Chapter 9
Reproductive Outcomes

Table 9.3*S* Summary of studies of orofacial clefts and maternal smoking, 2002–2011

Study	Design/population	Definition of smoking	Findings (95% CI)
Little et al. 2004a	• Infants with nonsyndromic orofacial clefts • 112 CL/P and 78 CP cases • 248 unaffected controls • Study period: September 1997–January 2000 • England (some regions) and Scotland	Self-reported smoking in the first trimester, with frequency and duration of smoking also obtained, collected by interview after the end of the pregnancy; questions also on exposure to secondhand smoke at home, work, and other locations	• First-trimester maternal smoking was associated with all orofacial clefts combined, OR = 2.0 (1.3–3.1), with CL/P, OR = 1.9 (1.1–3.1), and with CP, OR = 2.3 (1.3–4.1) • There was evidence of a dose-response effect for both CL/P and CP
Tamura et al. 2005	• Recruited mothers of children with and without orofacial clefts in 2003 • 57 with CL/P, 17 with CP, and 283 controls • Philippines	Self-reported smoking during pregnancy	• No association between maternal smoking and orofacial clefts (OR = 0.84) • Relatively low prevalence of maternal smoking (11% in control mothers)
Krapels et al. 2006	• Case-control triad study of nonsyndromic orofacial clefts • 284 CL/P and 66 CP cases • 222 control families (friends and convenience sample) • Births 1998–2003 • The Netherlands	Self-reported smoking in the periconceptional period, defined as 3 months before pregnancy through the end of the first trimester; data collected approximately 24 months after periconceptional period	• Reported maternal smoking (any amount) during the periconceptional period was not significantly associated with CL/P, OR = 1.2 (0.8–1.8), or with CP, OR = 0.9 (0.5–1.8) • Reported paternal smoking had borderline associations with CL/P, OR = 1.5 (1.0–2.1), and CP, OR = 1.5 (0.9–2.6)
Bille et al. 2007	• Singleton infants • 134 CL/P and 58 CP cases • Random sample of all births (n = 828) • Births 1997–2003 • Denmark	Self-reported smoking, with data collected during pregnancy, mean gestational age at data collection (week 17); any smoking during pregnancy; number of cigarettes/day in first trimester	• Combined effect estimate for all orofacial clefts excluding syndromes, OR = 1.52 (1.05–2.14) • Any smoking during pregnancy was moderately associated with CL/P, OR = 1.48 (0.97–2.24) and with CP, OR = 1.53 (0.83–2.82) • Strongest effect estimates were observed for those reporting the heaviest smoking (>20 cigarettes/day), but CIs were very wide
Romitti et al. 2007	• NBDPS • 10 sites • Excluded infants with syndromes and single-gene disorders • 1,128 CL/P and 621 CP cases • 4,094 control infants without birth defects • Infants born after October 1, 1997, with an estimated date of delivery on or before December 31, 2002 • United States	Self-reported periconceptional smoking, data collected after pregnancy completion; any reported smoking from the month before pregnancy through the end of the first trimester	• Periconceptional smoking was associated with all orofacial clefts combined, OR = 1.37 (1.20–1.57) • Prior analyses in this dataset (Honein et al. 2007) showed a stronger association for heavy smoking (>25 cigarettes/day) and CL/P, OR = 1.8 (1.0–3.2), in particular for heavy smoking and bilateral CL/P, OR = 4.2 (1.7–10.3)
van den Boogaard et al. 2008	• 181 infants with orofacial clefts • Clinic-based case-control study in nine large cleft teams • Births from 1997–2000 • The Netherlands	Self-reported maternal periconceptional smoking (3 months before to 3 months after conception)	• Periconceptional smoking was associated with orofacial clefts, but the finding was nonsignificant, with OR = 1.6 (0.9–2.7)

Table 9.3*S* Continued

Study	Design/population	Definition of smoking	Findings (95% CI)
Chevrier et al. 2008	• Nonsyndromic orofacial clefts: 164 infants with CL/P and 76 infants with CP • All orofacial clefts were combined in analyses • Hospital-based controls • 1998-2001 • France	Self-reported regular smoking of at least one cigarette per day in the first trimester of pregnancy	• First trimester smoking was not associated with orofacial clefts, OR = 1.0 (0.7–1.6) • Among nonsmokers, exposure to tobacco smoke was associated with orofacial clefts, OR = 1.8 (1.2–2.8)
Grewal et al. 2008	• 502 infants with CL/P and 199 infants with CP • Births from selected counties (Los Angeles, San Francisco, and Santa Clara) • Births July 1999–June 2003 • California	Self-reported smoking during the first month of pregnancy, data collected after pregnancy completion; smoking categorized as >5 or ≤5 cigarettes/day for the first month of pregnancy	• Infants with an isolated cleft were analyzed separately from those with multiple major unrelated defects • There were no significant associations observed for smoking in the first month of pregnancy for any of the phenotypes assessed
Leite and Koifman 2009	• Hospital-based study • 208 CL/P and 66 CP cases 0–24 months of age • 548 controls • Study period: 2005 • Rio de Janeiro, Brazil	Maternal smoking in the year before pregnancy and maternal smoking in the first trimester	• Maternal smoking in the year before pregnancy was associated with CL/P, OR = 1.59 (1.04–2.44), but not with CP • No significant associations for first-trimester smoking with CL/P or CP
Shaw et al. 2009	• 89 infants with CL/P and 409 unaffected infants • Mid-pregnancy serum specimens from the 15th to 18th week of pregnancy collected from 2003–2005 • Women in selected regions of California	Mid-pregnancy serum cotinine levels of ≥2 ng/mL defined as exposed to maternal smoking; <2 ng/mL defined as unexposed	• Maternal smoking was associated with CL/P, AOR = 2.4 (1.1–5.3)
Wang et al. 2009	• Orofacial clefts identified from a population based birth defects surveillance program • Births 2000–2007 • Controls matched by gender, address, and date of birth • 606 infants with orofacial clefts and no other major birth defects • Shenyang, China	Self-reported smoking from one month before to two months after last menstrual period	• Prevalence of maternal smoking was very low (2.0% of case-mothers and 1.4% of control-mothers) • Maternal smoking was higher among case-mothers, but association was not significant, OR = 1.50 (0.52–4.36) • Paternal smoking was associated with orofacial clefts, OR = 2.05 (1.47–2.87)
Lebby et al. 2010	• Births (birth certificate records) • Study period: 2005 • United States	Smoking during pregnancy, reported on the birth certificate	• Maternal smoking was associated with orofacial clefts, OR = 1.66 (1.32–2.09)
Li et al. 2010	• 4 counties • Study period: 2003–2006 • Shanxi province, China	Exposure to passive smoking at least once a week from 1 month before to 2 months after conception	• Exposure to passive smoking was associated with CL/P, AOR = 2.0 (1.2–3.4) • Stronger effect estimate for those exposed >6 times per week, OR = 2.8, than for those exposed 1–6 times per week, OR = 1.6

Table 9.3*S* Continued

Study	Design/population	Definition of smoking	Findings (95% CI)
Johansen et al. 2009	• All children surgically treated for an orofacial cleft • Births from 1996-2001 • Norway	Self-reported smoking in the first trimester from a questionnaire completed by mothers	• First trimester smoking was associated with orofacial clefts combined, OR = 1.52 (1.21–1.90)
Zandi and Heidari 2011	• Hospital births • Study period: 1993–2008 • Hamedan, Iran	Smoking during pregnancy	• Smoking during pregnancy was more common among mothers of infants with clefts than controls, but it was very rare overall
Jia et al. 2011	• Sichuan University, Department of Cleft Lip and Palate Surgery • Cases with nonsyndromic CL/P and CP • Unaffected controls • Study period: 2008–2010 • West China	Self-reported maternal, paternal, and passive smoking	• Maternal passive exposure to tobacco during early pregnancy was associated with nonsyndromic orofacial clefts combined, AOR = 1.42 (6.87–19.00) • In unadjusted analyses, the association with passive smoking was reported for both CL/P and CP
Mirilas et al. 2011	• Aristotle University, Pediatric Surgery Department • 35 cases operated on for nonsyndromic CL/P • 35 residence-matched controls • Study period: 2004–2009 • Greece	Self-reported maternal smoking and passive smoking before and during pregnancy (first 3 months)	• Maternal passive exposure to tobacco was associated with increased risk of CL/P, OR = 1.81 (0.69-4.74), but the association was not significant
Zhang et al. 2011	• 304 infants with nonsyndromic orofacial clefts (140 with CLP, 77 with CP, and 86 with CLO) • 454 controls • Study period: 2006–2009 • Harbin, China	Self-reported maternal smoking (6 months before pregnancy and in the first trimester), paternal smoking (1 month before pregnancy through first trimester), and passive smoking	• AOR for maternal smoking before pregnancy was 4.97 (1.39–17.76) for CLO and 3.37 (1.04–10.88) for CLP for those reporting smoking 1–9 cigarettes/day before pregnancy; estimates were similar for maternal smoking in the first trimester • No association with maternal smoking and CP • Paternal smoking in the periconceptional period was strongly associated with CLP, CLO, and CP • The medium level of exposure to environmental tobacco smoke at home or work was associated with orofacial clefts

Notes: **AOR** = adjusted odds ratio*;* **CI** = confidence interval; **CL/P** = cleft lip with or without cleft palate; **CLO** = cleft lip only; **CLP** = cleft lip with cleft palate; **CP** = cleft palate; **mL =** milliliters; **n =** sample size; **NBDPS =** National Birth Defects Prevention Study; **ng** = nanogram; **OR** = odds ratio.

Table 9.4*S* Summary of studies of maternal smoking and clubfoot, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Honein et al. 2000	• 346 infants with isolated talipes equinovarus, or isolated clubfoot, NOS • 3,029 infants with no major birth defects • Births 1968–1980 • 5 counties in metropolitan Atlanta, GA	Self-reported maternal smoking, from telephone interviews conducted in 1981–1982	• Clubfoot was associated with maternal smoking among those with no family history of clubfoot, OR = 1.34 (1.04–1.72) • Much stronger association was found between clubfoot and maternal smoking among those with a first-degree family history of clubfoot, OR = 20.30 (7.9–52.17)
Honein et al. 2001	• U.S. natality data • Study period: 1997–1998 • 45 states, New York City, and District of Columbia	Birth certificate report of number of cigarettes/day during pregnancy by four categories: 1–5, 6–10, 11–20, and ≥21	• Maternal smoking during pregnancy was associated with clubfoot, PR = 1.62 (1.49–1.75) • Strongest effect at highest reported smoking level (≥21 cigarettes/day)
Skelly et al. 2002	• 239 infants with idiopathic talipes equinovarus • 356 unmatched controls selected by random-digit dialing • Births on or after January 1, 1986, of children who were treated through May 1994 • Western Washington state	Self-reported smoking during pregnancy, collected after pregnancy	• Smoking during pregnancy was associated with clubfoot • There was some evidence of a dose-response effect, with the strongest effect for those smoking ≥20 cigarettes/day, OR = 3.9 (1.6–9.2); a somewhat similar effect for those smoking 10–19 cigarettes/day, OR = 3.1 (1.7–5.8); and a weaker effect for those smoking <10 cigarettes/day, OR = 1.5 (0.9–2.5) • No information was available on the timing of smoking during pregnancy
Cardy et al. 2007	• 194 infants with talipes equinovarus and 60 controls • Children/parents recruited July 1993 – July 1997 • United Kingdom		• Maternal smoking was more common among case- than control-mothers, but the association was not significant, OR = 1.37 (0.72–2.62)
Dickinson et al. 2008	• 443 singleton infants diagnosed with isolated talipes equinovarus, or isolated clubfoot, NOS • Random sample of 4,492 live births without major birth defects • Births 1999–2003 • North Carolina	Maternal smoking as reported on birth certificates; reliability of exposure assessed by matching to the North Carolina PRAMS, giving a Kappa = 0.77	• Clubfoot was associated with any maternal smoking during pregnancy, OR = 1.40 (1.07–1.83) • There was no evidence of a dose-response effect • No information was available on the timing of maternal smoking
Parker et al. 2009	• 10 population-based birth defects surveillance programs • 6,139 infants with talipes equinovarus, or clubfoot, NOS, among 4,744,711 live births • Births 2001–2005	Birth certificate data on smoking during pregnancy	• Maternal smoking was associated with clubfoot, OR = 1.57 (1.45–1.70) • Case definition excluded infants with neural tube defects, lower limb defects, bilateral renal agenesis, and chromosomal abnormalities because the clubfoot was presumed to be secondary to these defects • Dose-response effect was observed

Table 9.4*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Kancherla et al. 2010	• Study period: 1997–2005 • Iowa	Smoking during pregnancy as reported on the birth certificate	• Smoking was associated with clubfoot, POR = 1.5 (1.2–1.9)

Note: **CI** = confidence interval; **NOS =** not otherwise specified; **OR** = odds ratio; **POR** = prevalence odds ratio; **PRAMS** = Pregnancy Risk Assessment Monitoring System.

Table 9.5*S* Summary of studies of maternal smoking and gastroschisis, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén 2000	• Isolated and multiple defects among all births • Births 1983–1996 • Sweden	Prenatal assessment of smoking during antenatal visit typically at 10–12 weeks gestation	• Maternal smoking was associated with isolated gastroschisis, OR 1.59 (1.00–2.54)
Stoll et al. 2001	• Birth defects registry • 1979–1998 • France (Strasbourg)		• No association between maternal smoking and gastroschisis, OR = 1.02 (0.44–2.37)
Werler et al. 2003b	• 205 infants with gastroschisis • 381 malformed controls • 416 nonmalformed controls • Study period: June 1995–March 1999 • 15 U.S. and Canadian cities	Self-reported exposures in the first 2.5 months of pregnancy of mothers interviewed within 6 months of delivery	• First-trimester smoking was associated with gastroschisis, OR = 1.5 (1.1–2.2) • Stronger effect was observed for the combination of vasoconstrictive medications and maternal smoking
Hougland et al. 2005	• Gastroschisis surgeries • 1998–2002 • Utah	Maternal tobacco use	• Maternal smoking was associated with gastroschisis, OR = 2.60 (1.48–4.55)
Lam et al. 2006a	• 55 singleton infants with gastroschisis • 94 age-matched controls • Study period: March 1988–August 1990 • California	Mothers interviewed 3–6 months after delivery to ascertain periconceptional exposures	• Smoking more than 1 pack of cigarettes/day had a borderline association with gastroschisis, OR = 2.0 (0.9–4.9) • Any smoking of marijuana was associated with gastroschisis, OR = 2.1 (1.0–4.4) • Study found some suggestion of an interaction between high exposure to carbon monoxide (from tobacco or marijuana) and low BMI
Chambers et al. 2007	• Case-control study recruiting in prenatal diagnosis centers • 1986–2003 • Southern California	Tobacco use in the first trimester	• Effect estimate was elevated, but there was no significant association between maternal smoking and gastroschisis, OR = 1.37 (0.63–2.96)
Zamakhshary and Yanchar 2007	• 54 gastroschisis cases • Study period: January 1990–December 2001 • 3 Canadian provinces	Maternal smoking in the first trimester abstracted from prenatal care medical records	• Study compared complicated gastroschisis cases (n = 17) with simple gastroschisis cases (n = 37) • Maternal smoking was more common in complicated gastroschisis but not significantly so, OR = 2.1 (0.6–7.2)
Draper et al. 2008	• Matched case-control study • 144 infants with gastroschisis and 432 control-mothers • January 2001–August 2003 • United Kingdom (3 regions)		• After adjustment for other risk factors, maternal smoking was associated with gastroschisis, OR = 1.70 (1.1–2.6)
Feldkamp et al. 2008	• 189 gastroschisis cases • 423,499 live-born infants without major defects • Births January 1997–December 2005 • Utah	Birth certificate information on smoking during pregnancy	• Maternal smoking was associated with gastroschisis after adjusting for maternal age, OR = 1.6 (1.1–2.3) • Study excluded infants with ventral body wall defects, amniotic band sequence, and chromosomal abnormalities

Table 9.5*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Bird et al. 2009	• NBDPS • Excluded infants with syndromes and single-gene disorders • 485 infants with gastroschisis, 168 with omphalocele • 4,967 controls • Infants born after October 1, 1997, and with an estimated date of delivery on or before December 31, 2003 • 10 U.S. sites	Self-reported maternal smoking from 1 month before conception to 3 months after conception, categorized as light (<1 pack/day), medium (1 pack/day), or heavy (>1 pack/day)	• Heavy smokers were twice as likely to have an infant with gastroschisis, but finding not significant, OR = 2.08 (0.90–4.78) • Heavy smoking was associated with omphalocele, OR = 4.26 (1.58–11.52)
Salemi et al. 2009	• Cohort with the birth defects registry identified cases • Births 1998–2003 • Florida	Smoking during pregnancy as reported on the birth certificate	• In the crude analyses, maternal smoking was associated with gastroschisis • After adjustment for maternal age, marital status, education, race/ethnicity, parity, and place of residence, there was no association, OR = 0.97 (0.73–1.28)
Werler et al. 2009b	• NBDPS • Excluded infants with syndromes and single-gene disorders • 514 mothers of infants with gastroschisis • 3,277 maternal age-matched controls • Infants born after October 1, 1997, and with an estimated date of delivery on or before December 31, 2003 • 10 U.S. sites	Self-reported smoking in the time period from 2 weeks before the last menstrual period to 14 weeks after the last menstrual period	• Maternal smoking was associated with gastroschisis, OR = 1.5 (1.2–1.9) • There was no association between maternal smoking and gastroschisis among mothers <19 years of age • The strongest association between maternal smoking and gastroschisis was observed for mothers ≥25 years of age, OR = 3.0 (1.8–5.0)
Chabra et al. 2011	• Birth certificate data • Study period: 1987–2006 • Washington state	Any smoking during pregnancy	• Smoking during pregnancy was associated with gastroschisis, adjusted RR = 1.58 (1.19–2.09)

Note: **BMI** = body mass index; **CI** = confidence interval; **NBDPS =** National Birth Defects Prevention Study; **OR** = odds ratio; **RR** = relative risk.

Table 9.6*S* Summary of studies of maternal smoking and congenital heart defects, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén 1999a	• 3,384 infants with congenital heart defects (excluding those with chromosomal abnormalities) among 1,413,811 infants • Study period: 1983–1996 • Sweden	Maternal smoking during pregnancy (none, <10 cigarettes/day, ≥10 cigarettes/day), reported at first antenatal visit	• Significant associations with maternal smoking were observed for transposition of the great arteries, OR = 1.32 (1.02–1.71); atrial septal defects, OR = 1.63 (1.04–2.57); and full-term infants with PDA, OR = 1.30 (1.05–1.62).
Woods and Raju 2001	• TriHealth Hospital system births • 18,016 live births; examined 22 categories of birth defects • Study period: January 1998–December 1999 • Cincinnati, Ohio	Self-reported maternal smoking during pregnancy, collected at the time of admission for delivery (prior to actual delivery)	• Congenital heart defects were more common among smoking mothers than nonsmoking mothers, RR = 1.56 (1.12–2.19) (p <0.01) • No other defect categories were significantly associated (p ≤0.01) with maternal smoking
Botto et al. 2001	• Case-control study • 905 infants with nonsyndromic congenital heart defects and 3029 controls • Births 1968-1980 • Metropolitan Atlanta	Self-reported maternal smoking	• Maternal smoking was not associated with all congenital heart defects combined, OR = 1.11 (0.95–1.30)
Steinberger et al. 2002	• Baltimore-Washington Infant Study • 55 infants with single ventricle • 3,572 control infants • Study period: 1981–1989 • District of Columbia, Maryland, and some counties in Northern Virginia	Maternal and paternal smoking (none, 1–20, 20–39, and ≥40 cigarettes/day), collected by interview after the pregnancy	• Paternal smoking was associated with single ventricle, and there was some evidence of a dose-response effect (ORs were 1.0, 1.9, and 3.7 for increasing smoking dose, p for trend = 0.02) based on 6 exposed cases • No significant association was found between maternal smoking and single ventricle
Morales-Suarez-Varela et al. 2006	• 76,768 pregnancies resulting in 3,767 infants with birth defects, 746 congenital heart defects • Limited to singletons • Study period: 1997–2003 • Denmark	Self-reported maternal smoking and use of nicotine substitutes (gum, patches, inhalers), collected by interview during pregnancy	• A modest but significant association was found between maternal smoking and congenital heart defects, OR = 1.20 (1.03–1.40)
Malik et al. 2008	• NBDPS • Excluded infants with syndromes and single-gene disorders • 3,067 congenital heart defects • 3,947 controls • Study period: October 1997–December 2002 • 8 U.S. sites	Self-reported smoking in the month before pregnancy through the first trimester, categorized as light (<1/2 pack/day), medium (1/2–1 pack/day), and heavy (≥25 cigarettes/day), reported by interview after pregnancy	• Light, medium, and heavy smoking were all associated with septal heart defects and especially atrial septal defects

Table 9.6*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Grewal et al. 2008	• Case-control study • 320 infants with conotruncal heart defects and 639 controls • Births from selected counties (Los Angeles, San Francisco, and Santa Clara) • Births July 1999–June 2004 • California	Self-reported smoking during the first month of pregnancy, data collected after pregnancy completion; smoking categorized as >5 or ≤5 cigarettes/day for the first month of pregnancy	• Smoking in the first month of pregnancy was not associated with conotruncal heart defects, OR = 0.78 (0.45–1.34)
Kučienė and Dulskienė 2009	• 187 newborns with congenital heart defects • 643 randomly selected newborns without defects • Study period: 1999–2005 • Kaunas, Lithuania	Maternal smoking during pregnancy and duration of smoking prior to pregnancy	• Smoking during pregnancy was associated with congenital heart defects, OR = 2.45 (1.43–4.20), and after adjusting for occupation and education, the OR was reduced, 1.48 (0.82–2.67) • Study found a stronger association for mothers who had smoked longer (≥3 years) prior to pregnancy
Kučienė and Dulskienė 2010	• 261 cases with congenital heart defect from newborns' register database • 1,122 controls with no defects • Study period: 1995–2005 • Kaunas, Lithuania	Self-reported maternal smoking before and during the first trimester and self-reported paternal smoking	• Increased risk of congenital heart septal defects was associated with maternal smoking, AOR = 2.20 (1.01–4.79); paternal smoking, AOR = 1.45 (1.03–2.03),; and both parents smoking, AOR = 2.27 (1.49–3.46)
Van Beynum et al. 2010	• Study period: 1996–2005 • Northern Netherlands	Maternal smoking, on the basis of questionnaire after pregnancy	• Smoking during pregnancy was not associated with congenital heart defects (p = 0.47)
Alverson et al. 2011	• Baltimore-Washington Infant Study • 2,525 infants with congenital heart defects but no other birth defects • 3,435 controls • Study period: 1981–1989	Self-reported maternal cigarette smoking during first trimester	• Smoking during first trimester was associated with increased risk of secundum-type atrial septal defects, OR = 1.36 (1.04–1.78); pulmonary valve stenosis, OR = 1.35 (1.05–1.74); truncus arteriosus, OR = 1.90 (1.04–3.45); and l-transposition of the great arteries, OR = 1.79 (1.04–3.10) • Associations were not observed for maternal smoking and most other congenital heart defects
Cresci et al. 2011	• 360 infants with congenital heart defects • 360 infants without defects from a pediatric cardiac center and maternity and pediatric units • Study period: 2008–2010 • Italy	Self-reported maternal and paternal smoking at conception	• Paternal smoking was associated with an increased risk of congenital heart defects, OR = 1.7 (1.1–2.6), but there was no significant association for maternal smoking, OR = 1.2 (0.7–1.8)

Table 9.6*S* Continued

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Karatza et al. 2011	• 157 neonates with congenital heart defects • 208 unaffected neonates • Study period: June 2006–June 2009 • Greece	Self-reported maternal smoking (1 month before conception through first trimester) obtained by interview prior to echocardiographic exam of the infant	• Congenital heart defects were identified in 61% of the neonates whose mother smoked and 36% of neonates whose mother did not smoke ($p < 0.001$) • In the adjusted analyses, maternal smoking was associated with congenital heart defects, OR = 2.74 (1.66–4.53)
Baardman et al. 2012	• 797 cases, born with isolated nonsyndromic congenital heart defect and identified from a population-based birth defects registry • 322 infants/fetuses with chromosomal anomalies but without cardiac anomalies served as controls • Study period: 1997–2008 • The Netherlands	Self-reported maternal smoking before and through first trimester of pregnancy	• Periconceptional smoking was associated with congenital heart defects among women with a high BMI, AOR = 2.65 (1.20–5.87) • Significant and elevated AORs were observed for septal heart defects and outflow tract defects based on the interaction between smoking and high BMI
Mateja et al. 2012	• Data from PRAMS, linked to state birth certificates • 237 infants with a congenital heart defect, as indicated on birth certificate, with no indication of Down syndrome • 948 controls with no indication of any congenital defect • Cases and controls limited to singletons • Study period: 1996–2005 • 9 U.S. states	Self-reported smoking 3 months before pregnancy	• Smoking during pregnancy was not associated with congenital heart defects • There was a significant interaction between exposure to alcohol and smoking before pregnancy ($p < 0.01$)

Note: **AOR** = adjusted odds ratio; **BMI** = body mass index; **CI** = confidence interval; **NBDPS =** National Birth Defects Prevention Study; **OR** = odds ratio; **PDA** = Patent ductus arteriosus; **PRAMS** = Pregnancy Risk Assessment Monitoring System; **RR** = relative risk.

Table 9.7*S* Summary of studies of maternal smoking and craniosynostosis, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén 1999b	• 304 infants with craniosynostosis and no chromosomal abnormality among 1,413,811 live births • Study period: 1983–1996 • Sweden	Self-reported smoking, ascertained during pregnancy at prenatal consultations with midwife	• Smoking was associated with craniosynostosis, OR = 1.45 (1.13–1.87), but the effect was limited to those with an isolated defect (i.e., they had no other major birth defect unrelated to craniosynostosis) • Strongest effect was found for sagittal craniosynostosis • Study found some evidence for a dose-response effect between maternal smoking and craniosynostosis
Honein and Rasmussen 2000	• Study period: 1968–1980 • 5 central counties of metropolitan Atlanta, Georgia	Reported smoking at any time in the first 3 months of pregnancy	• Smoking in the first trimester was associated with isolated craniosynostosis, OR = 1.92 (1.01–3.66)
Carmichael et al. 2008	• NBDPS • 531 infants with craniosynostosis • 5,008 controls • Study period: 1997–2003 • 10 U.S. sites	Self-reported number of cigarettes/day in the month before pregnancy, each month of the first 3 months of pregnancy, and the second and third trimesters of pregnancy	• There was a borderline association with heavy maternal smoking (≥15 cigarettes/day) for mothers still smoking in the third month of pregnancy, OR = 1.6 (0.9–2.6) • Study found some evidence for a stronger effect of maternal smoking among those without exposure to folic acid until very late in pregnancy
Butzelaar et al. 2009	• Surgical sagittal synostosis patients in 1 hospital • Study period: 2006 • The Netherlands	Smoking during pregnancy	• Smoking among case mothers did not differ from that reported by the general population

Note: **CI** = confidence interval; **NBDPS** = National Birth Defects Prevention Study; **OR** = odds ratio.

Table 9.8*S* Summary of studies of maternal smoking and anorectal atresia, 1999–2011

Study by defect	Design/population	Definition of smoking	Findings (95% CI)
Källén, 2000	• Isolated and multiple defects among all births • Births 1983–1996 • Sweden	Prenatal assessment of smoking during antenatal visit typically at 10–12 weeks gestation	• Maternal smoking was associated with isolated anal atresia, OR = 1.45 (1.11–1.90)
Honein et al. 2001	• U.S. natality data • Study period: 1997–1998 • 45 states, New York City, and District of Columbia • 564 infants with rectal atresia/stenosis indicated on birth certificate	Birth certificate report of number of cigarettes/day during pregnancy by four categories: 1–5, 6–10, 11–20, and ≥21	• Maternal smoking during pregnancy was modestly associated with anal atresia but not significant, PR = 1.19 (0.94–1.50) • No evidence of dose-response effect
Miller et al. 2009	• NBDPS • 464 infants with anorectal atresia (216 of the defects were isolated) • 4,940 controls • Study period: October 1997–December 2003 • 10 U.S. sites	Self-reported periconceptional smoking, defined as smoking in the month before conception or first 3 months of pregnancy, interviewed after pregnancy; exposure to environmental tobacco smoke defined as reported exposure at home or work in the same time period	• Any maternal smoking had borderline association with anorectal atresia, OR = 1.2 (1.0–1.5) • Exposure to secondhand smoke at home and work was associated with anorectal atresia, OR = 2.3 (1.2–4.1)
Van Rooij et al. 2010	• Radbound University, Pediatric Surgery Department • Children born between January 1996 and April 2008 who were treated for anorectal malformation (85 cases) • 650 controls who were boys with persistent middle ear infections and were participating in another study • Study period: 1996–2008 • The Netherlands	Maternal smoking from 3 months before conception and during pregnancy; paternal smoking from 3 months before pregnancy to conception	• Paternal smoking was significantly associated with increased risk of anorectal malformations: crude, OR = 1.8 (1.1–2.9) • Maternal smoking was not associated with anorectal malformations

Note: **CI** = confidence interval; **NBDPS** = National Birth Defects Prevention Study; **OR** = odds ratio; **PR** = prevalence ratio.

Table 9.10*S* Studies on associations between prenatal smoking and disruptive behavioral disorders in children, 2000–2012

Study	Design/population	Estimate of effects (95% CI)	Findings
Breslau and Chilcoat 2000	• Random sample of hospital cohort of 823 low birth weight births from socioeconomically disparate communities followed to 11 years of age • Parent and teacher report on behavior symptoms • Prenatal daily smoking assessed retrospectively at 6 years of age	Attention: β = 0.90 (0.60) NS Externalizing: β = 2.55 (0.78) p <0.05 Internalizing: β = 0.68 (0.71) NS	• Prenatal smoking significantly predicted externalizing behavior, but not internalizing or attention symptoms
Hill et al. 2000	• 150 children 8–18 years of age at high or low familial risk for alcoholism • Diagnostic interview for condition • Prenatal smoking rate reported retrospectively at assessment	Depression NS Conduct NS Oppositional NS Anxiety NS Phobia NS ADHD NS Adjusted OR not reported	• Prenatal smoking was associated with depression, conduct disorder, and oppositional disorder, but not ADHD, anxiety or phobia • These findings were no longer significant after controlling for other risk factors
Maughan et al. 2001	• Prospective birth cohort study of all children born in the first week of April 1970 • Parental report on hyperactivity, conduct problems, adolescent self-report on conduct problems and depressive symptoms • Prenatal smoking rate assessed retrospectively at birth • Followed up at ages 5, 10, and 16 years • England, Scotland, and Wales	Conduct problems adjusted OR (value not reported); p = 0.238	• Prenatal smoking was not associated with hyperactivity, conduct problems, or depressive symptoms after controlling for postnatal smoking
Wakschlag and Keenan 2001	• Sample of 129 predominantly minority 2–5-year-old children referred to behavior problem clinic plus control • Diagnosis of disruptive behavior disorder via clinical interview • Prenatal smoking rate assessed retrospectively at assessment	Disruptive behavior: β = 2.48, t = 3.45, p = 0.0008	• Prenatal smoking was significantly associated with disruptive behavior disorder after controlling for other risks
Burke et al. 2002	• 177 clinic referred boys 7–12 years of age; follow up to 13–17 years of age • Conduct disorder based on parent and teacher interview • Prenatal smoking rate assessed retrospectively at initial assessment	Persistent CD: β = 0.45, OR = 1.58, p = 0.047	• Prenatal smoking significantly predicts CD persisting into adolescence

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Mick et al. 2002	• Retrospective, hospital-based, case-control study with 280 ADHD cases and 242 non-ADHD controls 6–17 years of age • Psychopathology assessed via interview of children and parents • Retrospective assessment of heavy prenatal smoking	ADHD cases: OR = 2.1 (1.1–4.1)	• Heavy prenatal smoking was associated with ADHD diagnosis
Wakschlag and Hans 2002	• 77 participants of longitudinal follow-up study of African American youth from pregnancy until 10 years of age • Conduct symptoms assessed via clinical interview of mother and child • Prenatal smoking assessed during pregnancy	CD: Overall correlation: $r = 0.22$, $p < 0.05$ Boys: $\beta = 0.36$, $t = 2.14$, $p < 0.05$ Girls: $r = -0.07$, NS	• Prenatal smoking related to CD risk, specifically for boys but not girls
Batstra et al. 2003	• Birth cohort of 1,186 children followed up at 5.5–11 years of age • Parent and teacher report of attention and externalizing symptoms • Prenatal smoking assessed during pregnancy	Attention symptoms: $\beta = 0.46$ (0.15–0.76), $p = 0.01$, explained variance = 5.1% Externalizing: $\beta = 0.19$ (0.07–0.32), $p = 0.01$, explained variance = 2.0%	• Prenatal smoking associated with attention deficit symptoms and externalizing symptoms, controlling for other risks
Kahn et al. 2003	• Cohort of 161 children followed prospectively from 6–60 months of age • Parent rating on behavioral symptoms • Prenatal smoking assessed retrospectively at 6 months	Hyperactive-impulsive scores: 65.4 vs. 59.7, $p < .05$ Oppositional: 66.5 vs. 56.7, $p < 0.01$ Inattentive: 58.3 vs. 55.7, NS	• Prenatal smoking was associated with hyperactive and oppositional symptoms, but not inattentive symptoms
Kotimaa et al. 2003	• 9,357 children from 1985–1986 birth cohort followed to 8 years of age • Parent and teacher report on behavioral symptoms • Prenatal smoking assessed in pregnancy	Overall: Hyperactivity: OR = 1.30 (1.08–1.58) Smoking status: Quit before pregnancy: OR = 1.52 (1.16–2.01) Reduced OR = 1.84 (1.47–2.31) Unchanged or increased: OR = 2.12 (1.62–2.77)	• Prenatal smoking was associated with hyperactivity after controlling for other risks • Positive dose-response relationship between prenatal smoking and hyperactivity
Silberg et al. 2003	• 538 boys 8–16 years of age from the initial wave of a statewide cohort study of all twin boys • Child self-report of conduct symptoms • Prenatal smoking reported retrospectively at initial assessment	Conduct symptoms: NS	• Prenatal smoking was not associated to conduct symptoms after controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Thapar et al. 2003	• Population-based sample of twins • 1,452 twin pairs 5–16 years of age • Parent and teacher report of ADHD symptoms • Prenatal smoking rates reported retrospectively at assessment	Teacher ratings of ADHD: F = 9.42, df = 3,1432, p <0.0001 Rates of cigarettes/day and mean scores: None: 3.18 (2.87–3.52) 1– 10: 4.81 (3.69–6.20) 11–20: 5.36 (4.44–6.48) >20: 5.17 (2.87–8.76) Parent ratings of ADHD: F = 9.45, df = 3,2041 , p <0.0001 Rates of cigarettes/day and mean scores: None : 7.33 (6.93–7.80) 1–10: 9.18 (7.92–10.56) 11–20: 10.02 (9.00–11 .33) >20: 10.59 (7.36–14.97)	• Prenatal smoking is associated with offspring ADHD symptoms when controlling for other risks
Gray et al. 2004	• Prospective intervention RCT of 869 low birth weight infants • Parent report on behavior problems • Prenatal smoking assessed retrospectively at birth • Followed up at 3, 5, and 8 years of age	Behavior problems: OR = 1.57 (1.20–2.04)	• Prenatal smoking was a significant predictor of the development of behavior problems from 3–8 years of age, controlling for other risks
Maughan et al. 2004	• Representative sample of 1,116 twin pairs assessed at 5 and 7 years of age • Parent and teacher report of conduct problems • Prenatal smoking assessed retrospectively at 1 year of age	Conduct problems: 5 years of age (F3, 1,054 = 13.75; p <0.001) 7 years of age (F3, 1,030 = 13.92; p <0.001) Multivariate: heavy smoking: 5 years of age: β = 0.09 (-0.03–0.21) NS 7 years of age: β = 0.17 (0.02–0.32), p <0.05	• Heavy prenatal smoking significantly predicts conduct problems at 7 years of age, controlling for other factors • No significant relation to 5 years of age
Button et al. 2005	• 1,896 cases from a population-based twin study, followed to 5–18 years age • Parent-reported ADHD symptoms • Prenatal smoking rate assessed retrospectively at initial assessment	Antisocial behavior: r = 0.17, p <0.001 ADHD: r = 0.14, p <0.001	• Prenatal smoking was associated with antisocial behavior and ADHD, controlling for other risks

Table 9.10S Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Knopik et al. 2005	• 1,936 female twin pairs from a longitudinal sample, identified through birth records and enrolled in adolescence, 11–19 years of age • ADHD diagnosis based on maternal report on symptoms and impairment • Prenatal smoking assessed retrospectively at assessment	OR of prenatal smoking NS at any dose for either first trimester or beyond first trimester Maternal smoking during pregnancy: • First trimester: OR = 0.97 (0.50–1.86) 10 cigarettes/day: OR = 1.05 (0.48–2.37) 11–19 cigarettes/day: OR = 0.42 (0.11–1.63) ≥20 cigarettes/day: OR = 1.40 (0.48–4.07) • Beyond first trimester: OR = 1.50 (0.86–2.63) 1–10 cigarettes/day: OR = 1.24 (0.61–2.52) 11–19 cigarettes/day: OR = 1.83 (0.89–3.76) ≥20 cigarettes/day: OR = 1.79 (0.79–4.07)	• Prenatal smoking did not increase risk for ADHD diagnosis, controlling for other risk factors
Linnet et al. 2005	• Nested case-control study • 170 children with hyperkinetic disorder • 3,765 population-based control subjects, matched by age, gender, and date of birth • Diagnosis from psychiatric medical records • Prenatal smoking assessed during pregnancy	Hyperkinetic disorder: RR = 1.9 (1.3–2.8) Excluding children of parents with psychiatric hospitalization: RR =2.2 (1.5–3.2)	• Controlling for other risk factors, prenatal smoking increased risk for hyperkinetic disorder
Rodriguez and Bohlin 2005	• 393 participants from sample recruited during pregnancy and followed up to 7 years of age • ADHD diagnosis based on mother and teacher report on symptoms and impairment • Prenatal smoking assessed during pregnancy	Number of symptoms Total: $r = 0.18$, $p < 0.001$ boys: $r = 0.21$, $p < 0.01$ girls: $r = 0.10$, NS Smoking during the first half of pregnancy: $\beta = 0.16$, $p < 0.01$ Smoking during the latter half: NS for unique contribution ADHD diagnosis: $\beta = 0.14$, NS	• Prenatal smoking was correlated with ADHD symptoms, but was not significantly associated with ADHD diagnosis after controlling for other risk
Knopik et al. 2006	• Case-control with or without alcohol abuse, children-of-twin design, adult female twin mothers with a child 13–24 years of age • Offspring ADHD diagnosis based on maternal report on symptoms and impairment • Prenatal smoking rate assessed retrospectively at assessment	ADHD for heaviest smoking: >15 cigarettes beyond first trimester, OR = 3.83 (1.09–13.45) Regular smoker not during pregnancy: OR = 0.72 (0.23–2.22) First trimester only: OR = 1.88 (0.45–7.81) Smoking beyond first trimester: 1–15 cigarettes, OR = 0.54 (0.16–1.83)	• Controlling for other risks, heavy smoking was independently associated with ADHD

Table 9.10*S* **Continued**

Study	Design/population	Estimate of effects (95% CI)	Findings
Mathews et al. 2006	• 3 cohorts of individuals with tic disorders (DSM-IV) • 180 individuals 3–59 years of age (72% under 18 years of age). • Rating scales of severity, self-report • Prenatal smoking reported retrospectively at assessment	Increase total tic severity: F = 9.27, p <0.00001 Increase phonic tic severity: F = 25.84, p <0.00001 Motor tic severity: NS	• In this sample with tic disorders, prenatal smoking was associated with tic severity • There was no significant association between exposure to prenatal tobacco and presence of comorbid ADHD, controlling for other risks
Monuteaux et al. 2006	• Community sample of 682 pregnant women followed longitudinally from prenatal life to 22 years of age • Mothers reported overt and covert symptoms of CD • Prenatal smoking rate assessed during pregnancy	Overt CD symptoms for low SES: No smoking vs. moderate smoking, RR = 2.1 (1.2–3.9) No smoking vs. heavy smoking, RR = 2.1 (1.1–4.0) Moderate smoking vs. heavy smoking, RR = 1.0 (0.6–1.6) Overt CD symptoms for high SES: No smoking vs. moderate smoking, RR = 0.7 (0.4–1.2) No smoking vs. heavy smoking, RR = 0.8 (0.5–1.3) Moderate smoking vs. heavy smoking, RR = 1.2 (0.6–2.3) Covert CD symptoms: No smoking vs. moderate smoking, RR = 1.1 (0.8–1.6) No smoking vs. heavy smoking, RR = 1.0 (0.8–1.2) Moderate smoking vs. heavy smoking, RR = 0.9 (0.7–1.0)	• Prenatal smoking was significantly associated with increased overt CD symptoms for participants of low SES, but not for participants of high SES, whereas covert CD symptoms were not associated with prenatal smoking, adjusted for other risks
Romano et al. 2006	• Nationally representative longitudinal survey • 2,946 children assessed at 0–2 years of age and followed to 7 years of age • Parent report on hyperactivity symptoms • Prenatal smoking reported retrospectively at first assessment	High and persistent hyperactive symptoms: OR = 2.75 (1.63–4.64)	• Prenatal smoking was significant predictor for high and persistent hyperactivity when controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Schmitz et al. 2006	• Case-control study • Nonreferred public school sample • 100 children with ADHD-I • 100 non-ADHD controls • 6–18 years of age, matched by gender and age • Clinical diagnosed of ADHD • Retrospective report of smoking at assessment time	ADHD-I diagnosis: ≥10 cigarettes vs. none, OR=3.44 (1.17–10.06) 1–9 cigarettes vs. none: OR = 1.09 (0.32–3.66)	• Prenatal smoking is associated with ADHD diagnosis, controlling for other risk factors
Wakschlag et al. 2006b	• Representative school based sample oversampled for delinquency risk • 448 boys • Parental report on ADHD and ODD symptoms • Prenatal smoking reported retrospectively at assessment	ODD: OR = 2.61 (1.14–5.97) ADHD + ODD: OR = 2.66 (0.99–7.16) ADHD alone: OR = 1.16 (0.69–1.94)	• Boys exposed to prenatal smoking were significantly more likely to develop ODD and comorbid ODD/ADHD but not ADHD alone
Wakschlag et al. 2006a	• 93 cases from a prenatal clinic sample oversampled for smoking followed to 24 months of age • Behavior problems assessed via maternal report and observation and combined into pervasiveness aggregate • Prenatal smoking assessed during pregnancy	Pervasiveness ($\chi 2 = 21.7$, $p < 0.000$) No problems for maternal report or observation: 25% of exposed vs. 70% of nonexposed Pervasive problems in both contexts: 30% of exposed vs. 2% of nonexposed toddlers	• Prenatal smoking is associated with increased problem behavior based on both maternal report and observational measures from 18–24 months
Whitaker et al. 2006	• Cohort study • Maternal report of behaviors (CBCL) at 3 years of age (n = 2,886) • Report at birth of smoking none, <1 pack, or at least 1 pack/day during pregnancy	Adjusted odds of behavior problems by smoking rate (nonsmoker as referent group) Aggressive: <1 pack/day, OR = 0.91 (0.64–1.30) ≥1 pack/day, OR = 1.40 (0.70–2.82 Anxious/depressed: <1 pack/day, OR = 0.75 (0.53–1.06) ≥1 pack/day, OR = 1.28 (0.65–2.54) Inattention/hyperactivity: <1 pack/day, OR = 0.92 (0.64–1.32) ≥1 pack/day, OR = 1.78 (0.90–3.49)	• After controlling for other risks, prenatal smoking was not associated with aggressive, anxious/depressed, or inattention/hyperactivity

Table 9.10*S* **Continued**

Study	Design/population	Estimate of effects (95% CI)	Findings
Cornelius et al. 2007	• Prospective longitudinal study • 357 teen mothers • Maternal report on child behavioral symptoms • Prenatal smoking assessed each trimester during pregnancy • 6-year follow up	CBCL total: t = 2.5, p <0.01 Externalizing: t = 2.5, p <0.01 Internalizing: t = 2.39, p <0.01 Attention: t = 2.01, p <0.025 Aggression: t = 2.58, p <0.01 Delinquency: t = 2.5, p <0.05 Routh activity: t = 2.63, p <0.01 SNAP impulsivity: t = 2.3, p <0.025 Peer problem: t = 1.68, p <0.05	• Prenatal smoking was significantly associated with activity, impulsivity, aggression, externalizing, and behavior problems, controlling for other risks
Whitaker et al. 2006	• Cohort study • Maternal report of behaviors (CBCL) at 3 years of age (n = 2,886) • Report at birth of smoking none, <1 pack, or at least 1 pack/day during pregnancy	Adjusted odds of behavior problems by smoking rate (nonsmoker as referent group) Aggressive: <1 pack/day, OR = 0.91 (0.64–1.30) ≥1 pack/day, OR = 1.40 (0.70–2.82 Anxious/depressed: <1 pack/day, OR = 0.75 (0.53–1.06) ≥1 pack/day, OR = 1.28 (0.65–2.54) Inattention/hyperactivity: <1 pack/day, OR = 0.92 (0.64–1.32) ≥1 pack/day, OR = 1.78 (0.90–3.49)	• After controlling for other risks, prenatal smoking was not associated with aggressive, anxious/depressed, or inattention/hyperactivity
Cornelius et al. 2007	• Prospective longitudinal study • 357 teen mothers • Maternal report on child behavioral symptoms • Prenatal smoking assessed each trimester during pregnancy • 6-year follow-up	CBCL total: t = 2.5, p <0.01 Externalizing: t = 2.5, p <0.01 Internalizing: t = 2.39, p <0.01 Attention: t = 2.01, p <0.025 Aggression: t = 2.58, p <0.01 Delinquency: t = 2.5, p <0.05 Routh activity: t = 2.63, p <0.01 SNAP impulsivity: t = 2.3, p <0.025 Peer problem: t = 1.68, p <0.05	• Prenatal smoking was significantly associated with activity, impulsivity, aggression, externalizing, and behavior problems, controlling for other risks

Table 9.10S Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Gatzke-Kopp and Beauchaine 2007	• 171 (136 male) children between 7–15 years of age referred for psychiatric concerns • Parental report on behavioral and psychiatric symptoms • Prenatal smoking for each trimester reported retrospectively at assessment	Nonsmoking vs. smoking m(SD): CSI conduct disorder: 4.98 (4.66), 9.05 (5.41), p = 0.006, d = 0.81 CSI ADHD: 29.51 (11.67), 38.24 (9.75) p = 0.005, d = 0.82 CBCL aggression: 71.34 (12.29), 77.14 (10.44), p = 0.024, d = 0.14 CSI depression: 6.77 (4.61), 9.29 (6.08), NS CSI dysthymia: 6.65 (3.86), 8.71 (5.18), NS CBCL anxious/depressed: 73.51 (11.64), 71.57 (14.66), NS CD symptoms: β = 0.24, p = 0.013 ADHD symptoms: β = 0.25, p = 0.007	• Prenatal smoking predicted conduct disorder and ADHD symptoms, after controlling for other risks
Huijbregts et al. 2007	• Population sample • 1,745 children born in Quebec • Parent report on behavioral symptoms • Prenatal smoking rate assessed retrospectively at 5 months	Physical aggression: $\chi 2$ (2) = 8.4, p = 0.015; high vs. no aggression, OR = 1.33 (1.10–1.61) Hyperactivity: $\chi 2$ (2) = 5.8, p = 0.121 Contrast between co-occurring PA+ADHD and PA only: OR = 1.39 (1.01–1.92)	• Prenatal smoking independently predicted co-occurring high PA and high hyperactivity-impulsivity compared to low levels of both behaviors, to high PA alone, and to high hyperactivity-impulsivity alone
Indredavik et al. 2007	• Prospective study of mothers enrolled before 20 weeks gestation • Behavior symptoms measured by youth and parent report • Prenatal smoking rates assessed during pregnancy • Follow-up assessment of offspring at 14 years of age (n = 84, 32 had mothers who had reported smoking during pregnancy)	ADHD symptoms (p = 0.04) Externalizing behaviors (p = 0.003) Internalizing behaviors (p = 0.04)	• Controlling for confounding factors, smoking during pregnancy was associated with higher levels of ADHD symptoms and both internalizing and externalizing behaviors in adolescent offspring
Langley et al. 2007	• Clinical sample of 356 children diagnosed with ADHD 6 and 16 years of age • Psychiatric symptoms assessed by parent interview and teacher report • Prenatal smoking reported retrospectively at assessment	Diagnosis of CD: OR = 3.14 (1.54–6.41) CD symptoms (r2 = 0.04, β = 0.18, t = 3.34, p = 0.001) ODD symptoms (r2 = 0.01 β = 0.12, t = 2.20, p = 0.03) Hyperactive-impulsive symptoms (r2 = 0.02, β = 0.11, t = 1.96, p = 0.05) Inattentive symptoms (r2 = <0.001, β = 0.02, t = 0.36, p = 0.72)	• Prenatal smoking was associated with CD symptoms and diagnosis, ODD symptoms, and with hyperactive-impulsive symptoms, but not inattentive symptoms
Lehn et al. 2007	• 95 twin pairs from longitudinal twin register study followed to 12 years of age • Maternal report on behavior symptoms • Prenatal smoking reported retrospectively	Prenatal smoking in twins with concordantly high attention problems (6/17, 35%) vs. concordant-low twins (6/59, 10%): $\chi 2(1) = 6.27$, p = 0.012	• Prenatal smoking was associated with the likelihood that both twins had high attention problems

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Neuman et al. 2007	• Birth-record sample • 564 male and female twin pairs and 183 randomly chosen controls, 7–19 years of age • Maternal report on behavioral symptoms • Prenatal smoking assessed retrospectively at assessment	ADHD diagnosis: Any ADHD: OR = 1.58 (1.03–2.43) Combined: OR = 1.91 (0.97–3.76) Inattentive: OR = 1.52 (0.89–2.58) ADHD symptom count: Combined: OR = 1.92 (1.04–3.57) Inattentive: OR = 1.40 (0.79–2.46) Few symptoms: OR = 0.65 (0.49–0.92)	• Prenatal smoking is associated with ADHD diagnosis, and with overall symptoms, but not with inattentive symptoms
Nigg and Breslau 2007	• Population-based longitudinal study of 823 children 6–17 years of age • Parent and teacher report for ADHD, parent and child self-report interview for ODD, and child self-report interview for CD • Prenatal smoking assessed retrospectively at assessment	ODD: OR = 2.07 (1.13–3.81) CD: OR = 2.25 (1.03–4.91) ADHD: OR = 1.27 (0.85–1.90)	• Prenatal smoking predicted CD and ODD, but not ADHD when controlling for other risks
Smidts and Oosterlaan 2007	• Community based sample • 652 preschoolers 3–6 years of age • Randomly selected schools and centers • Parent report on behavior problems • Retrospective report on smoking	Hyperactive symptoms: $\beta = 0.088$, $p = 0.028$ Impulsive symptoms: $\beta = 0.122$, $p = 0.001$ Inattention: NS	• Prenatal smoking predicted ADHD behaviors, specifically hyperactivity and impulsivity
Todd and Neuman 2007	• Birth record drawn sample of 1,441 complete • Male and female twin pairs and 6 individual twins 7–19 years of age • Parent report on ADHD symptoms • Prenatal smoking reported retrospectively at assessment	ADHD symptoms or diagnosis: NS Interaction with all the 3 gene polymorphisms: severe ADHD, OR = 14.9 (1.6–136.1) Combined type ADHD: NS	• Prenatal smoking interacted with genotype to increase risk for severe combined type ADHD, but was not independently associated with ADHD

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Altink et al. 2008	• 539 clinic-referred children with the combined subtype of ADHD and their 407 unaffected siblings, 6–17 years of age • Parent and teacher report of symptoms and clinical interview • Prenatal smoking rate reported retrospectively at assessment	ADHD diagnosis: $\chi 2 = 6.91$, p = 0.009 7-repeat allele by ADHD diagnosis: carriers ($\chi 2 = 5.8$, p = 0.015); non-carriers ($\chi 2 = 2.2$, p = 0.142) Behavioral symptoms: Teacher: Total: F = 9.58, p = 0.002 Hyperactive: F = 10.87, p = 0.001 Inattentive: F = 6.87, p = 0.009 Oppositional: F = 1.66, p = 0.20 Parent: Total: F = 0.09, p = 0.76 Hyperactive: F = 0.20, p = 0.66 Inattentive: F = 0.00, p = 0.95 Oppositional: F = 2.22, p = 0.14	• Affected children were more often exposed to prenatal smoking than unaffected children • There were limited main effects of prenatal smoking on severity of symptoms
Becker et al. 2008	• Prospective longitudinal study of 305 children from birth into early adulthood • Parent or teen report on ADHD, CD/ODD symptoms • Prenatal smoking assessed retrospectively at 3 months of age	Regression model of ADHD hyperactive-inattentive symptoms: Prenatal smoking: β = -0.647, p = 0.024 Prenatal smoking by *DAT1*+/+ genotype: β = 0.907, p=0.012 Inattentive: Prenatal smoking: β = -0.103, p = 0.724 Prenatal smoking by *DAT1*+/+ genotype: β = 0.11, p = 0.784 ODD/CD: Prenatal smoking: β = -0.426, p = 0.141 Prenatal smoking by *DAT1*+/+ genotype: β = 0.6, p = 0.1 Note: Data in text and table do not appear to match	• Prenatal smoking was associated with ADHD hyperactive-inattentive symptoms but not inattentive symptoms or ODD/CD
D'Onofrio et al. 2008	• Longitudinal follow-up study of nationally representative sample • 4,886 participants followed from youth through adulthood and their 8,889 children, 4–10 years of age • Maternal report on behavioral symptoms of ADHD and ODD • Prenatal smoking assessed during pregnancy	Offspring ADHD symptoms not significant when controlling for household. Note: text says there is residual effect but table does not show significance.	• When offspring were compared to their own siblings who differed in their exposure to prenatal nicotine, there was no effect of SDP on offspring ADHD CP and ODP

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Kukla et al. 2008	• Longitudinal follow-up of 1,460 cases from a birth cohort followed at 8, 11, and 13 years of age • Data collected from parents, physicians, teachers • Prenatal smoking reported retrospectively at assessment	Selected outcomes: Behavior problems in class: Age 11: 30.3% vs. non 14.8%, p <0.001 Age 13: 31.7% vs. 16.0%, p <0.001 Attention: Age 11: 43.8% vs. 31.2%, p <0.01 Age 13: 50.0% vs. 29.8%, p <0.001 Memory: Age 11: 37.8% vs. 21.9%, p <0.001 Age 13: 21.0% vs. 16.8%, NS	• Prenatal smoking was associated with a range of externalizing behavior items as well as learning and school difficulties
Robinson et al. 2008	• Prospective cohort study of 2,868 live-born children to 2,979 mothers recruited at 18-weeks gestation • Parent report on behavioral checklist (CBCL) at 2 and 5 years of age • Prenatal smoking measured as number of cigarettes smoked/day at 18 weeks gestation	2-year, total behavior: OR = 1.30 (1.06–1.59) 2-year, internalizing: OR = 1.26 (1.02–1.55) 2-year, externalizing: OR = 1.23 (1.02–1.49) 5-year, total behavior: OR = 1.19 (1.03–1.17) 5-year, internalizing: OR = 0.97 (0.83–1.14) 5-year, externalizing: OR = 1.34 (1.17–1.54)	• Increasing rates of cigarettes smoked/day during pregnancy was predictive of internalizing and externalizing behaviors in young offspring, after controlling for other risks
Altink et al. 2009	• 50 clinic-referred children with the combined subtype of ADHD • 23 siblings • 105 controls • Parent and teacher report of symptoms and clinical interview • Prenatal smoking rate reported retrospectively at assessment	ADHD status: OR = 3.29 (1.48–7.30) ADHD status mediated by attentional control: OR = 2.42 (1.04–5.61)	• Prenatal smoking was associated with ADHD while controlling for other risks
Biederman et al. 2009	• Longitudinal case-control family studies • 536 siblings of children with and without ADHD from 2 identically designed • Clinical diagnosis with parental report • Retrospective report on prenatal smoking frequency	ADHD: OR = 2.5 (1.39–4.51) CD significant in control families only: OR = 3.3 (1.23–8.88) Bipolar disorder: HR = 3.28 (1.60–6.71) (exploratory) Depression: HR = 0.90 (0.49–1.64) Anxiety: HR = 1.20 (0.73–1.97) Alcohol dependence: HR = 1.12 (0.63–2.01) Smoking dependence: HR = 1.49 (0.94–2.36) Illicit drug dependence: HR = 1.03 (0.47–2.27)	• Prenatal smoking is a risk for ADHD and CD, independently of each other • The risk for CD appears to be conditional on family risk status • There was also an increased risk for bipolar disorder after controlling for other risk factors; prenatal smoking not associated with depression, anxiety disorders, or drug dependence

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Buschgens et al. 2009	• Prospective population-based cohort study • 2,230 cases • Enrolled at 10–12 years of age • Maternal and teacher report on child behavior • Prenatal smoking rate assessed retrospectively at initial assessment	Inattention: (parent) β = 0.12; (teacher) β = 0.14 Hyperactive/impulsive: (teacher) β = 0.10 Aggression: (parent) β = 0.08; (teacher) β = 0.10 Delinquency: (parent) β = 0.11; (teacher) β = 0.07 Severe vs. no/some prenatal smoking: Hyperactive/impulsive: (teacher) β = 0.06 Aggression: (teacher) β = 0.07 Delinquency: (teacher) β = 0.10	• Prenatal smoking was associated with inattention, hyperactivity/impulsivity, aggression, and delinquency reported by parents and teachers
Froehlich et al. 2009	• Cross-sectional, nationally representative sample • 2,588 participants 8–15 years of age • ADHD diagnosis based on parental report of symptoms • Prenatal smoking reported retrospectively at assessment	ADHD diagnosis: OR = 2.4 (1.5–3.7) Prenatal smoking with third-tertile lead levels: OR = 8.1 (3.5–18.7)	• Prenatal smoking is associated with ADHD controlling for other factors • Children exposed to prenatal smoking and lead are at particular risk
Knopik et al. 2009	• Longitudinal female twin study • 2,892 adolescent twin pairs • Maternal report on inattentive, hyperactive/impulsive and conduct symptoms • Prenatal smoking reported retrospectively at assessment	Hyperactive/impulsive symptoms: First trimester: 1–10 cigarettes/day: β = 0.288, p <0.01 ≥11 cigarettes/day, β = 0.070, NS Beyond 1st trimester: 1–10 cigarettes/day, β = 0.199, p <0.01 ≥11 cigarettes/day, β = 0.134, p <0.05 Inattentive symptoms: First trimester: 1–10 cigarettes/day: β = 0.165, p <0.05 ≥11 cigarettes/day: β = 0.106, NS Beyond first trimester: 1–10 cigarettes/day: β = 0.214, p <0.01 ≥11 cigarettes/day: β = 0.082, NS Conduct problems: First trimester: 1–10 cigarettes/day: β = 0.140, p <0.01 ≥11 cigarettes/day: β = 0.097, NS Beyond first trimester: 1–10 cigarettes/day: β = 0.110, p <0.01 ≥11cigarettes/day: β = 0.059, NS	• Prenatal smoking of light to moderate frequency predicted risk for externalizing behavior • Heavy smoking only significant for hyperactivity/impulsivity beyond the first trimester

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Kollins et al. 2009	• 151 children between 5–12 years of age with ADHD and 97 siblings • ADHD diagnosis based on parent report and clinical diagnosis • Prenatal smoking reported retrospectively at assessment	Adjusted for maternal postnatal smoking: Parent: Oppositional problems(log): 4.16 vs. 4.23, NS Inattentive: 74.60 vs. 76.78, NS Hyperactive: 76.70 vs. 80.38, NS Teacher Oppositional problems: OR = 1.46 (0.25–8.43) Inattentive: 72.92 vs. 61.69, p <0.001 (negatively associated) Hyperactive (log): 4.19 vs. 4.18, NS Adjusted for paternal postnatal smoking: Parent: Oppositional problems(log): 4.10 vs. 4.31, p <0.01 Inattentive: 73.29 vs. 79.11, NS Hyperactive:75.10 vs. 84.06, NS Teacher: Oppositional problems: OR = 2.75 (0.60–12.65) Inattentive: 68.25 vs. 67.11, NS Hyperactive(log): 4.16 vs. 4.24, NS	• After accounting for other factors, including postnatal smoking by mothers and fathers, few relations between prenatal smoking and behavioral symptoms emerged and in opposite direction
Obel et al. 2009	• Population-based pregnancy cohorts followed up to 7–8 years of age • 20,936 women with singleton pregnancies • Parent and teacher report on behavioral symptoms • Prenatal smoking assessed during pregnancy	Parent ratings of hyperactive symptoms: Low to moderate (1–9 cigarettes): Site 1: OR = 1.3 (1.0–1.6) Site 2: OR = 1.0 (0.8–1.3) Heavy (≥10): Site 1: OR = 1.6 (1.3–1.9) Site 2: OR = 1.4 (1.1–1.8) Teacher ratings: Low to moderate: Site 2: OR = 1.3 (0.9–1.7) Site 3: OR = 1.5 (1.1–2.1) Heavy: Site 2: OR = 1.5 (1.2–2.0) Site 3: OR = 1.3 (0.8–2.2)	• Prenatal smoking was associated with hyperactivity-inattention, controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Pringsheim et al. 2009	• Nested case-control study of children 5–17 years of age • Tourette syndrome + ADHD cases (n=181) • Tourette syndrome, no ADHD controls (n = 172) • Diagnoses established via clinical diagnostic interview • Prenatal smoking reported retrospectively at assessment	Tourette syndrome + ADHD vs. Tourette syndrome/no ADHD: OR = 2.43 (1.23–4.82)	• Children with Tourette syndrome + ADHD were more likely to have been exposed to prenatal smoking compared to children with Tourette syndrome but no ADHD, controlling for other risks
Rodriguez et al. 2009	• Population-based pregnancy cohorts followed up to 7–8 years of age • 21,678 women with singleton pregnancies • Parent and teacher report on behavioral symptoms • Prenatal smoking reported during pregnancy	Behavior problems: Boys: Site 1: (parent) OR = 1.15 (0.90–1.47) Site 1: (teacher) OR = 1.40 (1.09–1.80) Site 2: (parent) OR = 1.48 (1.22–1.79) Site 3: (teacher) OR = 1.64 (1.33–2.02) Girls: Site 1: (parent) OR = 1.46 (1.05–2.02) Site 1: (teacher) OR = 1.52 (0.92–2.51) Site 2: (parent) OR = 1.84 (1.37–2.47) Site 3: (teacher) OR = 1.57 (1.04–2.38)	• Prenatal smoking was consistently associated with an increase in risk of child symptoms (inattention/hyperactivity) when controlling for other risks
Stene-Larsen et al. 2009	• Population-based prospective cohort study • Followed 22,545 mothers from pregnancy to 18 months • Maternal report on behavior symptoms; prenatal smoking rate assessed during pregnancy	Externalizing behavior: ≥10 cigarettes: OR = 1.32 (1.03–1.70) 1–9 cigarettes: OR = 1.12 (0.94–1.35)	• Higher levels of prenatal smoking were associated with subsequent externalizing behaviors among 18-month-old children, controlling for other risk • Lower levels of prenatal smoking were not predictive
Thapar et al. 2009	• 815 families of children 4–11 years of age conceived with assisted reproductive technologies recruited from 20 fertility clinics • Parental report on behavior symptoms • Prenatal smoking rates reported retrospectively at assessment	ADHD symptoms: Related pairs: $\beta = 0.102$, $p < 0.02$ Unrelated pairs: $\beta = -0.052$, $p > 0.10$	• Association between prenatal smoking and outcome is higher in related siblings, suggesting an inherited effect
Agrawal et al. 2010	• Telephone interview data on 1,342 unique pregnancies, offspring of male twins aged 12–32, from 2 studies • Assessment of ADHD and CD not defined • Prenatal smoking rate assessed retrospectively at initial assessment	No significant association with ADHD or CD	• Prenatal smoking and ADHD or CD not significantly associated once controlling for other risks

Table 9.10*S* **Continued**

Study	Design/population	Estimate of effects (95% CI)	Findings
Anselmi et al. 2010	• Birth cohort, hospital based sample • 4,423 children followed to 11 years of age • Parental report on behavior problems • Prenatal smoking assessed retrospectively at birth	Attention and hyperactivity problems at 11 years of age: PR = 1.28 (1.13–1.45)	• Prenatal smoking is associated with increased prevalence of attention and hyperactivity problems at 11 years of age
Ball et al. 2010	• 2,024 participants of pregnancy cohort study followed to adulthood • Child self-report on ADHD symptoms and diagnosis • Prenatal smoking assessed during pregnancy	ADHD diagnosis (comparison group = no smoking group): < half pack/day: OR = 1.2 (0.81–1.7) > half pack vs. < full pack/day: OR = 1.1 (0.75–1.6) > Full pack/day OR= 1.1 (0.57 – 1.8) Clinical characteristics (none vs. < half pack vs. > half pack) Severe ADHD impairment: $\chi 2(2) = 1.5$, p = 0.47 Any treatment: $\chi 2(2) = 0.76$, p = 0.68 Age of ADHD onset: F(2,105) = 1.4, p = 0.26 Duration: F(2,104) = 0.90, p = 0.41 Remission for ≥1 years: $\chi 2(1) = 0.07$, p = 0.80	• No association was found between prenatal smoking and offspring ADHD diagnosis or clinical features
Boden et al. 2010	• 926 members of a longitudinal birth cohort, followed up to 14–16 years of age • Parent report and child self-report on CD and ODD symptoms for diagnostic clinical interview • Prenatal smoking assessed retrospectively at birth	CD: β = 0.14 (SE = 0.04), p = 0.001 ODD: β = 0.09 (SE = 0.04), p = 0.008	• Prenatal smoking is significantly associated with conduct disorder and ODD at 14–16 years of age controlling for other risks
Bos-Veneman et al. 2010	• Clinic sample of 75 children 6–18 years of age with Tourette syndrome (62) or chronic motor (12) or vocal tic (1) disorder • 11 participants exposed to prenatal smoking • Parent report of symptom severity; prenatal smoking reported retrospectively (any vs. none)	Children with a tic disorder and a first-degree relative with a mental disorder: Prenatal smoking was associated with a higher hyperactive-impulsive score (17.2 vs. 10.3) , t = -4.07, p <0.01. Tic severity: NS	• In this sample of children with tic disorders, prenatal smoking exposure was associated with severity of ADHD symptoms, but not tic symptoms
Hay et al. 2010	• Longitudinal sample of 178 pregnant women from a representative urban population followed to 16 years of age • Parent report on antisocial (CD diagnosis and arrest) and violent (aggressive CD symptoms, arrests for violence) • Prenatal smoking rate assessed in pregnancy	Antisocial behavior or violent behavior: NS Cigarettes/day, m(SD): Antisocial = 6.0 (9.0) Not antisocial = 3.6 (6.0) Violent = 6.9 (7.7) Not violent =4.0 (7.1)	• Prenatal smoking did not predict antisocial or violent behavior outcomes for the children

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Hutchinson et al. 2010	• Prospective study of 13,000 children from a child benefit registry followed to 3 years of age (13,788 for conduct problems and 13,654 for hyperactivity) • Parental report on behavioral symptoms • Prenatal smoking rates assessed retrospectively at 9 months	Boys: Conduct problems: Quit smoking: OR = 1.21 (0.83–1.78) Light smoking: OR = 1.44 (1.01–2.06) Heavy smoking: OR = 1.80 (1.28–2.54) Hyperactivity: Quit smoking: OR = 0.94 (0.67–1.32) Light smoking: OR = 1.56 (1.12–2.15) Heavy smoking: OR = 1.62 (1.13–2.33) Girls: Conduct problems: Quit smoking: OR = 0.61 (0.39–0.97) Light smoking: OR = 1.06 (0.70–1.63) Heavy smoking: OR = 1.34 (0.88–2.03) Hyperactivity: Quit smoking: OR = 0.96 (0.66–1.41) Light smoking: OR = 1.28 (0.90–1.81) Heavy smoking: OR = 1.17 (0.79–1.72)	• Prenatal smoking was associated with increased conduct problems and attention problem for boys, quitting smoking was associated with decreased conduct problems for girls, controlling for other risks
Lindblad and Hjern 2010	• Register study of 927,007 cases from a nationwide medical registry • ADHD medication use retrieved from medical records • Prenatal smoking rate assessed during pregnancy	ADHD medication: OR = 2.86 (2.66–3.07) 2 pregnancies of the same mother analyzed in a within-subjects design: OR = 1.26 (0.95–1.58)	• Prenatal smoking has a strong association with ADHD medication use, but this risk is primarily explained by genetic and socioeconomic confounding
Motlagh et al. 2010	• Case control study • Cases recruited from clinics and controls from community • Diagnostic interview of 222 children (7–18 years of age): 45 Tourette syndrome, 52 ADHD, 60 Tourette syndrome + ADHD • 65 controls: N = 1 exposed; control, 3 exposed Tourette syndrome only; 7 Tourette syndrome + ADHD; 9 with ADHD/no Tourette syndrome; low participation rate • Retrospective report of heavy smoking (>10 cigarettes/day) during pregnancy	ADHD: OR = 13.5 (1.6–113.2) TS: OR = 4.6 (0.45–46.6) TS+ADHD: OR = 8.5 (0.97–75.2)	• After controlling for sex, there was an association between heavy prenatal smoking and ADHD, but no association between heavy prenatal smoking and Tourette syndrome in offspring

Table 9.10*S* **Continued**

Study	Design/population	Estimate of effects (95% CI)	Findings
Murray et al. 2010	• Prospective population survey • More than 16,000 children born in 1970, followed up to 34 years of age • Parent report on behavioral symptoms at 10 years of age, child self-report on criminal conviction at 30–34 years of age • Prenatal smoking assessed retrospectively shortly after birth	CP at age 10: Girls: OR = 1.8 (1.3–2.5) Boys: OR= 1.7 (1.4–2.2) Convictions at age 16–34: Girls: OR = 1.8 (1.2–2.7) Boys: OR = 1.4 (1.1–1.7)	• Prenatal smoking was predictive of conduct problems and criminal conviction, controlling for other risk
Nomuraet al. 2010	• Longitudinal study • 214 preschool children at risk for ADHD • Parent and teacher report on behavioral symptoms • Clinical interview for diagnoses • Prenatal smoking rate assessed retrospectively at 3–4 years of age	Behavioral symptoms: Inattention (χ2(3) = 8.03, p = 0.045) Hyperactivity (χ2(3) =10.49, p = 0.015) Total ADHD (χ2(3 = 9.28, p = 0.015 Diagnoses: ADHD: OR = 4.00 (1.36–11.12) ODD: OR = 3.37 (0.22–38.46) ADHD+ODD: OR = 5.05 (1.47–12.50)	• Prenatal smoking was significantly associated with elevated inattention, hyperactivity/impulsivity, and total ADHD symptoms, comorbid ADHD and ODD and ADHD, but not ODD, controlling for other risks
Wakschlag et al. 2010	• Follow-up of 176 children into adolescence, from a prospective pregnancy cohort study over-sampled for exposure to prenatal smoking • Parent and youth report on behavioral symptoms • Prenatal smoking assessed in pregnancy via maternal report and cotinine	Parent reported CD symptoms: Girls: β = 0.066 (0.034), p = 0.048 Boys: β = 0.213 (0.069), p = 0.004	• Boys exposed to prenatal smoking with the low-activity *MAOA5´uVNTR* genotype were at increased risk for CD symptoms • In contrast, exposed girls with the high-activity *MAOA5´uVNTR* genotype were at increased risk for CD symptoms
Xu et al. 2010	• Nationally representative sample of 5,305 of children 4–15 years of age • Parent report of ADHD diagnosis • Prenatal smoking reported retrospectively at assessment	ADHD: OR = 2.06 (1.40–3.03)	• Prenatal smoking was significantly associated with parent reported ADHD diagnosis
Brennan et al. 2011	• 430 adolescents, hospital birth cohort sampled to include mothers with and without depression, followed up to 15, 20–21 years of age • Parent and youth report on externalizing behavior • Prenatal smoking assessed during pregnancy	Aggressive behavior Age 15: β = 0.16, p <0.01 Age 20: β = 0.11, p <0.05. Not associated with attention problems	• Prenatal smoking was associated with aggressive behavior in adolescence and young adulthood, including genetic risk • Not significant for youth attention problems

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Gustafsson and Kallen 2011	• Case control sample • 237 children with ADHD and 31,775 without ADHD from a city wide birth register • Diagnoses from medical records; prenatal smoking assessed from medical records	ADHD diagnosis: OR = 1.35 (1.14–1.60)	• Prenatal smoking is predictive of a diagnosis of ADHD, controlling for other risks
Koshy et al. 2011	• Cross-sectional community study • 1,074 school children 5–11 years of age • Parent report of ADHD diagnosis • Prenatal smoking reported retrospectively at assessment	ADHD: Presence of smoking: OR = 3.19 (1.08–9.49) Heavy maternal smoker: OR = 10.03 (1.62–61.99)	• Prenatal smoking was associated with ADHD diagnosis, and there was a positive dose–response association of ADHD with the number of cigarettes smoked, while controlling for other risks
Lavigne et al. 2011	• Community sample • 678 preschool children (4 years of age) and their families • Diagnostic interviews, in-home visit using observation, interviews, and questionnaires conducted to assess symptoms of targeted conditions • Prenatal smoking reported retrospectively at assessment.	ADHD, ODD, anxiety, and depression measures: NS	• Prenatal smoking was not associated with symptoms of ADHD, ODD, anxiety, or depression among 4-year olds, controlling for other risks
Motlagh et al. 2011	• 81 clinic or CHADD referred children with ADHD, 8–18 years of age • Diagnoses established via clinical evaluation, parent and child interview, and rating scales • Retrospective report of heavy prenatal smoking at time of assessment	Exposed to heavy smoking: 12 out of 81 overall (15%) 9 out of 58 ADHD combined (16%, ns) 0 out of 3 ADHD hyperactive (0%, ns) 3 out of 20 ADHD inattentive (15%, ns) 4 out of 38 Tourette syndrome (11%, ns).	• Prenatal smoking was not associated with type of ADHD or Tourette syndrome comorbidity
Obel et al. 2011	• Population-based longitudinal birth cohort • Linked record set of 868,449 cases followed up to 5–19 years of age • Diagnoses from medical record set • Prenatal smoking recorded during pregnancy	Hyperkinetic disorder: Entire cohort: HR = 2.01 (1.90–2.12) Matched siblings: HR = 1.20 (0.97–1.49)	• Prenatal smoking and hyperkinetic disorder were not related when controlling for other risks using sibling-matched comparison
Palili et al. 2011	• Nationally representative longitudinal study • Following 2,695 children from birth to 7 and 18 years of age • Parent and teacher report on single item behavioral symptoms • Prenatal smoking assessed at birth	Prenatal smoking and outcome at age 7: Hyperactivity: OR = 3.24 (1.95–5.36) Inattention: OR = 1.68 (1.04–2.72) Impulsivity: OR = 1.89 (1.14–3.13) Age 18: Hyperactivity: OR = 8.78 (1.73–44.62) Inattention: OR = 4.19 (1.38–12.71) (impulsivity not analyzed due to now n)	• Prenatal smoking was predictive of ADHD-like symptoms at 7 and 18 years of age, controlling for psychosocial factors

Table 9.10*S* **Continued**

Study	Design/population	Estimate of effects (95% CI)	Findings
Bandiera et al. 2011	• Nationally representative cross-sectional survey • 2,901 children and adolescents 8–15 years of age • Parental report on ADHD diagnosis • Prenatal smoking reported retrospectively at assessment	ADHD: OR = 2.62 (1.58–4.33)	• Prenatal smoking during pregnancy was positively associated with a diagnosis of ADHD, controlling for other risks
Sciberras et al. 2011	• Longitudinal study • 3,474 participants assessed at 4–5 years of age and followed to 6–7 years of age • Parent report of ADHD and SDQ hyperactivity symptoms • Prenatal smoking rate assessed retrospectively at 4–5 years of age	ADHD: Prenatal smoking on most days: OR = 3.31 (1.49–7.39) Occasional prenatal smoking: OR = 0.62 (0.17–.26) Hyperactive/inattentive symptoms: Prenatal smoking most days: OR = 1.86 (1.31–2.66) Occasionally prenatal smoking: OR = 1.26 (0.87–1.83)	• Prenatal smoking on most days was significantly predictive of parent reported ADHD diagnosis and symptoms, controlling for other risks; occasional smoking was not significant
St Pourcain et al. 2011	• Longitudinal birth cohort study • 5,383 singletons followed up from pregnancy to 18 years of age • Maternal report on behavior symptoms. Prenatal smoking assessed at 18 weeks of pregnancy.	Persistently impaired symptoms: OR = 1.95 (1.34–2.85) Intermediate symptoms: OR = 1.31 (0.94–1.83) Childhood limited symptoms: OR = 1.33 (0.91–1.96)	• Prenatal smoking during the first trimester was significantly associated with hyperactive-inattentive traits, specifically trajectories of persistent impairment, controlling for other risks
Wakschlag et al. 2011	• Follow-up of 211 children into adolescence, from a prospective pregnancy cohort study over-sampled for exposure to prenatal smoking • Parent report on composite symptoms for aggression, non-compliance, temper loss, low concern • Prenatal smoking assessed in pregnancy	Noncompliance ($\beta = 0.003$, $p < 0.01$) Aggression ($\beta = 0.002$, $p < 0.05$) Temper loss ($\beta = -0.001$, NS) Low concern ($\beta = 0.000$, NS) Paternal responsive engagement × exposure with disruptive behavior ($\beta = -0.004$, $p < 0.01$)	• Prenatal smoking uniquely predicted aggression and noncompliance, controlling for other risks • Paternal responsive engagement moderated exposure effects • Low concern and loss of temper were not significant
Biederman et al. 2012	• Case-control • 262 ADHD cases only 6–17 years of age • Parental report on psychiatric symptoms, also child report for children over 12 years of age • Heavy prenatal smoking assessed retrospectively	Lifetime prevalence of ADHD symptoms, ADHD subtype, age of ADHD onset, and persistent ADHD: NS ADHD subtype: Inattentive: OR = 1.3, p = 0.50 Hyperactive-impulsive: OR = 1.0, p = 0.98 Age of ADHD onset: $\beta = 0.1$, $p = 0.29$ ADHD impairment: OR = 1, p = 0.89 ADHD persistence: OR = 1, p = 0.98 Lifetime history of medication for ADHD: χ 2 (1) = 0.0009, p = 0.98	• No significant differences were found between persistent prenatal smoking and offspring ADHD diagnosis or clinical features, controlling for other risks

Table 9.10*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Ellis et al. 2012	• Birth cohort sample • 995 children 4 years of age 4 (citywide community stratified by SDQ scores) • Diagnoses established via parent interview • Prenatal smoking reported retrospectively at assessment	ADHD: OR = 2.59 (1.5–4.34) ODD: OR = 2.69 (1.84–3.91) Comorbid ADHD/ODD: OR = 2.68 (1.84–3.91)	• Prenatal smoking was found to increase the odds for ADHD, ODD, and comorbid ADHD/ODD, controlling for other risk factors
Freitag et al. 2012	• 275 clinic-referred children with ADHD, aged 5–13 years • Diagnoses via structured child interview and parent and teacher report • Prenatal smoking reported retrospectively at assessment	CD: β = 0.84 (0.10–1.58), p = 0.027 Hyperactive/impulsive: β = 1.82 (0.05–3.59), p = 0.044 Inattentive symptoms: β = 0.83 (-0.40–2.81), p = 0.176 Comorbid anxiety: β = 0.25 (-0.33–0.84) p = 0.396 ODD: β = 0.46 (-0.16–1.07), p = 0.149	• Among youth with ADHD, prenatal smoking was only associated with co-occurring conduct disorder, but not with hyperactive-impulsive symptoms, inattentive symptoms, ODD or anxiety
Langley et al. 2012	• 8,324 children from a prospective cohort study followed to 7 years of age • Parent and teacher report on ADHD symptoms • Prenatal smoking assessed during pregnancy	ADHD symptoms: β = 0.19 (0.12–0.27) p <0.001	• Prenatal smoking is associated with ADHD, controlling for other risk factors
Sagiv et al. 2013	• Population-based sample • 604 children followed from birth to 8 years of age • Parent and teacher report on behavior problems. • Pediatric medical record of ADHD diagnosis and medication use • Prenatal smoking rate assessed retrospectively at 2 weeks	CRS t-score difference: 1–10 cigarettes: 1.5 >10 cigarettes: 2.3; p for trend = 0.02 ADHD diagnosis in pediatric record: 1–10 cigarettes: RR = 0.9 (0.4–1.8) >10 cigarettes: RR = 1.6 (0.8–3.2) ADHD diagnosis based on parent record: 1–10 cigarettes: RR = 0.6 (0.2–1.6) >10 cigarettes: RR = 2.0 (0.7–5.5)	• Prenatal smoking was associated with behavior ratings but not significantly associated with ADHD diagnosis or medication use when controlling for other risks
Wilson et al. 2013	• Nationally representative sample • 2,070 children from a nested case-control study, follow up at 3, 4, and 5 years of age • Parent report of behavioral symptoms • Prenatal smoking reported retrospectively at assessment	Inconsistent CP vs. never: OR = 1.52 (1.08–2.15) Persistent CP vs. never: OR = 5.02 (2.6–9.71)	• Prenatal smoking is associated with conduct problems, controlling for other risks

Note: **ADHD** = Attention deficit hyperactivity disorder; **CBCL** = child behavior checklist; **CD** = conduct disorder; **CHADD** = children and adults had attention deficit disorder; **CI** = confidence interval; **CSI** child symptom inventory; **DSM** = *Diagnostic and Statistical Manual of Mental Disorders;* **HR** = hazard ratio; **m(SD)** = mean (standard deviation); **NS** = not shown; **ODD** = oppositional defiant disorder; **ODP** = offspring of diabetic parents; **OR** = odds ratio; **PA** = physical aggression; **RCT** = randomized clinical trials; **RR** = relative risk; **SDP** = smoking during pregnancy; **SES** = socioeconomic status; **SNAP** = Swanson, Nolan and Pelham rating scale.

Table 9.11*S* Studies on associations between prenatal smoking and anxiety and depression in children, 2000–2012

Study	Design/population	Estimate of effects (95% CI)	Findings
Hill et al. 2000	• 150 children 8–18 years of age at high or low familial risk for alcoholism • Diagnostic interview for conditions • Prenatal smoking rate reported retrospectively at assessment	• Depression: NS • Conduct: NS • Oppositional: NS • Anxiety: NS • Phobia: NS • ADHD: NS • Adjusted OR: not reported	• Prenatal smoking associated with depression, conduct disorder, and oppositional disorder, but not ADHD, anxiety or phobia • These findings were no longer significant after controlling for other risk factors
Maughan et al. 2001	• Prospective birth cohort study of all children born in the first week of April 1970 • Parental report on hyperactivity, conduct problems, adolescent self-report on conduct problems and depressive symptoms • Prenatal smoking rate assessed retrospectively at birth • England, Scotland, Wales • Followed up at 5, 10, and 16 years of age	• Conduct problems AOR (value not reported), p = 0.238	• Prenatal smoking not associated with hyperactivity, conduct problems, or depressive symptoms after controlling for postnatal smoking
Kardia et al. 2003	• 257 daily smokers from community • 207 with data on maternal smoking during pregnancy (not stated how defined/collected)	• Depression: CES-D (mean±SD): – Never smoker: 11.0 ± 9.1 – Ever smoker, not during pregnancy: 11.7 ± 7.5 – Ever smoker, during pregnancy: 13.8 ± 9.3, NS • Anxiety: STAI-Trait (mean±SD): – Never smoker: 37.3 ± 9.4 – Ever smoker, not during pregnancy: 39.7 ± 10.7 – Ever smoker, during pregnancy: 40.2 ± 8.8, NS	• Maternal smoking during pregnancy not associated with symptoms of depression or anxiety among current smokers
Teramoto et al. 2005	• Cohort study • 670 Japanese children 3 years of age • Maternal report of behaviors (CBCL) • Retrospective report of smoking during pregnancy, by dose	• Internalizing problems: OR = 1.28 (1.05–1.55) Total and externalizing problems: NS	• After controlling for other risks, smoking during pregnancy increased internalizing problems in 3-year-old children, but was not associated with total or externalizing behavioral problems
Mathews et al. 2006	• 3 cohorts of individuals with tic disorders (*DSM-IV*) • 180 individuals 3–59 years of age (72% under 18 years of age) • Rating scales of severity, self-report • Prenatal smoking reported retrospectively at assessment	• Increase total tic severity: F = 9.27, p <0.00001 Increase phonic tic severity: F = 25.84, p <0.00001 Motor tic severity: NS	• In this sample with tic disorders, prenatal smoking was associated with tic severity; there was no significant association between exposure to prenatal tobacco and presence of comorbid ADHD, controlling for other risks

Table 9.11*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Whitaker et al. 2006	• Cohort study • Maternal report of behaviors (CBCL) at 3 years of age (n = 2,886) • Report at birth of smoking none, <1 pack, or at least 1 pack/day during pregnancy	• Adjusted odds of behavior problems by smoking rate (nonsmoker as referent group) • Aggressive: – <1 pack/day: OR = 0.91 (0.64–1.30) – ≥1 pack/day: OR = 1.40 (0.70–2.82 • Anxious/depressed: – <1 pack/day: OR = 0.75 (0.53–1.06) – ≥1 pack/day: OR = 1.28 (0.65–2.54) • Inattention/hyperactivity: – <1 pack/day: OR = 0.92 (0.64–1.32) – ≥1 pack/day: OR = 1.78 (0.90–3.49)	• After controlling for other risks, prenatal smoking was not associated with aggressive, anxious/depressed, or inattention/hyperactivity
Indredavik et al. 2007	• Prospective study • Mothers enrolled before 20 weeks gestation • Behavior symptoms measured by youth and parent report • Prenatal smoking rates assessed during pregnancy • Follow-up assessment of offspring at 14 years of age (n = 84, 32 had mothers who had reported smoking during pregnancy)	• ADHD symptoms (p = 0.04) – Externalizing behaviors (p = 0.003) – Internalizing behaviors (p = 0.04)	• Controlling for confounding factors, smoking during pregnancy was associated with higher levels of ADHD symptoms and both internalizing and externalizing behaviors in adolescent offspring
Gatzke-Kopp and Beauchaine 2007	• 171 (136 male) children between 7–15 years of age referred for psychiatric concerns • Parental report on behavioral and psychiatric symptoms • Prenatal smoking for each trimester reported retrospectively at assessment	• Nonsmoking vs. smoking m(SD) • CSI – conduct disorder: 4.98 (4.66), 9.05 (5.41), p = 0.006, d = 0.81 – ADHD: 29.51 (11.67), 38.24 (9.75), p = 0.005, d = 0.82 – depression: 6.77 (4.61), 9.29 (6.08), NS – dysthymia: 6.65 (3.86), 8.71 (5.18), NS • CBCL – aggression: 71.34 (12.29), 77.14 (10.44), p = 0.024, d = 0.14. – anxious/depressed: 73.51 (11.64), 71.57 (14.66), NS • CD symptoms: β = 0.24, p = 0.013 • ADHD symptoms: β = 0.25, p = 0.007	• Prenatal smoking predicted conduct disorder and ADHD symptoms, after controlling for other risks
Robinson et al. 2008	• Prospective cohort study • 2,868 live-born children to 2,979 mothers recruited at 18-weeks gestation • Parent report on behavioral checklist (CBCL) at 2 and 5 years of age • Prenatal smoking measured as number of cigarettes smoked/day at 18 weeks gestation	• 2-year, total behavior: OR = 1.30 (1.06–1.59) • 2-year, internalizing: OR = 1.26 (1.02–1.55) • 2-year, externalizing: OR = 1.23 (1.02–1.49) • 5-year, total behavior: OR = 1.19 (1.03–1.17) • 5-year, internalizing: OR = 0.97 (0.83–1.14) • 5-year, externalizing: OR = 1.34 (1.17–1.54)	• Increasing rates of cigarettes smoked/day during pregnancy was predictive of internalizing and externalizing behaviors in young offspring, after controlling for other risks

Table 9.11*S* **Continued**

Study	Design/population	Estimate of effects (95% CI)	Findings
Biederman et al. 2009	• 2 identically designed, longitudinal case-control family studies • 536 siblings of children with and without ADHD from • Clinical diagnosis with parental report • Retrospective report on prenatal smoking frequency	• ADHD: OR = 2.5 (1.39–4.51) • CD significant in control families only: OR = 3.3 (1.23 –8.88) • Bipolar disorder: HR = 3.28 (1.60 – 6.71) (exploratory) • Depression: HR = 0.90 (0.49–1.64) • Anxiety: HR = 1.20 (0.73–1.97) • Alcohol dependence: HR = 1.12 (0.63–2.01) • Smoking dependence: HR = 1.49 (0.94–2.36) • Illicit drug dependence: HR = 1.03 (0.47–2.27)	• Prenatal smoking is a risk for ADHD and CD, independently of each other • The risk for CD appears to be conditional on family risk status • Increased risk for bipolar disorder after controlling for other risk factors. • Prenatal smoking not associated with depression, anxiety disorders, or drug dependence
Liu et al. 2011	• Collaborative Perinatal Project • 611 adult offspring (38–48 years of age) of mothers enrolled in the cohort study • Self report on symptom scales • Prospective report of smoking.	• Anger temperament: T score 7.4 higher, β = 7.4 (0.5–14.4) • Depression: β = -0.2 (-1.3–0.9), NS • Anxiety: β = -0.5 (-2.7–1.8), NS	• Maternal smoking during pregnancy was not associated with symptoms of depression or anxiety in adulthood, but was associated with anger temperament, after controlling for other risks
Lavigne et al. 2011	• Community sample • 678 preschool children (4 years of age) and their families • Diagnostic interviews, in-home visit using observation, interviews, and questionnaires conducted to assess symptoms of targeted conditions • Prenatal smoking reported retrospectively at assessment	• ADHD, ODD, anxiety, and depression measures: NS	• Prenatal smoking was not associated with symptoms of ADHD, ODD, anxiety, or depression among 4-year olds, controlling for other risks
Freitag et al. 2012	• 275 clinic-referred children with ADHD, 5–13 years of age • Diagnoses via structured child interview and parent and teacher report • Prenatal smoking reported retrospectively at assessment	• CD: β = 0.84 (0.10–1.58), p = 0.027 • Hyperactive/impulsive: β = 1.82 (0.05–3.59) p = 0.044 • Inattentive symptoms: β = 0.83 (-0.40–2.81), p = 0.176 • Comorbid anxiety: β = 0.25 (-0.33–0.84), p = 0.396 • ODD: β = 0.46 (-0.16–1.07), p = 0.149	• Among youth with ADHD, prenatal smoking was only associated with co-occurring conduct disorder, but not with hyperactive-impulsive symptoms, inattentive symptoms, ODD or anxiety

Note: **ADHD** = attention deficit hyperactivity disorder; **AOR** = adjusted odds ratio; **CBCL** = child behavior checklist; **CD** = conduct disorder; **CES** = Center for Epidemiologic Studies for Depression; **CI** = confidence interval; **CSI** = Children's Somatization Inventory; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorder-IV*; **HR** = hazard ratio; **NS** = not shown; **ODD** = oppositional defiant disorder; **OR** = odds ratio; **SD** = standard deviation; **STAI-Trait** = State Trait Anxiety Inventory-Triat.

Table 9.12*S* Studies on associations between prenatal smoking and Tourette syndrome in children, 2000–2011

Study	Design/population	Estimate of effects (95% CI)	Findings
Motlagh et al. 2010	• Case control study • Cases recruited from clinics and controls from community; diagnostic interview • 222 children (7–18 years of age): 45 Tourette syndrome, 52 ADHD, 60 Tourette syndrome + ADHD, 65 control • N = 1 exposed; control, 3 exposed Tourette syndrome only, 7 Tourette syndrome+ADHD, 9 with ADHD/no Tourete syndrome • Low participation rate • Retrospective report of heavy smoking (>10 cigarettes/day) during pregnancy • United States	• ADHD: OR = 13.5 (1.6–113.2) • ADHD: OR = 13.5 (1.6–113.2) • Tourette syndrome: OR = 4.6 (0.45–46.6) • Tourette syndrome + ADHD: OR = 8.5 (0.97–75.2)	• After controlling for sex, there was an association between heavy prenatal smoking and ADHD, but no association between heavy prenatal smoking and Tourette syndrome in offspring
Motlagh et al. 2011	• 81 clinic or CHADD referred children with ADHD, 8–8 years of age • Diagnoses established via clinical evaluation, parent and child interview, and rating scalesRetrospective report of heavy prenatal smoking at time of assessment	• Exposed to heavy smoking: – 12 out of 81 overall (15%) – 9 out of 58 ADHD combined (16%, ns) – 0 out of 3 ADHD hyperactive (0%, ns) – 3 out of 20 ADHD inattentive (15%, ns) – 4 out of 38 Tourette syndrome (11%, ns)	• Prenatal smoking not associated with type of ADHD or Tourette syndrome comorbidity

Note: **ADHD** = attention deficit hyperactivity disorder; **CHADD** = children and adults with attention deficit/hyperactivity disorder; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorder*; **NS** = not shown; **OR** = odds ratio.

Table 9.13*S* Studies on associations between prenatal smoking and intellectual disability in children, 2000–2009

Study	Design/population	Estimate of effects (95% CI)	Findings
Fried et al. 2000	• Ottawa Prenatal Prospective Study • 146 children 9–12 years of age • 44% female • 58% exposed to tobacco smoke • Canada	• Exposure associated with poorer scores on intelligence ($\beta = -0.10$, $p < .05$)	• Maternal cigarette smoking during pregnancy appears to have an impact on the fundamental aspects of visuoperceptual and cognitive functioning
Cornelius et al. 2001	• Maternal Health and Child Development Project • 593 children and adolescents 9–14 years of age • 50% female • 52% exposed to tobacco smoke • United States	• Reduced performance on verbal learning ($\beta = -0.04$, $p < .01$) • Assessment of cognitive efficiency errors ($\beta = 0.03$, $p < .025$)	• Observed significantly lower scores on standardized IQ tests among children and adolescents of mothers who smoked during pregnancy compared to offspring of mothers who did not smoke was accounted for entirely by maternal IQ • Smoking during pregnancy is unlikely to be a causal factor in children's IQ
Fried et al. 2003	• Ottawa Prenatal Prospective Study • 145 adolescents 13–16 years of age • 46% female • 56% exposed to tobacco smoke • Canada	• Heavy exposure associated with reduced overall intelligence ($\beta = -11.8$, $p \leq .001$)	• Association between maternal cigarette exposure during pregnancy and intelligence scores remained after adjusting for maternal education at birth
Breslau et al. 2005	• Randomly selected from lists of newborns from 2 hospitals • 713 children, adolescents, and young adults 6, 11, 17 years of age • 51.4% female • 31% exposed to tobacco smoke • United States	• ($\beta = -3.52$, $p \leq .005$) but attenuated after adjustment for mother's cognitive performance ($\beta = 0.04$, $p > .05$)	• Controlling for maternal education and IQ, eliminated association between maternal smoking during pregnancy and offspring IQ • Maternal smoking has no direct causal effect on child's IQ
Motensen et al. 2005	• Copenhagen Perinatal Cohort • 1,829 adolescent and young adults 16–26 years of age • 0% female • 50% exposed to tobacco smoke • Denmark	• Heavy exposure associated with an increased risk: OR = 3.4 (1.60–7.00) after controlling for parental social status, education, maternal age, maternal height, gestational age, birth weight.	• Maternal cigarette smoking during the third trimester, showed significant negative associations with young adult intelligence
Batty et al. 2006	• National Longitudinal Survey of Youth • 5,578 young people between 5–14 years of age on January 1, 1979 • % female not given • United States	• Light exposure associated with a 1.73-point decrement and heavy exposure associated with a 2.87-point decrement compared to no exposure (trend $p \leq .0001$); ≤0.3-point decrement when adjusted for mother's education (trend $p > .05$)	• Controlling for maternal education and maternal IQ eliminated the association between maternal smoking and reduced offspring IQ and cognitive ability

Table 9.13*S* Continued

Study	Design/population	Estimate of effects (95% CI)	Findings
Huijbregts et al. 2006	• Québec Longitudinal Study of Children's Development • 1,544 children 3.5 years of age • 27% exposed to tobacco smoke • Canada	• Exposure associated with reduced intelligence (β = –.126, p <.001); after adjustment for additional covariates (β = –.006, p = .805)	• Prenatal smoking was related to performance on the WPPSI-R, the PPVT, and the VCR, although it did not independently predict any cognitive ability after maternal education was taken into account
Lambe et al. 2006	• Population-based registers • 375,942 adolescents 15 years of age • 49% female • 30% exposed to tobacco smoke in utero • Sweden	• Heavy exposure associated with increased risk of poor school performance: OR = 1.92 (1.86–1.98)	• Observed associations between maternal smoking during pregnancy and poor cognitive performance in the offspring might not be causal
Alati et al. 2008	• Avon Longitudinal Study of Parents and Children • 14, 541 singleton babies still alive at 1 year of age • Data collected from mothers and partners at approximately 8- and 18-week gestation (for the assessment of maternal and paternal alcohol and smoking) and from the assessment conducted as part of (clinic assessments) the children at 8 years of age	• Exposure not associated with increased risk: OR = 0.93 (0.75–1.16) after adjustment for sex, social class, parity, ethnicity, house ownership, crowding, maternal education, maternal smoking	• No strong statistical evidence that maternal alcohol and tobacco consumption during pregnancy were associated with childhood IQ with any greater magnitude than paternal alcohol and tobacco consumption
Braun et al. 2009	• Autism and Developmental Disabilities Monitoring Network Surveillance Project • 105,572 children 8 years of age • 49% female • 11% exposed to tobacco smoke • United States	• Exposure not associated with increased risk: RR = 1.34 (0.96–1.87) after adjustment for maternal age, maternal race, maternal education, marital status, child sex	• The risk of ID was mildly elevated among children whose mothers smoked ≥20 cigarettes/day during pregnancy but the risk was attenuated after adjustment for maternal factors
Kafouri et al. 2009	• Saguenay Youth Study • 503 adolescent and young adults 12–18 years of age • 52% female • 47% exposed to tobacco smoke • Canada-French speakers	• Exposure not associated with any cognitive measures with or without adjustment (full scale IQ: mean difference = 0.0, p = .99)	• No effect of maternal cigarette smoking during pregnancy on cognitive abilities of the adolescent offspring, after adjusting for maternal education (the most common confounder of maternal cigarette smoking during pregnancy)
Lundberg et al. 2009	• Population-based registers • 161,048 adolescents 15 years of age • 49% female • 30% exposed to tobacco smoke in utero • Sweden	• Heavy exposure of ≥10 cigarettes/day associated with increased risk of OR = 1.22 (1.14–1.31) after adjustment for parental factors	• Exposure associated with increased risk of intellectual impairment compared to no exposure

Note: **CI** = confidence interval; **ID** = intellectual disability; **IQ** = intelligence quotient; **OR** = odds ratio; **PPVT** = Peabody Picture Vocabulary Test; **RR** = relative risk; **VCR** = visually cued recall; **WPPSI-R** = Wechsler Preschool and Primary Scale of Intelligence-Revised.

Table 9.14*S* Association between maternal smoking and ectopic pregnancy, studies included in 2001–2010 Surgeon General's reports and subsequently published through March 2013

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
WHO 1985	• Case-control study • 1,108 cases ectopic pregnancy (histologically confirmed, presenting to OB-GYN wards) • First subjects who met matching criteria and were admitted within 6 months of case presentation (matched to cases on age, parity, marital status) • 1,108 pregnant and 1,108 nonpregnant women • Nonpregnant women first eligible subjects admitted within 6 months of each case who presented for nongynecological related surgery (trauma, acute medical condition, elective surgery) • Study period: 1978–1980 • 12 centers (8 in developing countries and 4 developed countries)	Source: interview Current smoking = smoking at the time of conception [cases and pregnant controls] or at the time of interview [non-pregnant controls]	RR Pregnant controls: 3.1 (2.3-4.2) Non-pregnant controls: 1.8 (1.3-2.4)	• RRs calculated using referent group of women not using contraception, and with no history of PID, STI, or prior ectopic pregnancy • Adjustment for past PID or STI, ectopic pregnancy, and IUD use did not change RR estimates • Developing countries, pregnant controls (RR = 3.9, 95% CI, 2.7–5.9) and non-pregnant controls (RR = 2.4, 95% CI, 1.7–3.5) • Developed countries, pregnant controls (RR = 2.0, 95% CI, 1.2 -2.4) and nonpregnant controls (RR = 1.0, 95% CI, 0.6-1.8) • Did not collect data on sexual practices (too sensitive)
Handler et al. 1989	• Case-control study using medical record abstraction • 634 cases, women with ectopic pregnancy • 4,287 controls, women who delivered a singleton, live-born infant. • Excluded from cases and controls women with prior ectopic pregnancy • Excluded from controls women with history of spontaneous abortion or fetal deaths • Study period: 1983–1987 • University of Illinois Perinatal Network, 12 hospitals	Source: medical records Current smoking: smoking during pregnancy as recorded in medical record (ascertainment similar for cases and controls)	AOR* Overall: 2.5 (1.9-3.2) By cigarettes/day <10: 1.4 (.8-2.5) 10–19: 2.3 (1.5-3.4) 20–29: 3.2 (2.3-4.7) ≥ 30: 5.0 (2.9-8.7) Smoking as a continuous variable showed evidence of a dose-response relationship (regression coefficient = 0.049, S.E.=0.006)	• Results adjusted for maternal age and race • Adjustment for gravidity, parity, and prior abortion did not change findings (range of estimates 2.2–2.4) • Among women with a prior spontaneous abortion OR= 1.6, 95% CI, 1.1–2.3 • Among women with no prior spontaneous abortion OR=2.5, 95% CI, 2.1–3.1, AOR=2.5, 95% CI, 1.9–3.2 • Did not collect data on past or present PID, contraceptive use, or history of delayed fertility • Had no information on smoking at conception or duration of smoking

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Coste et al. 1991	• Case-control study • 7 Paris maternity hospitals • 279 cases women with ectopic pregnancy confirmed by celioscopy or laparotomy • 279 control women who delivered in the same center, immediately following the operation of index case • Study period: 1988 • France	Source: Interview Current smoking: smoking at the time of conception	COR Overall: 1.6 (1.1-2.3) Cigs/day 1-10: 1.2 (0.8-2.0) 11-20: 1.4 (1.2-3.1) >20: 1.6 (0.9-6.6) AOR* Cigs/day 1-10: 1.3 11-20: 2.0 >20: 2.5 (CIs not shown)	• Adjusted for hospital, age, prior appendectomy, prior ectopic pregnancy, prior tubal surgery, prior spontaneous abortion, previous use of IUD, history of PID, induced conception, type of contraception at conception • Restriction of analysis to married women not using contraception at conception did not change findings
Kalandidi et al. 1991	• Case-control study • Maternity hospital and outpatient clinics • 63 cases, women with ectopic pregnancy admitted to hospital • 133 controls, women visiting outpatient clinic of the same hospital, matched for age, education, residence, hospital, date of interview, socioeconomic status and parity, and stage of pregnancy • Study period: 1986–1987 • Athens, Greece	Source: interview Current smoking: not clearly defined	ARR* 2.35 (1.19-4.67)	• Adjusted for being married, ever users of IUDs, and any induced abortions
Stergachis et al. 1991	• Group Health Cooperative HMO case-control study • 274 cases (women diagnosed with tubal ectopic pregnancy, hospitalized in participating hospitals • 727 control (women of childbearing age selected randomly from HMO's membership files, then matched by age and county of residence) • Reference date assigned to each control, excluded women >4 months pregnant at the reference date • Study period: 1981–1986 • Washington	Source: interview Current smoking: at the time of conception (if pregnant) or the corresponding reference frame (non-pregnant controls)	AOR* Overall: (1.0-2.0) Cigarettes/day <10: 1.8 (1.0-3.2) 10-19: 1.6 (0.8-2.4) ≥ 20: 1.2 (0.8-1.8) Test for linear trend not significant	• Adjusted for age, reference date, county of residence, gravidity, and lifetime number of sex partners • Assessed confounding of additional variables: race, education, income, history of gonorrhea, history of IUD use, age at first intercourse, douching history, use of contraception at the reference date, type of contraception used at the reference date) • These did not alter odds ratios and were not included in final models

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Parrazzini et al. 1992	• Case-control study • Maternity hospital and obstetric and gynecology clinic • 120 cases, women diagnosed with ectopic pregnancy, confirmed by laparoscopy or laparotomy admitted to 2 sites • 209 controls, women who gave birth to healthy term (>37 weeks gestation) infants randomly selected days at the hospital where the cases had been identified, within 1 month of case ascertainment and with comparable age distributions between cases and controls. • Study period: 1989–1991 • Milan, Italy	Source: interview Current smoking: smoking in the preconception period	ARR* cigarettes/day: ≤ 10: 1.1 (0.5–2.3) >10: 1.9 (.1.1–3.5) ARR** cigarettes/day: ≤ 10: 0.8 (.4-1.6) >10: 1.1 (.6–2.6)	• Adjusted for age • Reference group is never smoked • Adjusted for age, education, infertility, abdominal surgery, PID/salpingitis, age at first intercourse, number of sexual partners • Test for trend was not significant • Retrospective recall of smoking after delivery from controls
Phillips et al. 1992	• Brigham and Women's Hospital • Case-control study • Three main exposures: smoking, chlamydia infection, and douching • 69 cases, women 18–40 years of age with surgically confirmed ectopic pregnancy receiving care at the study hospital • 101 controls, women with IUP pregnancy <= 14 weeks gestation receiving care from physicians at the study hospital • Excluded women with history of tubal reconstructive surgery or tubal sterilization, previous in vitro fertilization, IUD in place within 14 weeks before enrollment, inability to speak English • Study period: 1986–1987 • Boston, MA	Source: interview Current smoking: smoking during the month of conception Former smoking: smoking during the month before conception	COR Overall: 4.2 (2.1–8.2) AOR* Overall: 2.4 (1.2–5.1) Cigarettes/day: 0-10: 3.2 (1.1–8.9) 11-20: 3.2 (0.6–18.1) ≥21: 1.4 (0.4–5.3)	• Nonsmokers and former smokers combined for reference group. • Adjusted for number of previous sexual partners, prior ectopic pregnancy, and prior PID • When prior PID omitted from models as potential mediating factor, AOR = 2.7 (1.3-5.6) • When the analysis restricted to women with no previous ectopic pregnancy, AOR = 1.9 (0.9-4.1) • No increased risk for former smokers

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Saraiya et al. 1998	• Case-control study • Inner-city hospital • 196 cases, Non-Hispanic black women, 18–44 years of age, surgically confirmed ectopic pregnancy and admitted to study hospital • 1,119 controls, Non-Hispanic black women who delivered a live or stillborn infant weighing ≥500gm at the same hospital during the same period, women who sought an induced abortion identified at the preabortion visit to the ambulatory surgical clinic of their hospital • Controls from a systematic random sample of the two groups, selected in 4:1 proportion to reflect pregnant women in the population served by the hospital (planning to complete pregnancy vs. those who don't seek to carry their pregnancy to term) • Excluded women with a history of ectopic pregnancy, tubal surgery, or current IUD use • Study period: 1988–1990 • Atlanta, GA	Source: interview Current smoking: smoked ≥ 100 cigarettes in their lifetime, smoking in the periconceptional period (in 6 months before LMP through 1 month after LMP) Never smoked: smoked < 100 cigarettes in their lifetime	COR Overall: 2.4 (1.7–3.3) AOR* Overall: 1.9 (1.4–2.7) Cigarettes/day: 1–5: 1.6 (.9–2.9) 6–10: 1.7 (1.1–2.8) 11–20: 2.3 (1.3–4.0) >20: 3.5 (1.4–8.6)	• Never and former smokers combined for reference group • Adjusted for age, previous parity, infertility, and douching • No effect modification by age, previous parity, infertility, or douching • Dose-response with smoking as continuous variable was significant (p = 0.0002) • Collected data on other variables that were not significant in final models • Education, marital status, household income, previous gravidity, former IUD use, prior pelvic surgery, history of induced abortions, history of spontaneous abortions, number of sexual partners, history of douching, history of PID, history of any STIs.
Bouyer et al. 2003	• Case-control study • 803 cases ectopic pregnancy cases included in a regional register; married or living with a partner and not using contraception • 1,683 controls deliveries to women who gave birth at the center in which the case was treated and, which occurred very shortly after treatment of the case. Excluded women with induced abortion. • Study period: 1993–2000 • Central France	Source: interview and medical records Current smoking: smoking at conception	COR Cigarettes/day: 1–9: 1.6 (1.2, 2.1) 10–19: 2.9 (2.2–3.7) ≥20: 3.7 (2.8–5.0) AOR* Cigarettes/day: 1–9: 1.7 (1.2, 2.4) 10–19: 3.1 (2.2–4.3) ≥20: 3.9 (2.6–5.9)	• Adjusted for age, prior spontaneous abortion, prior induced abortions, appendectomy, prior STDs, prior tubal surgery, prior use of IUD, history of infertility • Used random effects model to account for repeat pregnancies. • Adjusted attributable risk = 35% • Because some case women might have undergone induced abortion if their pregnancies had been intrauterine, the authors restricted cases and controls to women married or living as a couple

Table 9.14*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Karaer et al. 2006	• Case-control study • Zekai Tahir Burak Women Health Education and Research Hospital • 225 cases women with histopathological examination-confirmed ectopic pregnancy • 3 controls groups (combined for analysis) • 195 women with uncomplicated intrauterine pregnancy at 14 weeks gestation or less • 29 women with induced abortions • 150 nonpregnant women • Study period: 2003–2005 • Ankara, Turkey	Source: interview Current smoking: smoking at the time of conception	COR Cigarettes/day: 1–9: 1.4 (0.8–2.1) 10–19: 2.0 (1.0–3.9) >20: 3.6 (1.7–7.3) AOR* Overall: 1.7 (1.1–2.6)	• Adjusted for age, marital status, prior ectopic pregnancy, prior caesarean section, age at first intercourse, multisexual partner, vaginal douching, prior PID, prior infertility, induced conception cycle, in vitro fertilization, barrier methods, IUD • No statistical test results presented for dose-response • Did not discuss selection of control groups, distribution of women across control groups, or analysis of separate control groups
Roelands et al. 2009	• Hospital discharge data from exposure and diagnosis, prevalence of outcomes compared between smokers and nonsmokers • Representing 90% of all US hospital discharges • 21,207,981 weighted and 4,387,959 unweighted count of pregnancy-related hospital discharges (2,122 smokers with ectopic pregnancy • 11,566 nonsmokers with ectopic pregnancy) • United States	Source: ICD-9 codes from hospital discharge records: used to identify smoking status (305.1 and V15.82)	OR 5.4 (4.6–6.3) Crude	• No adjustments. • Smoking likely underreported in hospital discharge data: smoking prevalence in study population only 4%

Note: **AOR** = adjusted odds ratio; **ARR** = adjusted relative risk; **CI** = confidence interval; **COR** crude odds ratio; **HMO** = health maintenance organization; ***ICD*** = *International Classification of Diseases*; **IUD** = intrauterine device; **IUP** = intrauterine pregnancy; **LMP** = ?; **PID** = Pelvic Inflammatory Disease; **RR** = relative risk; **S.E.** = standard error; **STD** = sexually transmitted disease; **STI** = sexually transmitted infection.

Table 9.15*S* Studies on the effect of maternal active smoking on spontaneous abortion (SAB) risk

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Maconochie et al. 2007	• Nested case-control study, 2-stage postal survey • 603 cases women 18–55 years of age whose most recent pregnancy ended in first trimester miscarriage • 6,116 controls women 18–55 years of age whose most recent pregnancy progressed beyond 12 weeks • Study period: 2001	Source: survey Smoking status: smoked in first trimester of pregnancy	AOR* Cigarettes/day: <5: 0.97 (0.69–1.36) 5–10: 0.91 (0.60–1.37) 11–20: 1.68 (1.16–2.42) 21–30: 1.29 (0.56–2.99)	• Adjusted for year of conception, maternal age, previous miscarriage, previous live birth
Blohm et al. 2008	• Longitudinal study of 3 cohorts of women (born in 1962, 1972, 1982) • Followed every 5 years through questionnaires and hospital record reviews for legal abortions, miscarriages, and other pregnancy outcomes • Main outcomes assessed at 29 years of age • Study period: 1981–2001 • Götegorg, Sweden	Source: questionnaire Smoking status: no additional details provided	COR Overall: 1.8 (1.1–2.9) AOR* Not significant (data not reported)	• Adjusted for BMI, exercise, ever use of combined oral contraceptive pill • 5- and 10-year follow-up >80%
Gallicchio et al. 2009	• Design: cross-sectional survey • Women age 21–50 registered as cosmetologists (n = 350) or other (realtors, teachers, nurses, retail clerks) (n = 397) • Excludes women with hysterectomy or oophorectomy • Women asked about past pregnancies and outcomes by survey; miscarriage defined as SAB at <20 weeks gestation; data collected on up to 5 pregnancies per woman • Study period: 2005–2008 • Setting: Baltimore, MD, metropolitan region	Source: mailed survey Smoking status defined by whether women reported smoking during pregnancy	AOR* 1.53 (1.09–2.16)	• Adjusted for age, race, education, alcohol use • Used repeated measures analysis of variance to take into account multiple pregnancies per mother • Collected data on marital status, BMI, income, health insurance, hormone and oral contraceptive use, family medical history
Bhattacharya et al. 2010	• Cohort study • Data on first pregnancies abstracted from the Aberdeen Maternity and Neonatal Databank. Miscarriages identified from *ICD-9* codes (spontaneous pregnancy loss <24 or 28 weeks gestation depending on coding rules) • Study period: 1950–2000 • 22,988 women with complete data for smoking analysis • Scotland	Source: self-reported smoking status coded at first contact with hospital staff for each pregnancy	AOR* Overall: 1.13 (1.05–1.22)	• Adjusted for age, year of event • Smoking status missing for 44,237 women

Table 9.15*S* Continued

Study	Design/population	Source and definition of smoking status	Estimate of effects (95% CI)	Findings
Zhang et al. 2010	• Case-control study • 326 cases women with 3–6 miscarriages never investigated, excluded those with endocrine or metabolic disorders, autoimmune diseases, venous thrombosis, uterine abnormalities • Women controls randomly selected from 1,000 women with no history of pregnancy loss and at least 1 live birth or an ongoing pregnancy of >20 weeks • Matched to cases on age and education • Study period: 2007–2009 • 3 institutions on Guangdong Province, China	Source: questionnaire Smokers: smoking at enrollment Never smokers: smoked <100 cigarettes in past 5 years	AOR* Cigarettes/day: <10: 1.42 (0.12–17.17) 10–19: 1.62 (0.13–20.87) ≥20: 2.11 (0.09–47.66)	• *Adjusted for BMI, family history of miscarriage, smoking exposure to ETS, alcohol consumption, and coffee intake • Response rates of cases and controls differed (95% and 40%, respectively) • Smoking status at early pregnancy not clearly defined
Baba et al. 2011	• Case-control study medical record review • 430 cases of women consecutively hospitalized in the study hospital for medical procedure for early spontaneous abortion (<12 weeks gestation) • 860 controls women with term deliveries in the study hospital, randomly selected, matched to cases on age and calendar year • Study period: 2001–2005 • Osaka Medical Center and Research Institute for Maternal and Child Health, Osaka, Japan	Source: medical records Smoking status: smokers included women who quit after becoming pregnant; no additional details provided	COR Cigarettes/day: 1–19: 1.24 (0.83–1.85) ≥20: 1.99 (1.18–3.35) *P* for trend = 0.03 AOR* Cigarettes/day: 1–19: 1.30 (0.84–2.02) ≥20: 2.39 (1.26–4.53) *P* for trend = 0.02	• Adjusted for past spontaneous abortion, induced abortion, treatment for infertility, BMI, drinking status, employment, husband's age, and husband's smoking
Campbell et al. 2011	• Cross-sectional study • Aboriginal and Torres Straight Islander women 15–44 years of age surveyed, linked to hospital records for pregnancy-related conditions from survey through 2008 (births of >20 weeks gestation, miscarriages, no elective terminations) • Study period: 1999–2008 • 16 rural and remote indigenous communities in Bowen, Cairns, and Cape York, Torres Straight, and Mount Isa Health Service Districts	Source: baseline survey, self-reported	PR 0.89 (0.52–1.53) APR* 0.94 (0.55–1.61)	• Adjusted for age and ethnicity • Smoking status at the time of the pregnancy subsequent to the survey not assessed • Also collected data on alcohol use, BMI, diet, physical activity, urine tested for STIs (Chlamydia trachomatis and Neisseria gonorroeae). SAB significantly associated with alcohol use and STIs

Note: **AOR** = adjusted odds ratio; **APR** = adjusted prevalence ratio; **BMI** = body mass index; **CI** = confidence interval; **COR** = crude odds ratio; **ETS** = environmental tobacco smoke; ***ICD*** = *International Classification of Diseases*; **PR** = prevalence ratio; **STI** = sexually transmitted infection.

Table 9.16*S* Experimental studies of the association between smoking and erectile dysfunction

Study	Design/population	Stimulus	Findings
Gilbert et al. 1986	• Humans: randomized controlled trial with 42 smokers • 18–44 years of age	Visual sexual stimulation	• High-nicotine cigarettes reduced the extent to which penile diameter increased
Glina et al. 1988	• Humans: acute experiment with 12 smokers • 22–65 years of age	Erection pharmocostimulation	• Smoking 2 cigarettes reduced intracavernous pressure measurements
Juenemann et al. 1987	• Animals: acute experiment using dogs	Cavernous nerve electrostimulation	• Inhalation of cigarette smoke reduced erectile parameters
Xie et al. 1997	• Animals: chronic experiment using rats	Cavernous nerve electrostimulation	• Inhalation of cigarette smoke did not alter erection parameters
Guay et al. 1998	• Humans: acute experiment with 10 smokers • 32–62 years of age	Sleep-related erection	• Cessation of cigarette smoking improved erectile parameters

Table 9.17*S* Cross-sectional studies of the association between smoking and the risk of erectile dysfunction

Study	Design/population	Prevalence (%) of erectile dysfunction by smoking status	*p* Value
Feldman et al. 1994[a]	• U.S. residents • 40–70 years of age • Studied during 1987–1989 • Boston, MA	• Never and former: 9.3 • Current: 11.0	>0.200
Mannino et al. 1994[a]	• U.S. veterans • 31–49 years of age • Studied during 1985–1986	• Never: 2.2 • Current: 3.7 • Former: 2.0	0.005[b]
Feldman et al. 2000[c]	• U.S. residents • 40–70 years of age • Studied during 1987–1997 • Boston, MA	• Never and former: 14.0 • Current: 24.0	0.03
Kleinman et al. 2000	• U.S. men • 40–70 years of age • Studied during 1987–1997 • Boston, MA	• Never: NR • Current: NR • Former: NR	NR
Parazzini et al. 2000[a]	• Italian men • >18 years of age • Studied during 1996–1997	• Never: 24.2 • Current: 35.6 • Former: 40.2	NR
Blanker et al. 2001[a]	• Dutch men • 50–78 years of age • Studied during 1995–1998	• Never and former: NR • Current: NR	NR
Martin-Morales et al. 2001[a]	• Spanish men • 25–70 years of age • Studied during 1998–1999	• Never and former: NR • Current: NR	NR
Bacon et al. 2003[a]	• U.S. male health professionals • 53–90 years of age • Data from 2000	• Never: NR • Current: NR • Former: NR	NR
Shiri et al. 2005	• Finnish men • 50–75 years of age • Studied during 1994–1999	• Never: 16.3 • Current: 20.9 • Former: 26.1	NR
Lam et al. 2006b	• Chinese men • Studied in 2001 • Hong Kong	• Never: 42.5 • Former: 40.8 • Current: • ≤20 cigarettes/day: 43.0 • >20 cigarettes/day: 51.2	NR
Millett et al. 2006[a]	• Australian men • 16–59 years of age • Studied during 2001–2002	• Nonsmokers: 8.8 • Current: • ≤20 cigarettes/day: 9.4 • >20 cigarettes/day: 14.7	<0.001
He et al. 2007	• Chinese men • 35–74 years of age • Studied during 2000–2001	• Smokers vs. never smokers: • 35–44 years of age: 6.4 vs. 4.6 • 45–54 years of age: 17.8 vs. 14.8 • 55–64 years of age: 44.0 vs. 35.6 • 65–74 years of age: 54.7 vs. 45.6	0.01 (overall); <0.0001 (age trend)

Table 9.17*S* Continued

Study	Design/population	Prevalence (%) of erectile dysfunction by smoking status	*p* Value
Kupelian et al. 2007	• U.S. men • 30–79 years of age • Studied during 2002–2005 • Boston, MA	• Never: NR • Never (passive): NR • Current: NR	NR

Note: **NR** = not reported.
[a]Prevalence study.
[b]Significant results.
[c]Incidence study.