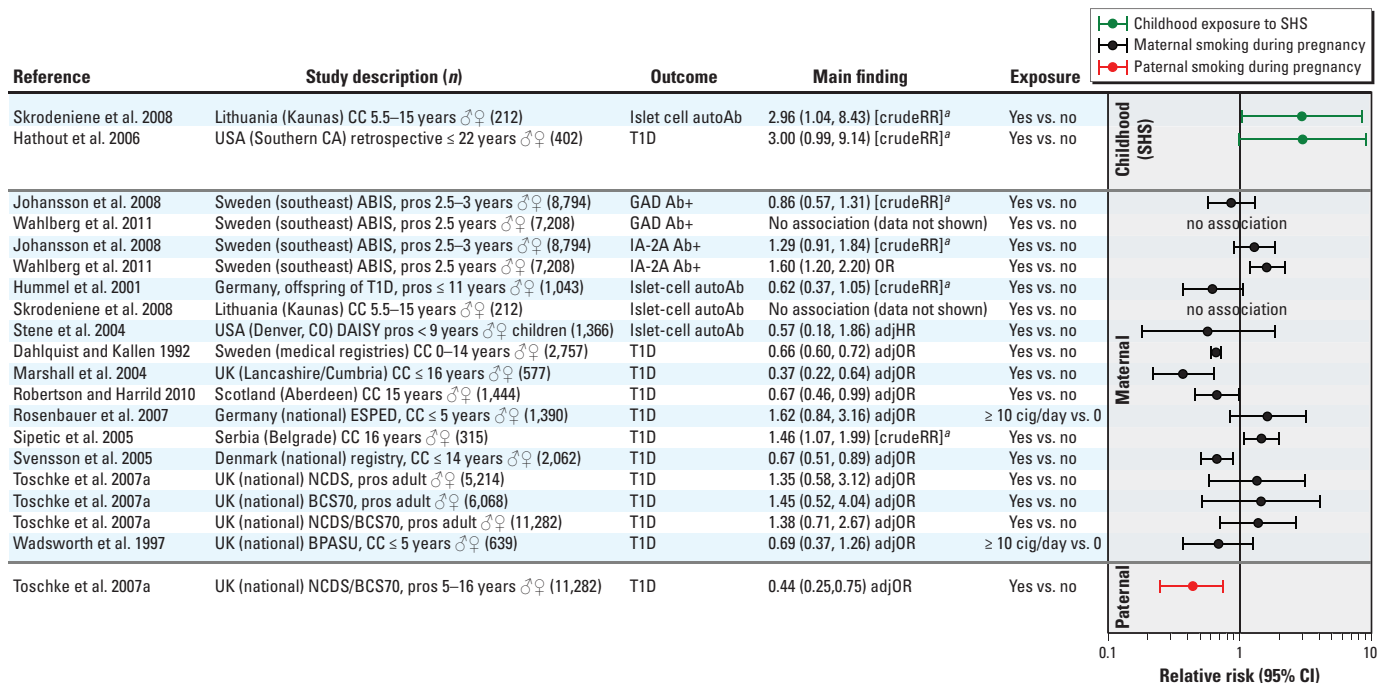


Figure 2. Human studies on exposure to smoking during pregnancy related to T1D. Studies are grouped by the nature of the smoke exposure (maternal, paternal, or secondhand smoke during childhood). Studies are then sorted by specific outcome measure (e.g., GAD Ab+), and presented alphabetically within a given outcome measure. Abbreviations: ABIS, All Babies in Southeast Sweden cohort; adjHR, adjusted hazard ratio; autoAb, auto antibodies; BBC, British Birth Cohort; BCS70, 1970 British Birth Cohort study; BPASU, British Paediatric Association Surveillance Unit; CC, case-control; cross-sect, cross-sectional; DAISY, Diabetes Autoimmunity Study in the Young; ESPED, German pediatric surveillance unit; GADA, glutamic acid decarboxylase antibodies; IA-2A, insulinoma antigen 2A; NCDS, National Child Development Study; pros, prospective; retro, retrospective; SHS, secondhand smoke.

^aRelative risk estimates [crudeRR] calculated based on data presented in the paper using an open source epidemiology statistics programs, OpenEpi (<http://www.openepi.com/menu/openEpiMenu.htm>).

children who were islet-cell autoantibody positive were more likely to live in a home where family members smoked indoors than children who were islet-cell autoantibody negative [7 of 13 (53.8%) vs. 53 of 199 (26.6%), respectively, $p = 0.004$; unadjusted OR = 3.21; 95% CI: 1.03, 10.00]. The frequency of mothers who reported smoking during pregnancy did not differ between the groups in this study. Hathout et al. (2006) reported that children with T1D were more likely to have been exposed to passive smoking than control children in Southern California [31 of 102 cases (30%) vs. 3 of 10 controls (10%), $p = 0.0001$; unadjusted OR = 3.90; 95% CI: 1.19, 17.24]. One limitation in the existing literature that needs to be addressed in future studies investigating the association of smoking or other environmental exposures and T1D is use of statistical models that consider potential confounding factors (e.g., viruses, nutrition, or socioeconomic psychosocial factors).

T2D and metabolic syndrome. Fewer studies have looked at associations between maternal smoking during pregnancy and T2D, blood glucose, blood insulin, or metabolic disease (Horta et al. 2011; Huang et al. 2007; Montgomery and Ekblom 2002; Thiering et al. 2011; Thomas et al. 2007) (Figure 3). It is not possible to reach conclusions with confidence based on the existing literature because of the variation in health outcomes assessed among the studies [i.e., HbA1C (hemoglobin A1C); fasting glucose, nonfasting glucose, HOMA-IR (homeostatic model assessment–insulin resistance), blood insulin; T2D; and metabolic syndrome. In addition, although most of the studies do not report positive associations with these outcomes, the age at assessment in many of the studies was relatively young, and additional

follow-up may be required. It is worth noting that no association with $\text{HbA1C} \geq 6\%$ was found in the oldest and largest cohort assessed [7,518 men and women from the 1958 British birth cohort enrolled in the Perinatal Mortality Survey (PMS) evaluated at 45 years of age] (Thomas et al. 2007). This finding does not confirm an earlier report for the same cohort of an association between heavy smoking during pregnancy and T2D in offspring at 33 years of age (adjOR = 4.02; 95% CI: 1.14, 14.14) (Montgomery and Ekblom 2002). A related analysis of the cohort by Power et al. (2010) also reported no association with HbA1C in adults at 45 years of age (fully adjusted mean difference = 0.13; 95% CI: -0.33, 0.58). Power et al. (2010) reported a positive association between maternal smoking during pregnancy and metabolic syndrome based on an unadjusted model [unadjusted OR = 1.21; 95% CI: 1.05, 1.39], but there was a significant negative association between maternal smoking and metabolic syndrome after adjustment for adult life covariates such as social class, education, physical activity and inactivity (television/computer use), smoking, and consumption of fruit/vegetables, cakes/sweets, and alcohol (adjOR = 0.55; 95% CI: 0.47, 0.64).

Animal Studies on Developmental Exposure to Nicotine

There are 599 known cigarette additives (Rabinoff et al. 2007), and most are uncharacterized for potential toxicity, including metabolic effects. One exception is cadmium, a constituent of tobacco of smoke shown to alter glucose homeostasis or insulin sensitivity in animals exposed as adults (Edwards and Prozialeck 2009) but has not been assessed for

metabolic effects after developmental exposure. Only two studies assessed prenatal exposure to cigarette smoke during pregnancy and body weight later in life in offspring (Chen et al. 2011; Ng et al. 2009).

Body weight and adiposity. Most animal studies have reported that rats exposed to nicotine during perinatal development tended to have a higher body weight and more fat mass compared with controls (Figure 4), with the effect typically first apparent at weaning and persisting through adulthood (Gao et al. 2005; Newman et al. 1999; Oliveira et al. 2009, 2010; Somm et al. 2008). However, there are exceptions to this pattern (Gao et al. 2008; Holloway et al. 2007), which do not appear to be attributable to strain differences, dosing, or the timing of exposure. Food intake was unaffected in studies that evaluated it as an end point (Oliveira et al. 2009, 2010; Somm et al. 2008). The potential interaction between perinatal nicotine exposure and postnatal diet has been explored in only one study, which examined whether a high-fat diet (HFD) postnatally would exacerbate the weight gain in nicotine-exposed animals (Somm et al. 2008). Although the nicotine-treated animals that were fed an HFD did not consume more kilocalories than controls fed the same diet, they were heavier. The nicotine-treated animals were less physically active than control animals that consumed the same diet. There were no differences in oxygen consumption or respiratory exchange ratio, suggesting that increased weight gain in HFD animals with the same caloric intake was perhaps attributable to the dysregulation of adipose tissue development, thereby leading to higher amounts of fat storage.

Glucose homeostasis and insulin sensitivity. There are several reports in the literature on impaired glucose homeostasis in the male

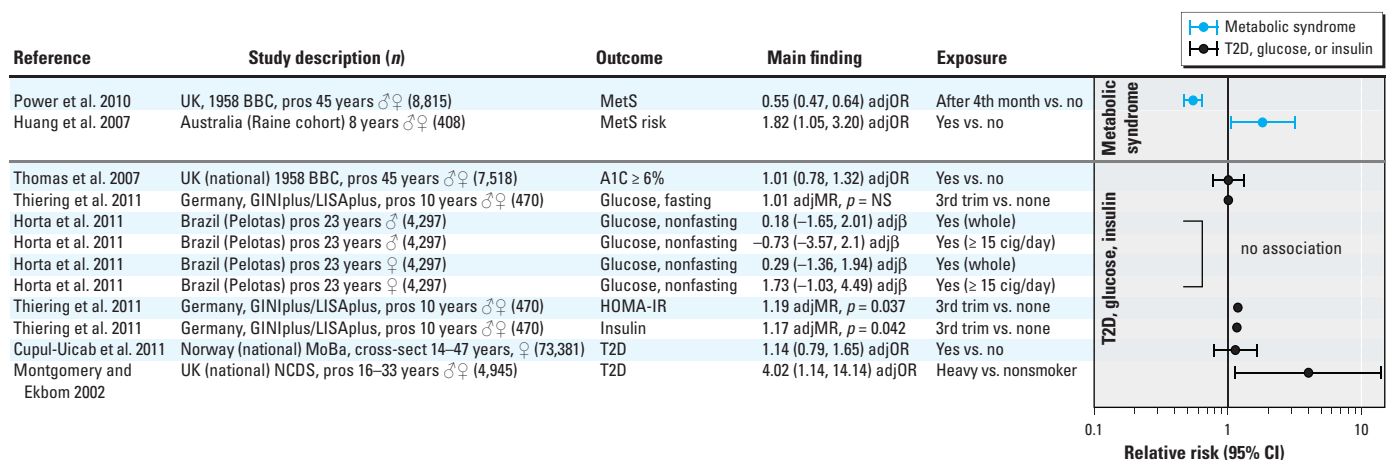


Figure 3. Human studies on exposure to smoking during pregnancy and findings related to T2D or metabolic syndrome. The primary grouping is whether the outcome was related to T2D, glucose, or insulin or metabolic syndrome. Studies are then sorted by specific outcome measure (e.g., HOMA-IR) and presented alphabetically within a given outcome measure. Abbreviations: A1C, glycosylated haemoglobin A1c; adjMR, adjusted mean ratio; BBC, British Birth Cohort; cig, cigarettes; cross-sect, cross-sectional; GINIplus, German Infant Nutritional Intervention study; HOMA-IR, Homeostatic model assessment for insulin resistance; LISAplus, Lifestyle-Related Factors on the Immune System and the Development of Allergies in Childhood study; MoBa, Norwegian Mother and Child Cohort Study; NCDS, National Child Development Study; NS, not significant; pros, prospective; trim, trimester.

offspring of rats that were treated with nicotine during gestation (Somm et al. 2008), lactation (Oliveira et al. 2010), or gestation and lactation (Bruin et al. 2007, 2008c; Holloway et al. 2005) (Figure 5). Administered doses ranged from 1 to 6 mg/kg-day delivered to the mother either via an osmotic minipump implanted under the skin or via daily subcutaneous injections. These dosing protocols resulted in maternal serum cotinine levels considered relevant to women who smoke or use nicotine patches as cigarette substitutes (Bruin et al. 2007; Hackman et al. 1999; Somm et al. 2009). The most consistent findings from these studies were indications of insulin resistance in adulthood based on increased insulin area under the curve (AUC) following an oral or intraperitoneal glucose challenge (Bruin et al. 2007, 2008c; Holloway et al. 2005; Somm et al. 2008) or on an increased insulin resistance index (Oliveira et al. 2010). These effects were seen across studies despite the use of different doses of nicotine, different administration protocols, and different windows of developmental exposure within the perinatal period (i.e., gestation and/or lactation). A study by Holloway et al. (2007), reported increased insulin resistance in 15-week-old F2

generation male offspring of dams that were treated with nicotine only during gestation and lactation compared with untreated controls. Impairments in glucose tolerance also have been reported following nicotine exposure (Bruin et al. 2007, 2008c; Holloway et al. 2005; Somm et al. 2008). Effects on fasting insulin levels have been less consistent, with some studies showing no effect (Bruin et al. 2007; Somm et al. 2008) and others reporting increased levels in adult rodents compared with untreated controls (Holloway et al. 2005, 2007; Oliveira et al. 2010). At low dose levels (1 mg/kg-day) permanent changes in glucose homeostasis were observed only when exposure occurred during both fetal and neonatal life (i.e., pregnancy and lactation); however, when dams were exposed to 3 mg/kg-day (Somm et al. 2008) or 6 mg/kg-day (Oliveira et al. 2010), then either fetal or lactational exposure was sufficient to affect glycemic control. Importantly, no effects on glucose homeostasis were observed in Wistar rats (Jose et al. 2009) or in a series of studies (Jose et al. 2009; Swislocki 2003; Swislocki and Fakiri 2008; Swislocki et al. 1997) in Sprague-Dawley rats treated with nicotine after weaning. Taken together, these data suggest

that cigarette smoke or nicotine exposure during gestation and lactation is the critical window of exposure.

Pancreatic effects. Changes in pancreatic weight, morphology, and function have been reported in animals that were treated with nicotine during gestation alone or during gestation and lactation (Bruin et al. 2007, 2008a, 2008b; Grove et al. 2001; Holloway et al. 2005; Somm et al. 2008) (Figure 6). These pancreatic effects include increased β -cell apoptosis and decreased β -cell mass in rodents (Bruin et al. 2007; Holloway et al. 2005; Somm et al. 2009). Other findings include decreased pancreatic weight in infant rhesus monkeys (Grove et al. 2001). As noted earlier, the treatment protocols used in the rodent studies result in maternal serum cotinine levels that are considered relevant to women who smoke or use nicotine patches as cigarette substitutes. The pancreatic effects are hypothesized to occur as a direct effect of nicotine binding to nicotinic acetylcholine receptors in the developing pancreas, leading to oxidative stress and mitochondrial damage and eventual β -cell apoptosis (Bruin et al. 2007, 2008a, 2008b, 2008c). Pancreatic tissue is considered to be especially susceptible to oxidative stress-mediated

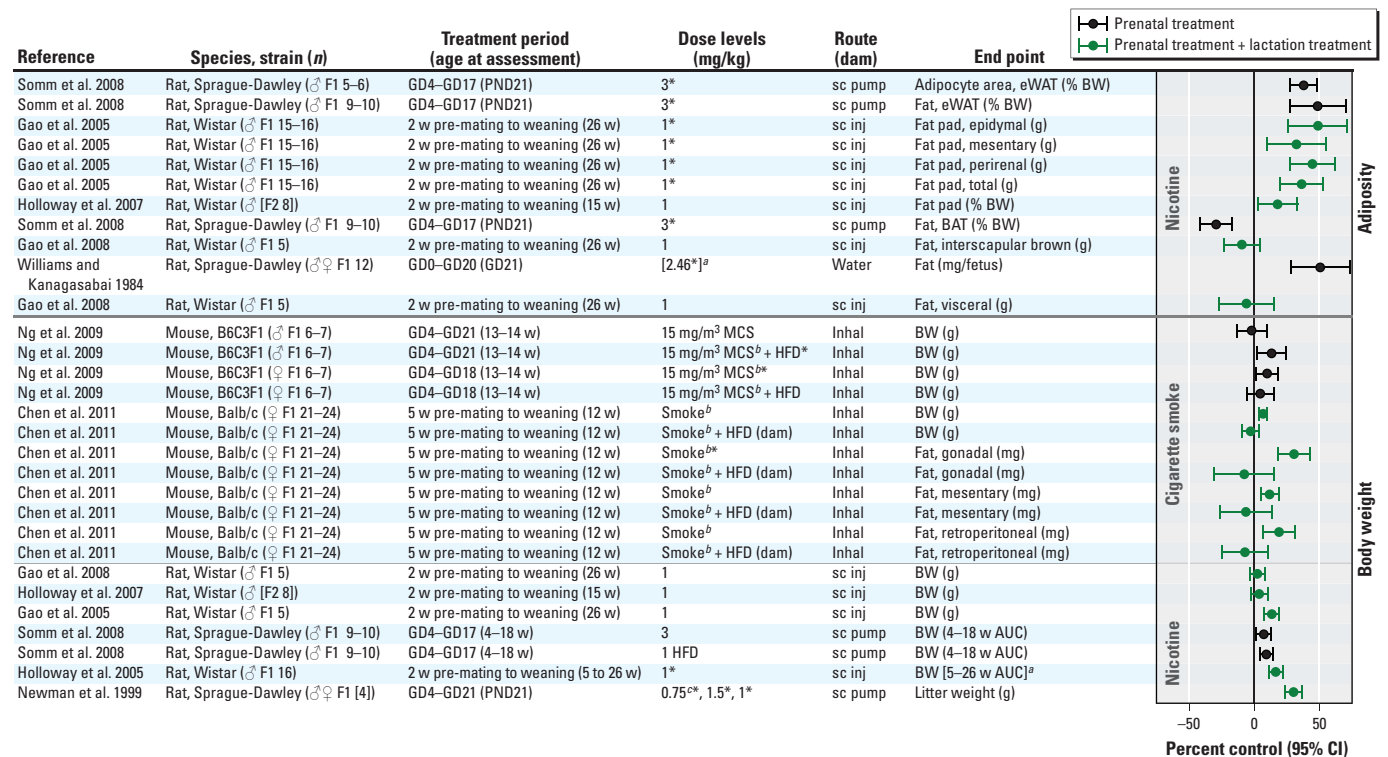


Figure 4. Animal studies of prenatal or prenatal + lactational exposure to nicotine or cigarette smoking and adiposity-related end points. The primary grouping of studies is based on whether the end point was related to adiposity or body weight. Within each end point category, main findings were sorted based on specific end point (A to Z). Abbreviations: AUC, area under the curve; BAT, brown adipose tissue; BW, body weight; eWAT, epididymal white adipose tissue; GD, gestational day; inhal, inhalation; inj, injection; MCS, mainstream cigarette smoke; PND, postnatal day; sc, subcutaneous; w, weeks.

^aValue was assumed or estimated based on data presented in publication. ^bIn Ng et al. (2009) animals were exposed via whole body inhalation to mainstream cigarette smoke (smoke inhaled by an active smoker) at a particle concentration of 15 mg/m³; in Chen et al. (2011) dams were exposed to cigarette smoke via a perspex chamber for 30 min 5 days/week (2 cigarettes/day, nicotine \leq 1.2 mg, carbon monoxide \leq 15 mg). ^cDose level summarized in graph. *Statistically significant effect at specified dose level as reported in publication. In some cases statistical significance of percent control response differs from author's interpretation (e.g., author's statistical analysis considered multiple comparisons, i.e., analysis of variance).

tissue damage due to low levels of antioxidant enzyme expression (Lenzen et al. 1996; Tiedge et al. 1997).

Leptin signaling. Adipose tissue is increasingly recognized as an active endocrine organ with many secretory products. In addition, adipose tissue is considered to be part of the innate immune system (Gaspari et al. 2011). Leptin is one of the key hormones involved in feeding behavior and energy expenditure

[reviewed by Belgardt et al. (2010)]. In general terms, leptin is secreted from the adipocytes of white adipose tissue and delivers information on peripheral energy stores to the central nervous system. Leptin resistance that involves impairment in leptin transport, leptin signaling, and/or the neurocircuitry of energy balance is a risk factor for obesity (Morris and Rui 2009). Several studies have assessed leptin levels or the expression of proteins involved

in leptin signaling after developmental nicotine exposure (Grove et al. 2001; Huang and Winzer-Serhan 2007; Santos-Silva et al. 2010). Findings from animal studies reveal that early exposure to nicotine appears to be associated with dysregulation of leptin levels, likely via hypertrophy of adipocytes and increased gene expression of pro-adipogenic transcription factors (Somm et al. 2008) and hypothalamic leptin signaling (Oliveira et al. 2009, 2010).

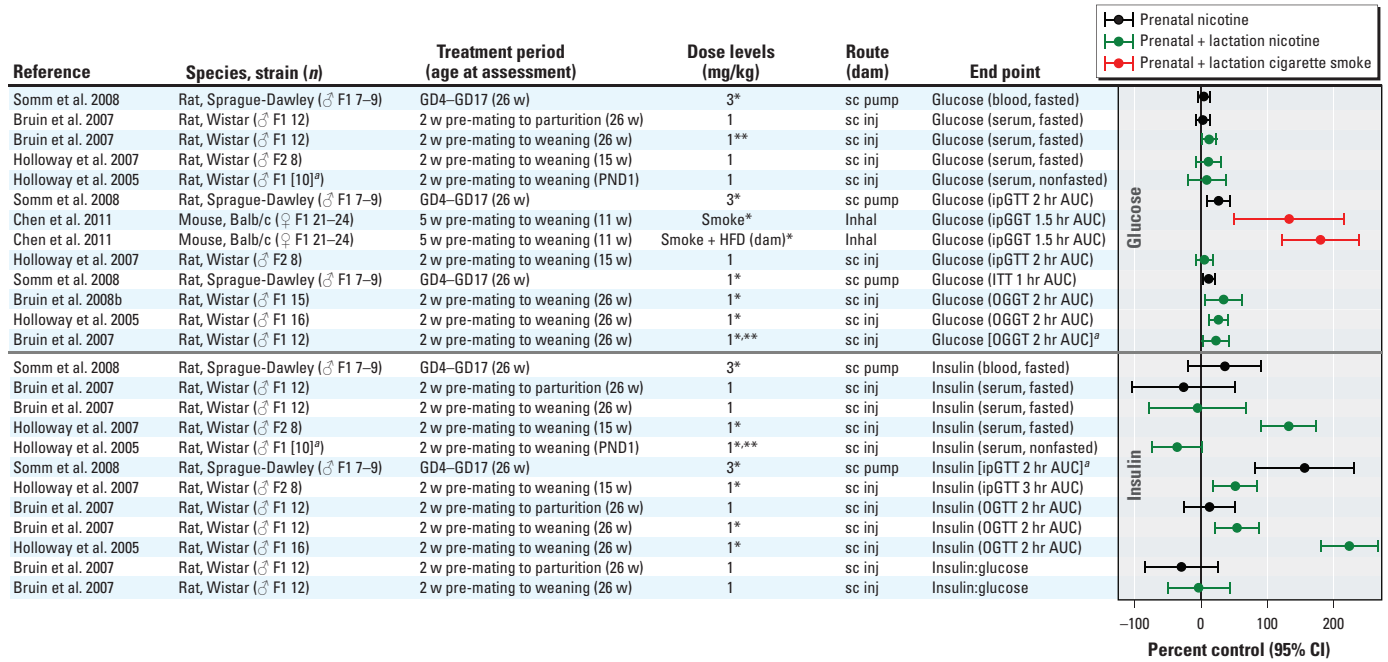


Figure 5. Animal studies of prenatal or prenatal + lactational exposure to nicotine and glucose homeostasis-related end points. The primary grouping of studies is based on whether the end point was based on glucose or insulin. Within the end point category, main findings were sorted based on specific end point (A to Z). Abbreviations: AUC, area under the curve; GD, gestational day; ipGTT, intraperitoneal glucose tolerance test; inj, injection; OGTT, oral glucose tolerance test; PND, postnatal day; sc, subcutaneous; w, weeks.

ªValue was assumed or estimated based on data presented in publication. *Statistically significant effect at specified dose level as reported in publication. **In some cases statistical significance of percent control response differs from author’s interpretation (e.g., author’s statistical analysis considered multiple comparisons, i.e., analysis of variance).

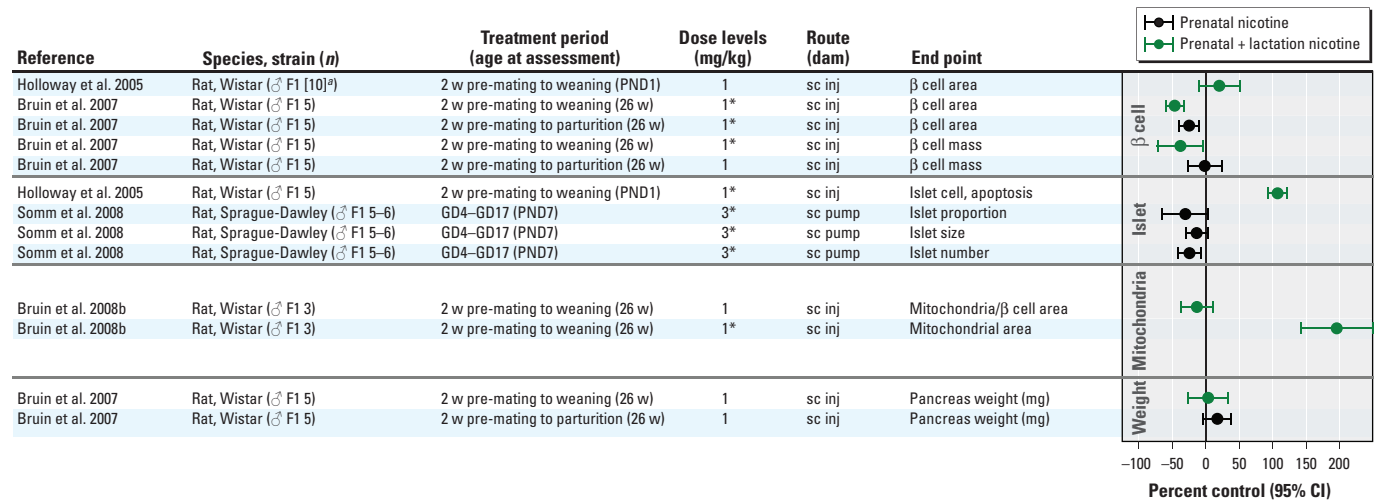


Figure 6. Animal studies of prenatal or prenatal + lactational exposure to nicotine and pancreatic end points. The primary grouping of studies is based on the type of pancreatic effect. Within the effect category, main findings were sorted based on whether treatment occurred only during prenatally (black) or prenatal + lactational (green). Abbreviations: GD, gestational day; PND, postnatal day; sc, subcutaneous; w, weeks.

ªValue was assumed or estimated based on data presented in publication. *Statistically significant effect at specified dose level as reported in publication.

The association between smoking and leptin levels in human infants remains controversial, with both hyper- and hypoleptinemia being reported (Coutant et al. 2001; Helland et al. 2001; Kayemba-Kay's et al. 2008; Mantzoros et al. 1997; Ozkan et al. 2005; Pardo et al. 2004, 2005; Vatten et al. 2002).

Conclusions and Research Recommendations

Based on human epidemiological studies and animal experiments reported in the literature, current evidence supports a causal relationship between maternal smoking and increased risk of obesity or overweight in offspring; however, the possibility that the association is attributable to unmeasured residual confounding cannot be completely ruled out. The literature is not sufficient to evaluate the potential impact of maternal smoking after delivery, or the contribution of exposure to secondhand smoke during pregnancy and early childhood. Existing studies in humans do not provide strong support for an association between maternal or parental smoking and childhood T1D, and too few epidemiological studies have assessed outcomes related to T2D to reach conclusions. However, findings from animal studies identify associations between perinatal nicotine exposure and disruption of pathways important in the pathophysiology of T2D, including reduced β -cell mass and impaired β -cell function.

In Appendix 1 we identify research gaps and provide specific study recommendations noting in particular the need to better understand the *a*) relationship between developmental exposure to tobacco smoke as a risk factor for T2D or metabolic syndrome, *b*) consequences of pre- and postnatal exposure to secondhand smoke (also called environmental tobacco smoke, involuntary smoke, and passive smoke), *c*) impact of timing of exposure, dose, duration and route (e.g., nicotine replacement therapy), and *d*) mechanistic basis for the association between cigarette smoke or nicotine exposure with childhood obesity and metabolic outcomes. Elucidating the mechanistic basis for these associations could be an important component of developing a toxicological screening approach that could be used to identify other environmental chemicals for targeted assessment of obesogenic and metabolic effects. For example, a number of pesticides included in Phase 1 of the U.S. Environmental Protection Agency (U.S. EPA 2012) ToxCast™ high throughput screening program interact with nicotinic receptors but have never been assessed for potential adipogenic or metabolic effects [see Supplemental Material, Figure S2 (<http://dx.doi.org/10.1289/ehp.1205404>)]. Addressing the data gaps can help us understand more about the nature of the association as well as inform decisions regarding

intervention strategies. Epidemiological studies will also need to consider the challenges related to validity of self-reported maternal tobacco use or secondhand smoke exposure, especially in studies evaluating the long-term health consequences for offspring where exposure assessment may occur many years after the exposure event. With respect to mechanistic research, more attention should be given to the possibility that environmental exposures could alter central nervous system regulation of energy and body weight homeostasis. The brain is the primary organ involved with determining behavior and obesity; metabolic diseases are often considered to be manifestations of behavioral excess (i.e., consuming calories in excess of one's energy needs). A number of pathways are important for the development of obesity and/or diabetes, including but not limited to alterations in neurohumoral signaling, feeding behavior, energy balance, brain and peripheral inflammation, and insulin resistance. To date, the effects of maternal cigarette smoking and/or nicotine exposure on these pathways remains largely unexplored (Wilborn et al. 2005; Woods 2009; Woods and D'Alessio 2008; Zheng et al. 2009). Another largely unexplored hypothesis is that

fetal/neonatal exposure to smoking/nicotine sensitizes the offspring to adverse effects of obesogenic diets. Although perturbations in the microbiome profile have been associated with diabetes and obesity, the contribution of or interactions with smoking have not been explored and may also influence susceptibility to adverse diets.

The association between maternal smoking and childhood obesity adds to the recognized health burden from tobacco exposure, which is estimated at almost 5 million deaths per year globally (World Health Organization 2010). Maternal smoking during pregnancy may not account for as many cases of childhood obesity or overweight as more traditional risk factors such as decreased physical activity, watching television > 1 hr/day, and low parental education level (Toschke et al. 2007b), but it is a risk factor that, if prevented, can help reduce the burden of childhood obesity at the population level. From a toxicological perspective, the linkages between maternal smoking during pregnancy and childhood overweight/obesity provide proof-of-concept of how early-life exposure to an environmental toxicant can act as a risk factor for childhood obesity.

Appendix 1. Data Gaps and Research Needs

Epidemiology

- Additional assessment of association between maternal smoking and risk of T2D and metabolic syndrome in offspring
- Clarification of the pre- and postnatal consequences of secondhand smoke on childhood obesity and metabolic outcomes
- Characterization of factors such as timing of exposure (including adolescence), dose, duration and route (e.g., nicotine replacement therapy)
- Evaluate potential confounding by or interactions with postnatal diet and activity levels
- Consider studies of nicotine replacement therapy (NRT) to better establish the association between nicotine and obesity or diabetes and other metabolic disorders in humans
 - NRT during pregnancy trials, NRT following smoking cessation, nicotine therapeutics for nonsmokers, Snus (a moist powder tobacco product similar to dry snuff)
 - Other data may be available from FDA for nicotinic acetylcholine receptor agonist drugs, and putative “reduced” harm cigarettes

Animal and in vitro

- Better understanding of the basic biology of critical cells (i.e., adipocytes, β cells) and their function in health and disease, including how the biology that controls body weight and metabolic set points change with life stage
- Further characterize impact of factors such as timing of exposure, dose, duration, and route (e.g., NRT) on adiposity, diabetes, and metabolic-related health outcomes
- Mechanistic effects of smoking on genomic/epigenomic and molecular targets that coordinate central and peripheral nutrient homeostasis and metabolic function
- Determine the relative contribution of other constituents of cigarette smoke
 - Graded step wise manner—starting with high throughput-type screening with relevant cell types, then *in vivo* alone, and then *in vivo* in combination with nicotine
- Evaluate interactions between fetal/neonatal exposure to smoking/nicotine and postnatal diet and activity levels
- Assess the effects of other chemicals that act as agonists for nicotinic acetylcholine receptors (nAChRs), such as neonicotinoid pesticides as well as chemicals identified in the U.S. EPA's ToxCast™ high throughput screening program [see Supplemental Material Figure 2 (<http://dx.doi.org/10.1289/ehp.1205404>)].

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