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Systematic Reviews and Meta- and Pooled Analyses

Systematic Review and Meta-Analysis of Miscarriage and Maternal Exposure to Tobacco Smoke During Pregnancy

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We conducted a systematic review and meta-analysis to characterize the relationship between smoking and miscarriage. We searched the PubMed database (1956–August 31, 2011) using keywords and conducted manual reference searches of included articles and reports of the US Surgeon General. The full text of 1,706 articles was reviewed, and 98 articles that examined the association between active or passive smoking and miscarriage were included in the meta-analysis. Data were abstracted by 2 reviewers. Any active smoking was associated with increased risk of miscarriage (summary relative risk ratio = 1.23, 95% confidence interval (CI): 1.16, 1.30; n = 50 studies), and this risk was greater when the smoking exposure was specifically defined as during the pregnancy in which miscarriage risk was measured (summary relative risk ratio = 1.32, 95% CI: 1.21, 1.44; n = 25 studies). The risk of miscarriage increased with the amount smoked (1% increase in relative risk per cigarette smoked per day). Secondhand smoke exposure during pregnancy increased the risk of miscarriage by 11% (95% CI: 0.95, 1.31; n = 17 studies). Biases in study publication, design, and analysis did not significantly affect the results. This finding strengthens the evidence that women should not smoke while pregnant, and all women of reproductive age should be warned that smoking increases the risk of miscarriage.

abortion; miscarriage; pregnancy; smoking; tobacco

Abbreviations: CI, confidence interval; OR, odds ratio; RRR, relative risk ratio.

Smoking during pregnancy causes low birthweight, placental abruption, and sudden infant death syndrome (1, 2). Nonetheless, 14% of pregnant women and 23% of women of reproductive age report being smokers, with secondhand smoke exposure even more prevalent, at 37% of pregnant women (3–5). Miscarriage, or loss of the fetus before it is viable, is the most common complication of pregnancy, occurring in 12%–26% of recognized pregnancies. Although many studies have addressed the association between miscarriage and smoking, the evidence has been considered inconclusive. The US Surgeon General's most recent conclusion, from the 2004 report (2), classified the evidence as suggestive but not sufficient to infer causation, and the most recent edition of the authoritative textbook, *Williams Obstetrics*, also describes the lack of consistency (6). Most miscarriages end early in pregnancy, during an interval over which a woman might not yet have learned of being pregnant or begun prenatal care. The benefits of quitting smoking early in pregnancy include increased birthweight and a lower risk of preterm birth, but these effects would never manifest for a woman who quits smoking but also miscarries in the first trimester (6). Thus, a more complete understanding of the relationship between smoking and miscarriage is important for preconception counseling and public health programs for women of reproductive age. This systematic review and meta-analysis focuses on the association of smoking (active and passive) with miscarriage (7).

METHODS

We conducted a systematic review and meta-analysis using the guidelines of the Meta-Analysis of Observational Studies in Epidemiology consensus statement and the Preferred

Reporting Items for Systematic Reviews and Meta-Analysis statement (8, 9).

Inclusion criteria

Studies eligible for inclusion in the meta-analysis were original observational or experimental studies. Eligible studies compared the risks of miscarriage between women who were exposed and those who were not exposed to tobacco smoke from cigarettes. Relevant exposures were smoking of cigarettes by the mother and secondhand smoke exposure in pregnant women. Articles in any language were eligible and were translated as necessary using Google Translate (http://translate.google.com/). We excluded duplicate publications and publications with duplicated data (e.g., studies conducted on the same registry with overlapping years). No quality measures were used to select studies for inclusion.

Literature search strategy

Two reviewers independently searched the PubMed database for articles published between 1956 and August 31, 2011, relevant to smoking and risk of adverse pregnancy outcomes. The search terms were ("smoking" OR "tobacco") AND "pregnancy." From the chosen articles, those relevant to miscarriage or perinatal death were selected for inclusion and/or review of references. We then conducted manual searches by checking references of the articles identified in the PubMed searches. The articles referenced by all relevant articles (original articles, reviews, and letters) were searched by at least 1 reviewer, and the articles referenced by included articles and all Surgeon General reports regarding tobacco and health were searched by 2 reviewers. Disagreements on final inclusion status were resolved by discussion.

Data abstraction

Study data were collected and managed using REDCap electronic data capture tools (10). Two reviewers independently extracted data from all articles on study type, country, calendar years of the pregnancies in the studies, population characteristics, participant inclusion and exclusion criteria, recruitment methods, participation and follow-up rates, exposure and outcome definitions, features of data collection, numbers of participants, effect sizes, and statistical significance tests. Differences in item coding were resolved through discussion between the reviewers, and the κ statistic was computed to assess agreement between reviewers. The median Strout-Fleiss reliability statistic for continuous variables was 0.99, and the median κ statistic for covariates analyzed was 0.52.

Definition of outcomes

Miscarriage was defined in different ways, including by gestational age ranges, karyotype, and fetal weight. Common upper thresholds for gestational age were between 12 and 28 weeks. Many authors did not provide a definition of miscarriage, and for these studies, any outcome described as "miscarriage," "spontaneous abortion," or "pregnancy loss" without other description was used and combined with other miscarriage outcomes. Reproductive lifetime history of miscarriage (ever had at least 1 miscarriage over the lifetime) was analyzed separately from miscarriage in an individual pregnancy.

Grouping of exposures

Any study that used as its exposure indicator "smoking," "smoker," "secondhand smoke," "environmental tobacco smoke," "lives with a smoker," or "partner/husband is a smoker" was considered eligible. Studies were included that described the amount of smoking exposure. Exposures were categorized by type (active/passive), timing in relation to pregnancy, amount of exposure, and the source of exposure if given. Reference exposures included "0 cigarettes per day," "nonsmoker," "never smoker," "no secondhand smoke exposure," and others indicating no exposure to tobacco smoke. Studies that collected smoking exposure data before or during pregnancy were categorized as prospective, and case-control studies or others that collected smoking exposure data after pregnancy were categorized as retrospective. The window of smoking exposure was categorized as follows: 1) before pregnancy (including those who continued and those who quit during pregnancy), 2) during pregnancy, 3) lifetime exposure or after all studied pregnancies, 4) ex-smoker at the time of pregnancy, 5) quit at conception or in early pregnancy, and 6) not specified. "Any active smoking" refers to definitions of smoking as at least 1 cigarette per day and to the undefined terms of "smoker" and "smoking."

Analysis

The random-effects model of DerSimonian and Laird (11) was chosen to account for heterogeneity of study populations and designs. The estimate of relative risk ratio used was the odds ratio, risk ratio, or hazard ratio, as given in the original article. For studies without an estimated relative risk ratio, risk ratios or odds ratios were calculated from available data as appropriate. A continuity correction (12) of 0.5 was applied to studies (13–15) with counts of 0 in 1 or more cells of the 2×2 table.

Relative risk ratios for "any active smoking" were combined, as were those for categories of 1–10, 11–20, and 21 or more cigarettes smoked per day (16). Because too few studies that examined secondhand smoke or history of miscarriage gave results by the amount of exposure, no dose-response analyses were conducted for this exposure and outcome, respectively. Instead, all studies that included relative risk ratios for various categories of exposure were included in "any exposure" analyses after combining the multiple relative risk ratios into a single estimate for each study (17). Analyses were conducted using SAS, version 9.2, software (SAS Institute, Inc., Cary, North Carolina).

Dose-response analysis

All relative risk ratios given for the risk of stillbirth, neonatal death, or perinatal death based on the number of cigarettes smoked per day, regardless of categorization scheme, were

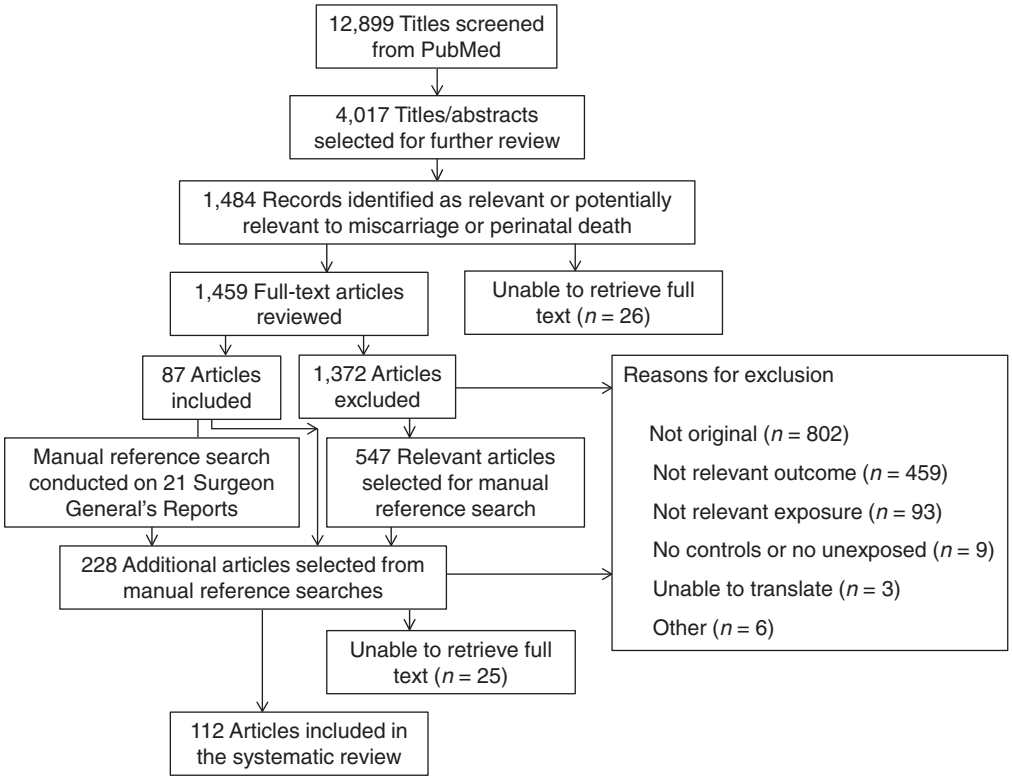

Figure 1. Selection of studies included in the systematic review and meta-analysis of smoking and risk of miscarriage.

analyzed in a dose-response meta-regression separately for each outcome. We used a SAS macro for meta-analysis of linear and nonlinear dose-response relationships that combines studies of the same relationship that have different exposure levels (18, 19). For closed-ended categories, the midpoints were taken as the dose. For open-ended categories (those specified with minimum but not maximum numbers of cigarettes per day, such as "20 or more"), we imputed a maximum number of cigarettes per day based on the category minimum, then took the midpoint of the minimum and the imputed maximum as the dose. The imputed maximum was based on the approximate mean number and categorical distribution of cigarettes smoked per day among women in the National Health Interview Survey (20). For categories with minima of 40 or more cigarettes per day, the maximum was 45; for categories with minima of 30–39 cigarettes per day, the maximum was 40; for categories with minima of 25–29 cigarettes per day, the maximum was 35; for categories with minima of 20–24 cigarettes per day, the maximum was 30; for categories with minima of 15–19 cigarettes per day, the maximum was 25; and for categories with minima of 2–14 cigarettes per day, the maximum was 20.

Heterogeneity and study quality

Heterogeneity between studies was assessed using the I^2 statistic, which represents the percent of total variation that is true between-studies heterogeneity (21). Statistical significance of the heterogeneity was analyzed with the Q statistic. When heterogeneity was statistically significant and high, reasons for the heterogeneity were examined using random-effects meta-regression for both continuous and dichotomous variables (22, 23). Subgroups were contrasted on the basis of exposure timing in relation to pregnancy (specified as during pregnancy vs. not specified or other). Many studies likely collected data on smoking and miscarriage but did not include this information in the title, abstract, or indexed keywords and, consequently, studies that focused specifically on smoking are likely overrepresented in the included articles compared with the universe of eligible articles on the outcome. To estimate the potential impact of including only studies focused on smoking, we compared the results from subgroups on the basis of keywords in the article titles. We searched for the terms, "smok," "tobac," and "cigar" in the titles of the articles and considered these to be articles that focused on smoking. Articles without any of these terms in the titles we considered not to be focused on smoking. Because miscarriage is relatively common (occurring in 10%–20% of pregnancies), odds ratios were converted to risk ratios, and the results from using these data were compared with those obtained with odds ratios, risk ratios, and hazard ratios combined (24). If unexplained heterogeneity remained, post hoc meta-regression and subgroup analyses were conducted on other variables collected. Study quality assessment was

Table 1. Characteristics of Included Studies

First Author, Year (Reference No.)	Study Design	Exposure	Exposed, %	Outcome	Location	Study Years	No. of Subjects
Adolfsson, 2006 (47)[a]	Cross-sectional	Active	19.6	Miscarriage	Sweden	1983–2003	2,503,605
Agnesi, 1997 (15)[b]	Case-control	Active	9.7	Miscarriage	Italy	1987–1988	216
Agnesi, 2011 (48)[b]	Case-control	Active	6.7	Miscarriage	Italy	1987–1999	462
Ahlborg, 1991 (49)	Prospective cohort	Active/passive	36/15	Miscarriage to 13 weeks	Sweden	1980–1983	3,261
Ancel, 2000 (50)	Case-control	Active	12	Miscarriage at 14–21 weeks	Multiple European	1994–1997	4,507
Armstrong, 1992 (51)	Retrospective cohort	Active	33	Miscarriage to 28 weeks	Canada	1953–1984	47,146
Axelsson, 1984 (52)	Cross-sectional	Active	27	Miscarriage	Sweden	1950–1982	1,131
Baba, 2011 (53)	Case-control	Active/passive	17/26	Miscarriage to 12 weeks	Japan	2001–2005	1,290
Baird, 1985 (54)	Cross-sectional	Active	19	History of miscarriage	United States	1954–1983	468
Baste, 2008 (55)	Cross-sectional	Active	63	History of miscarriage	Norway	1965–1999	10,512
Bech, 2005 (56)	Prospective cohort	Active	17	Miscarriage to 28 weeks	Denmark	1996–2002	88,482
Bernhard, 1948 (57)	Cross-sectional	Active	8	History of miscarriage	Germany	1916–1947	5,548
Bernhard, 1964 (58)	Retrospective cohort	Active	8	Miscarriage to 25.5 weeks	Germany	1943–1949	10,803
Bhattacharya, 2010 (59)[c]	Retrospective cohort	Active	34	Miscarriage to 28 weeks	United Kingdom	1950–2005	49,272
Blanco-Muñoz, 2009 (60)	Nested case-control	Active/passive	42/46	Miscarriage to 20 weeks	Mexico	2001–2004	107
Blohm, 2008 (61)	Cross-sectional	Active	25	History of miscarriage	Sweden	1977–2001	733
Boyles, 2000 (62)[d]	Case-control/prospective cohort	Active[e]	26	Miscarriage to 22 weeks	United States	1995–1997	970
Campbell, 2011 (63)	Prospective cohort	Active	70	Miscarriage to 20 weeks	Australia	1999–2008	279
Cavedon, 1987 (64)	Retrospective cohort	Active	5	Miscarriage to 28 weeks	Italy	1930–1982	3,332
Chatenoud, 1998 (65)	Case-control	Active/passive	16/45	Miscarriage 4–12 weeks	Italy	1990–1995	2,325
Cnattingius, 2000 (66)[a]	Case-control	Active[e]	16	Miscarriage 6–12 weeks	Sweden	1996–1998	1,515
Cone, 1998 (67)	Retrospective cohort	Active	13	Miscarriage 6–28 weeks	United States	1990–1991	418
Cope, 1973 (68)	Cross-sectional	Active	25	History of miscarriage to 20 weeks	Australia	1941–1971	4,992
Coste, 1991 (69)	Case-control	Active	28	Miscarriage	France	1988–1988	558
Danish Health Board, 1995 (70)	Cross-sectional	Active	33	History of miscarriage	Denmark	1963–1992	68,065
de Weerd, 2003 (71)	Prospective cohort	Active	25	Miscarriage to 16 weeks	Netherlands	1987–1990	240
Domínguez-Rojas, 1994 (72)	Retrospective cohort	Active	38	Miscarriage to 20 weeks	Spain	1963–1991	691
Donovan, 1977 (73)	Prospective cohort	Active	65	Miscarriage to 28 weeks	United Kingdom	1972–1973	1,274
Downing, 1966 (74)	Prospective cohort	Active	47	Miscarriage	United States	1952–1958	5,659
Ericson, 1986 (75)	Nested case-control	Active/passive	17/55	Miscarriage	Sweden	1980–1981	1,142
Eskenazi, 1995 (14)	Prospective cohort	Active	15	Miscarriage	United States	1965–1994	52
Fabiani, 1988 (76)	Case-control	Active	30	Miscarriage	Italy	1983–1984	227

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Design	Exposure	Exposed, %	Outcome	Location	Study Years	No. of Subjects
Fergusson, 1979 (27)	Cross-sectional	Active	40	History of miscarriage	New Zealand	1948–1977	1,248
Fuentes, 2010 (77)	Prospective cohort	Passive	18	Miscarriage 2–8.5 weeks	Chile	2004–2005	57
Gallicchio, 2009 (78)	Cross-sectional	Active	19	Miscarriage to 20 weeks	United States	1965–2008	1,882
Farioli, 2010 (79)[a]	Case-control	Active/passive	15/21	Miscarriage 6–12 weeks	Sweden	1996–1998	1,327
George, 2006 (43)[a]	Case-control	Active/passive[e]	15/21	Miscarriage 6–12 weeks	Sweden	1996–1998	1,327
Guerra-Shinohara, 2010 (80)	Prospective cohort	Active	13	Miscarriage to 20 weeks	Brazil	2004–2005	100
Habek, 2011 (81)	Retrospective cohort	Active	64	Miscarriage	Croatia	1994–1994	53
Hafez, 2001 (33)	Cross-sectional	Passive	52	History of miscarriage	Egypt	1963–2000	1,934
Hall, 1992 (82)[c]	Prospective cohort	Active	28	Miscarriage	United Kingdom	1980–1989	1,261
Halmesmaki, 1989 (83)	Case-control	Active/passive	26/36	Miscarriage 6–23 weeks	Finland	1988–1988	161
Hansteen, 1990 (42)	Case-control	Active	39	Miscarriage to 26 weeks	Norway	1985–1987	610
Hardy, 1972 (84)	Prospective cohort	Active	44	Miscarriage	United States	1962–1963	1,329
Harlap, 1980 (85)	Prospective cohort	Active	25	Miscarriage 5–27 weeks	United States	1974–1977	32,019
Harrison, 1990 (86)	Prospective cohort	Active	1	Miscarriage	Australia	1988–1988	650
Hemminki, 1983 (87)	Cross-sectional	Active	15	Miscarriage	Finland	1931–1981	2,714
Himmelberger, 1978 (88)	Retrospective cohort	Active	Not stated	Miscarriage to 20 weeks	United States	1963–1972	12,914
Hrubá, 1997 (89)	Cross-sectional	Active/passive	45	Miscarriage/history of miscarriage	Czech Republic	1911–1993	7,397
Hudson, 1945 (90)	Retrospective cohort	Active	38	Miscarriage	United States	1943–1945	645
Hughes, 1994 (13)	Cross-sectional	Active	48	Miscarriage	Canada	1990–1992	48
Kharazmi, 2010 (91)	Cross-sectional	Active	21	History of miscarriage	Finland	1916–2001	3,636
Khoury, 2004 (92)	Prospective cohort	Active	30	Miscarriage to 20 weeks/ history of miscarriage	United States	1978–1993	191
Kizer, 1967 (93)	Cross-sectional	Active	39	Miscarriage	Venezuela	1966–1967	6,566
Kline, 1977 (94)[f]	Case-control	Active	36	Miscarriage	United States	1974–1976	883
Kline, 1980 (95)[f]	Case-control	Active	34	Miscarriage	United States	1974–1978	1,293
Kline, 1980 (96)[f]	Case-control	Active	34	Miscarriage	United States	1974–1978	1,295
Kline, 1983 (97)[f]	Case-control	Active	34	Miscarriage of trisomic fetus	United States	1974–1979	1,603
Kline, 1995 (41)[f]	Case-control	Active	34	Miscarriage to 28 weeks	United States	1974–1986	3,911
Koller, 1983 (98)	Prospective cohort	Active	19	Miscarriage	Germany	1964–1971	6,533
Kullander, 1971 (99)	Prospective cohort	Active	44	Miscarriage 8–30 weeks	Sweden	1963–1964	6,195
Kyyronen, 1989 (100)	Case-control	Active	37	Miscarriage	Finland	1973–1983	419
Lacuska, 1968 (101)	Retrospective cohort	Active	4	Miscarriage	Czech Republic	1964–1967	3,670
Lemasters, 1989 (102)	Retrospective cohort	Active	20	Miscarriage to 20 weeks	United States	1963–1985	2,909

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Design	Exposure	Exposed, %	Outcome	Location	Study Years	No. of Subjects
Maconochie, 2007 (103)	Case-control	Active/passive	24	Miscarriage to 13 weeks	United Kingdom	1980–2001	6,709
Makay, 1968 (104)	Cross-sectional	Active	9	History of miscarriage	Hungary	1935–1966	2,341
Martin, 2000 (105)[c]	Retrospective cohort	Active	34	Miscarriage to 27 weeks	United Kingdom	1969–1997	3,150
Maximovich, 1995 (106)	Retrospective cohort	Active	19	Miscarriage	United States	1992–1993	80
Medina, 1990 (107)	Cross-sectional	Active	55	History of miscarriage	Chile	1943–1988	100
McKean, 1978 (108)[f]	Case-control	Active	36	Miscarriage	United States	1974–1976	883
Meeker, 2007 (109)[g]	Prospective cohort	Passive	11	Miscarriage to 20 weeks	United States	1994–2003	460
Meeker, 2007 (110)[g]	Prospective cohort	Passive[e]	50	Miscarriage to 20 weeks	United States	1994–1998	339
Mey, 1967 (111)	Cross-sectional	Active	14	History of miscarriage	Germany	1906–1965	1,981
Mishra, 2000 (112)	Cross-sectional	Active	44	History of miscarriage	Australia	1988–1996	2,617
Morales, 1997 (113)	Cross-sectional	Active	26	History of miscarriage	United Kingdom	1950–1984	119
Murphy, 1974 (114)[h]	Retrospective cohort	Active	46	Miscarriage	United Kingdom	1969–1973	12,013
Murphy, 1978 (115)[h]	Retrospective cohort	Active	46	Miscarriage	United Kingdom	1969–1973	12,013
Nakamura, 2004 (116)	Cross-sectional	Active/passive	24/45	Miscarriage/history of miscarriage	Brazil	2001–2001	596
Ness, 1999 (117)[d]	Case-control/prospective cohort	Active[e]	26	Miscarriage to 22 weeks	United States	1995–1997	970
Nielsen, 2006 (118)[i]	Nested case-control	Active	45	Miscarriage to 28 weeks	Denmark	1991–1995	1,921
O'Lane, 1963 (119)	Cross-sectional	Active	46	Miscarriage	United States	1961–1962	1,914
Padrón Garcia, 1990 (120)	Retrospective cohort	Active	44	Miscarriage	Cuba	1986–1987	1,018
Palmgren, 1971 (121)[j]	Prospective cohort	Active	48	Miscarriage 8–30 weeks	Sweden	1964–1967	4,312
Palmgren, 1973 (122)[j]	Prospective cohort	Active	48	Miscarriage	Sweden	1964–1967	4,312
Pandya, 1996 (123)	Cross-sectional	Active	3	Miscarriage 10–13 weeks	United Kingdom	1992–1995	16,806
Pattinson, 1991 (124)	Prospective cohort	Active/passive	28/22	Miscarriage	Canada	1984–1989	69
Raatikainen, 2007 (125)	Cross-sectional	Active	27	History of miscarriage	Finland	1960–2001	25,591
Rasch, 2003 (126)	Case-control	Active	22	Miscarriage 6–16 weeks	Denmark	1994–1996	1,486
Risch, 1988 (127)	Cross-sectional	Active	20	Miscarriage	United States and Canada	1914–1981	6,282
Rumeau-Rouquette, 1972 (128)	Cross-sectional	Active	10	History of miscarriage	France	1934–1967	3,984
Sandahl, 1989 (129)[a]	Case-control	Active	49	Miscarriage 5–28 weeks	Sweden	1980–1985	2,747
Scholl, 1986 (130)	Prospective cohort	Active	34	Miscarriage	United States	1982–1984	775
Schwartz, 1972 (131)	Prospective cohort	Active	17	Miscarriage	France	1963–1969	6,989
Selevan, 1985 (132)	Case-control	Active	13	Miscarriage	Finland	1972–1980	445

Table continues

Table 1. Continued

First Author, Year (Reference No.)	Study Design	Exposure	Exposed, %	Outcome	Location	Study Years	No. of Subjects
Simoes, 1985 (133)	Cross-sectional	Active	25	History of miscarriage	Brazil	1978–1979	6,179
Stein, 1981 (134)[f]	Case-control	Active	30	Miscarriage	United States	1974–1980	4,088
Stein, 1981 (135)[f]	Case-control	Active	30	Miscarriage	United States	1974–1980	4,088
Triopon, 2006 (136)	Prospective cohort	Active/passive	21/43	Miscarriage	France	2002–2005	63
Underwood, 1965 (137)	Retrospective cohort	Active	27	Miscarriage	United States	1931–1961	16,158
van Ravenswaaij, 2011 (138)	Retrospective cohort	Active	7	Miscarriage to 16 weeks	Netherlands	2002–2006	28,566
Venners, 2004 (139)	Prospective cohort	Passive	59	Miscarriage to 6 weeks	China	1996–1998	526
Wallander, 1970 (140)[j]	Prospective cohort	Active	50	Miscarriage	Sweden	1964–1967	4,478
Warburton, 1979 (141)[f]	Case-control	Active	30	Miscarriage to 28 weeks	United States	1974–1978	966
Wilcox, 1990 (142)	Prospective cohort	Active/passive	5/8	Miscarriage 1–6 weeks	United States	1982–1986	171
Windham, 1992 (143)	Case-control	Active/passive	20/28	Miscarriage to 20 weeks	United States	1986–1987	1,926
Windham, 1999 (144)	Prospective cohort	Active/passive	18/28	Miscarriage to 20 weeks	United States	1990–1991	5,142
Windham, 1999 (145)	Cross-sectional	Active	16	History of miscarriage	United States	1966–1990	362
Winter, 2002 (146)	Retrospective cohort	Active	11	Miscarriage to 7 weeks	Australia	1994–1999	1,196
Wisborg, 2003 (147)[i]	Prospective cohort	Active	29	Miscarriage 12–27 weeks	Denmark	1989–1996	17,497
Wu, 1998 (148)	Cross-sectional	Active	24	History of miscarriage	United States	1959–1988	12,465
Yuan, 1994 (149)	Cross-sectional	Active	19	History of miscarriage	Japan	1961–1992	261
Zabriskie, 1963 (46)	Cross-sectional	Active	48	Miscarriage	United States	1931–1961	5,619

[a] Only 1 article with this footnote was used in each analysis because all used data from the Swedish Medical Birth Register with overlapping time periods between 1980 and 2003.
[b] Only 1 article with this footnote was used in each analysis because these 2 case-control studies used 216 of the same pregnancies from 1987 to 1988.
[c] Only 1 article with this footnote was used in each analysis because all used data from the Aberdeen Maternity and Neonatal Databank in Scotland with overlapping time periods between 1950 and 2000.
[d] Only the article by Ness et al. (115) was used because the article by Boyles et al. (61) is a duplicate publication of the same data.
[e] Study used a biochemical measure to ascertain smoking or secondhand smoke exposure.
[f] Only 1 article with this footnote was used in each analysis because all used data from the same ongoing case-control study in Manhattan (New York, New York) with recruitment from 1974 to 1986.
[g] Only 1 article with this footnote was used in each analysis because both used data from 3 Boston, Massachusetts, clinics with overlapping time periods between 1994 and 2003.
[h] Only 1 article by Murphy et al. (112) was used because the second article by Murphy et al. (113) is a duplicate publication of the same data in a letter.
[i] Only 1 article with this footnote was used in each analysis because both used data from the Danish Hospital Discharge Register with overlapping time periods between 1989 and 1996.
[j] Only 1 article with this footnote was used in each analysis because all used data from the same subjects between 1964 and 1967.

undertaken using indicators to address information bias, confounding, selection bias, and violation of statistical assumptions. Adjusted estimates were compared with crude estimates, and estimates based on the best analytical model (best and most appropriate control of confounding) were compared with other estimates. Potential confounders considered important were maternal age, education, and socioeconomic status. Adjusting for prior pregnancy loss is inappropriate for estimation of the causal effect of smoking on miscarriage, so studies that adjusted for this were excluded from the "best analytical model" analysis (25).

Publication bias

Publication bias was analyzed for each comparison by visual analysis of funnel plots, Egger regression, Begg rank correlation, funnel plot regression, and trim-and-fill tests using the PUB_BIAS macro (26). Sensitivity analyses were conducted by comparing results obtained after excluding studies with very high relative risk ratios.

Imputation

One study required the use of imputed data for variance estimation because the numbers provided were miscarriage rates by categories of number of cigarettes per day, and only the total number of smokers was given (27). The distribution of cigarettes smoked per day was assumed to be similar to that reported by other studies; 50% of the smoking subjects were assigned to the category of 11–20 cigarettes per day, and 25% each were assigned to the categories of 1–10 and 21 or more cigarettes per day. Imputation of the covariates of national smoking prevalence and national cigarettes per capita was also performed for each study on the basis of year and country. Both the year of publication and the midpoint year of study pregnancies were used for the year value. Smoking prevalence data were primarily obtained from the World Health Organization Global Infobase (complete reference list available upon request) (28). Cigarettes per capita data were primarily obtained from 1 report (29), with values for the United States from the Centers for Disease Control and Prevention (30) and a few other data points from another source (31).

RESULTS

Studies included in the systematic review and meta-analysis

From the initial 12,899 articles identified by keywords for tobacco and pregnancy, 112 articles were selected for inclusion in the systematic review, and 98 were selected for the meta-analyses (Figure 1, Table 1). Articles were excluded if they did not study miscarriage or miscarriage alone (n = 459), they did not analyze smoking in relation to miscarriage (n = 93), they lacked a control group or unexposed group (n = 9), translation was not possible (n = 3), or for other reasons (n = 6). Twenty-eight studies were placed into 8 sets of overlapping data, with between 2 and 9 studies per set. These sets were identified on the basis of the studies being conducted in the same country, during the same years, and using the same registry or population. Often, these were duplicate publications by the same authors, though a few were registry studies with overlapping years. The largest study appropriate for each analysis was chosen from each set. Of the 112 studies, 21 examined secondhand smoke exposure of the mother, and 107 examined active maternal smoking. Thirty-one percent of the studies were conducted in the United States, and the remainder were conducted in 25 other countries or sets of countries. Sixteen were published in languages other than English. Twenty-three studies used history of miscarriage as the outcome, and 93 used miscarriage in an individual pregnancy. All results refer to miscarriage in an individual pregnancy unless otherwise specified. A list of the studies that were included in each analysis is provided in Web Table 1, available at http://aje.oxfordjournals.org/. Twelve duplicate studies and 2 studies without enough data given were not used in any analyses.

Active maternal smoking

Results of the meta-analysis. The summary relative risk for miscarriage among female smokers using only crude relative risk ratios was 1.27 (95% confidence interval (CI): 1.18, 1.37; n = 35 studies), and that using only adjusted relative risk ratios was 1.17 (95% CI: 1.04, 1.31; n = 19 studies). All further analyses used adjusted and crude relative risks together because of the similarity of these estimates, which were not significantly different (P = 0.45). The summary relative risk of miscarriage with any active smoking was 1.23 (95% CI: 1.16, 1.30; n = 50 studies, Figure 2). Former smokers were no more likely to have a miscarriage than were never smokers (summary relative risk ratio (RRR) = 0.90, 95% CI: 0.69, 1.16, n = 7 studies). Women who quit smoking at conception or early in pregnancy had a 25% lower risk of miscarriage than those who did not smoke around the time of pregnancy at all, but the difference was not statistically significant (summary RRR = 0.75, 95% CI: 0.55, 1.02; n = 4 studies).

History of miscarriage. Any active smoking was associated with an increased risk of having a history of miscarriage (at least 1 miscarriage in the woman's lifetime; summary RRR = 1.47, 95% CI: 1.26, 1.70; n = 22 studies). Former smokers had nonsignificantly increased risk of having a history of miscarriage (summary RRR = 1.33, 95% CI: 0.96, 1.85; n = 2 studies).

Assessment of heterogeneity. Heterogeneity of the summary relative risk of miscarriage with any active smoking was statistically significant and moderate (I^2 = 60%, P < 0.0001; see Web Table 2 for detailed results). None of the following factors significantly affected the summary relative risk: year of publication, midpoint year of the study pregnancies, the exposure prevalence in the study population, or per-capita cigarette consumption (P values > 0.25). Studies that defined miscarriage as pregnancy loss with a maximum gestational age of 20 weeks or greater had a higher summary relative risk of miscarriage than those that defined it with a maximum gestational age of less than 20 weeks (1.49 vs. 1.24, respectively, P < 0.05). Cohort studies had higher summary relative risks than studies with other designs (e.g., case-control or cross-sectional studies; 1.39 vs. 1.17, respectively, P < 0.05).

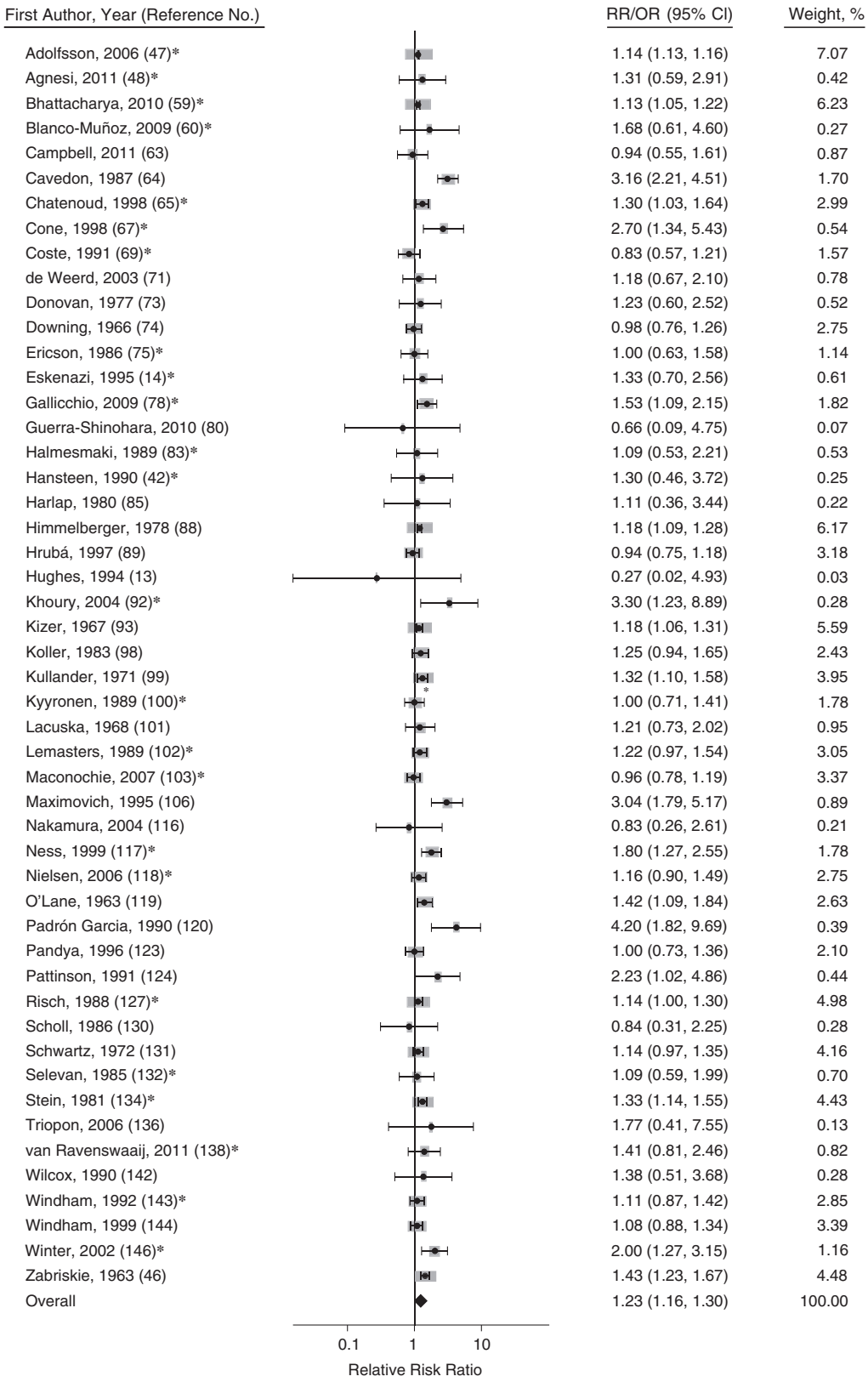

Figure 2. Forest plot for the association of any active maternal smoking and risk of miscarriage (150). Gray boxes represent the weight of the study in the meta-analysis. Studies with asterisks have odds ratios (ORs) presented; studies without asterisks have relative risks (RRs) presented. Bars, 95% confidence intervals (CIs).

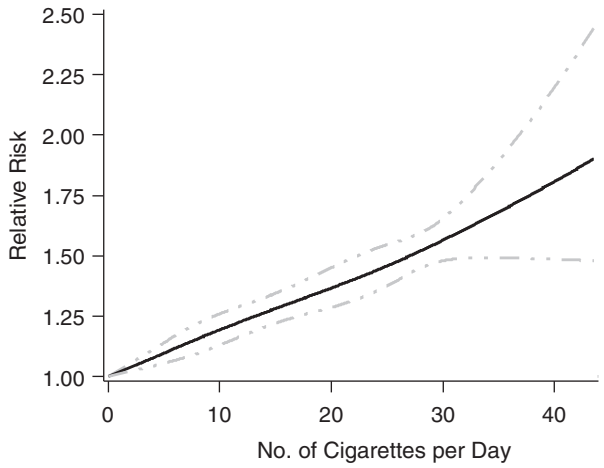

Figure 3. Relative risk of miscarriage versus number of cigarettes smoked per day.

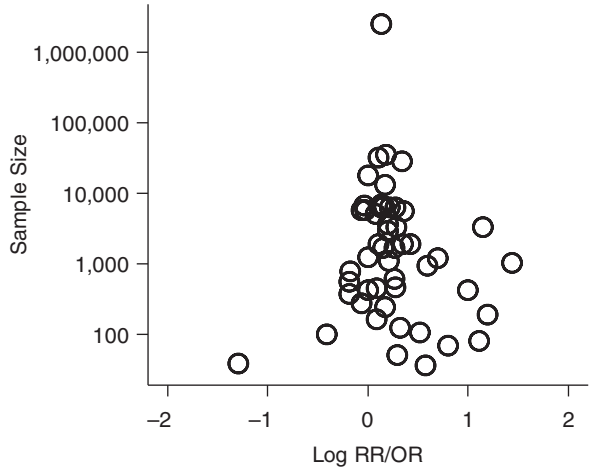

Figure 4. Funnel plot for studies that analyzed any active smoking and the risk of miscarriage. OR, odds ratio; RR, relative risk.

Studies that defined smoking as during the pregnancy in which miscarriage risk was measured gave a summary relative risk that was higher than those with exposures without a specified time or specified as smoking before pregnancy, lifetime smoker, smoking during subsequent pregnancy, or at another time (summary RRRs = 1.32 vs. 1.21, P for difference < 0.01). Studies conducted in the United States had a nonsignificantly higher summary relative risk than studies conducted in other countries (P for difference = 0.08). The summary relative risk ratio after converting odds ratios from 24 studies to risk ratios was 1.22 (95% CI: 1.15, 1.29; $n = 50$ studies).

Dose-response analysis. The relative risk increased with increasing numbers of cigarettes smoked per day. For 1–10, 11–19, and 20 or more cigarettes per day, the summary relative risks were 1.08 (95% CI: 0.96, 1.21; $n = 16$ studies), 1.25 (95% CI: 1.17, 1.34; $n = 9$ studies), and 1.42 (95% CI: 1.19, 1.70; $n = 11$ studies), respectively. Figure 3 shows the dose-response relationship with an estimated increment per cigarette of relative risk by 1.01 (95% CI: 1.01, 1.02; $n = 31$ studies). The relationship did not depart significantly from linearity based on the comparison of the log-likelihood for a model with cubic spline variables to that for a model with only a linear term ($P = 0.59$) (32).

Study quality. Studies that specified a gestational age range in their definitions of miscarriage had higher relative risk ratios than studies that did not (summary RRRs = 1.33 vs. 1.15, P for difference = 0.02, Web Table 2). Only 2 studies adjusted at least for maternal age in addition to education or socioeconomic status while not adjusting for prior pregnancy loss. Consequently, studies that adjusted at least for maternal age and did not adjust for prior pregnancy loss were considered to have used the best analytical model. Factors that did not affect the summary relative risk ratios were prospective or biochemical measurement of smoking exposure, adjustment for confounders, having the best analytical model, analysis of only 1 pregnancy per woman, and high (>80%) participation and follow-up rates (all P values > 0.35, Web Table 2).

Assessment of publication bias. Formal statistical tests for publication bias (Egger ordinary least squares regression, the Begg rank correlation, funnel plot weighted least squares regression, and the trim and fill tests) did not demonstrate bias among studies that reported "any active smoking" analyses (all P values > 0.35). The funnel plot was fairly symmetrical, suggesting no major impact of publication bias (Figure 4).

Maternal secondhand smoke exposure

Secondhand smoke exposure was not significantly associated with miscarriage, (Figure 5) (summary RRR = 1.11, 95% CI: 0.95, 1.31; $I^2 = 45\%$; $n = 17$ studies). Using studies that included nonsmokers only or those that adjusted for active smoking did not change the result (summary RRR = 1.13, 95% CI: 0.91, 1.42; $n = 13$ studies). The only study that examined history of miscarriage found that secondhand smoke exposure was associated with increased risk of having a history of miscarriage by 21% ($P < 0.05$) (33). None of the following publication bias tests was statistically significant: the Egger test, Begg rank correlation, funnel plot weighted least squares regression, and the trim and fill test (all P values > 0.5).

DISCUSSION

Most literature reviews published since the 1970s have emphasized inconsistency of the evidence on smoking as a cause of miscarriage (see representative articles (34, 35)), although several have concluded that smoking causes miscarriage (see representative articles (36–38)). Two meta-analyses published in 1984 (39) and 1995 (40) included only 6 and 13 studies, respectively, but found pooled relative risks very similar to the results in the present report (1.24 and 1.32, respectively). This systematic review and meta-analysis

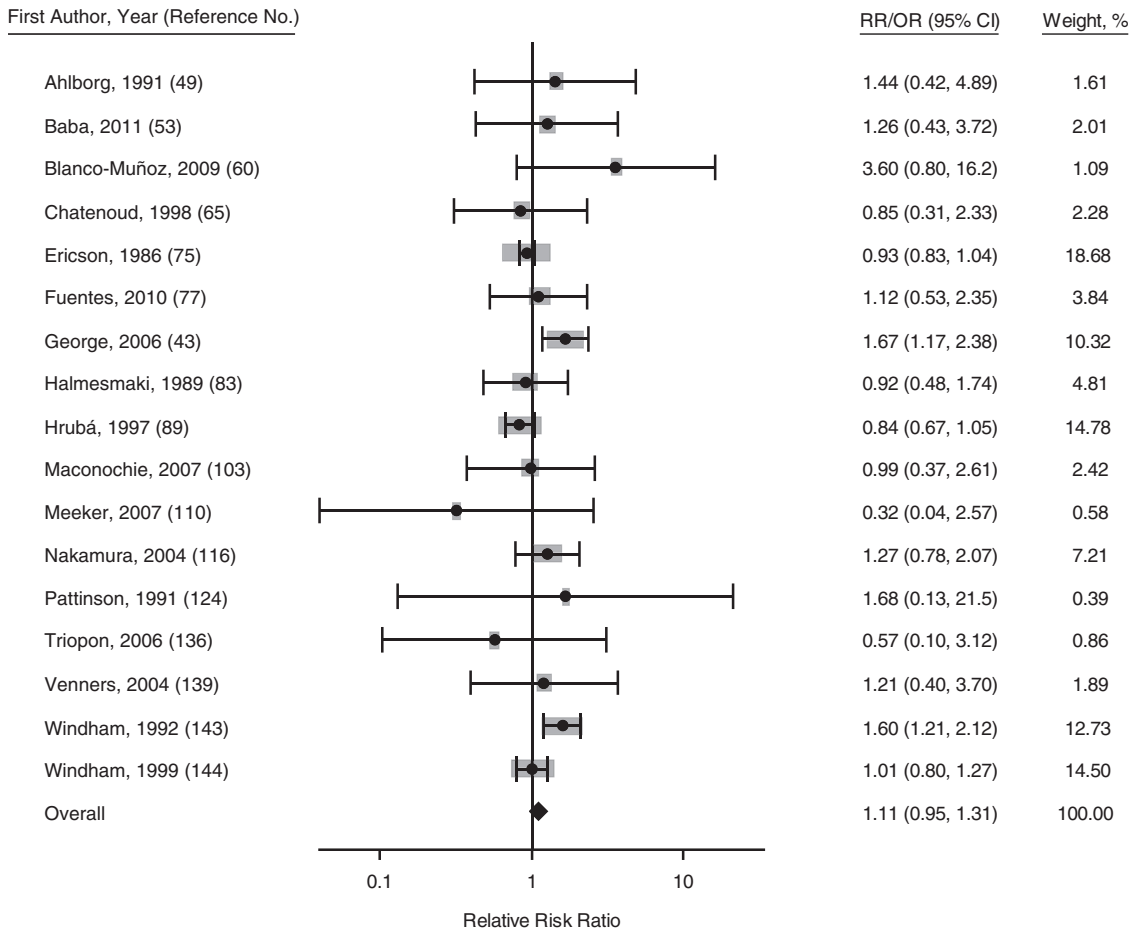

Figure 5. Forest plot for the association between maternal secondhand smoke exposure and risk of miscarriage (150). Gray boxes represent the weight of the study in the meta-analysis. Studies with asterisks have odds ratios (ORs) presented; studies without asterisks have relative risks (RRs) presented. Bars, 95% confidence intervals (CIs).

confirmed an association of maternal smoking during pregnancy with risk for miscarriage and also showed that risk increases with the amount smoked. The results are consistent with either no effect or a modest effect of secondhand smoke exposure on risk of miscarriage (95% CI: 0.95, 1.31).

Like other meta-analyses of observational data, our review has several limitations reflecting the reliance on secondary data gathered from publications. First, we were unable to fully investigate the effect of timing of smoke exposure across pregnancy on miscarriage risk. Although we found that women who had quit smoking were not at increased risk of miscarriage compared with never smokers, whether a woman needs to quit months before pregnancy, weeks into pregnancy, or at some other time to lower risk is currently unknown. Women who quit smoking upon recognition of their pregnancies had a lower risk of miscarriage than did never smokers. However, this result was based on only 4 studies and was not statistically significant. However, if true, this finding may reflect a selection bias, because women who quit upon learning of pregnancy are likely to be particularly health conscious. Lower risks of miscarriage in quitters could also be due to reverse causation, because death of the fetus often precedes clinical miscarriage. Viable pregnancies cause nausea and food aversions and may affect the mother's desire to smoke. Thus, a mother with a viable pregnancy may be more likely to quit than a mother with a nonviable pregnancy, leading to the apparent reduced risk of miscarriage in quitters. Another problem with exposure classification in some studies was the inclusion of occasional or social smokers with nonsmokers for estimation of risks. Such misclassification would bias the total effect of smoking toward the null, leading this meta-analysis to underestimate the true relative risk.

Miscarriage is a heterogeneous clinical entity that is typically classified by the gestational age of the loss and the karyotype of the conceptus. The relative risk of miscarriage for smokers was greater when miscarriage was defined as pregnancy loss with a maximum gestational age of 20 weeks or greater. However, the definition of miscarriage is only a proxy for the gestational ages at which women actually miscarried, and more precise data on gestational age–specific risks would be useful. Three papers examined differences in the effects of smoking on miscarriages classified by karytyope

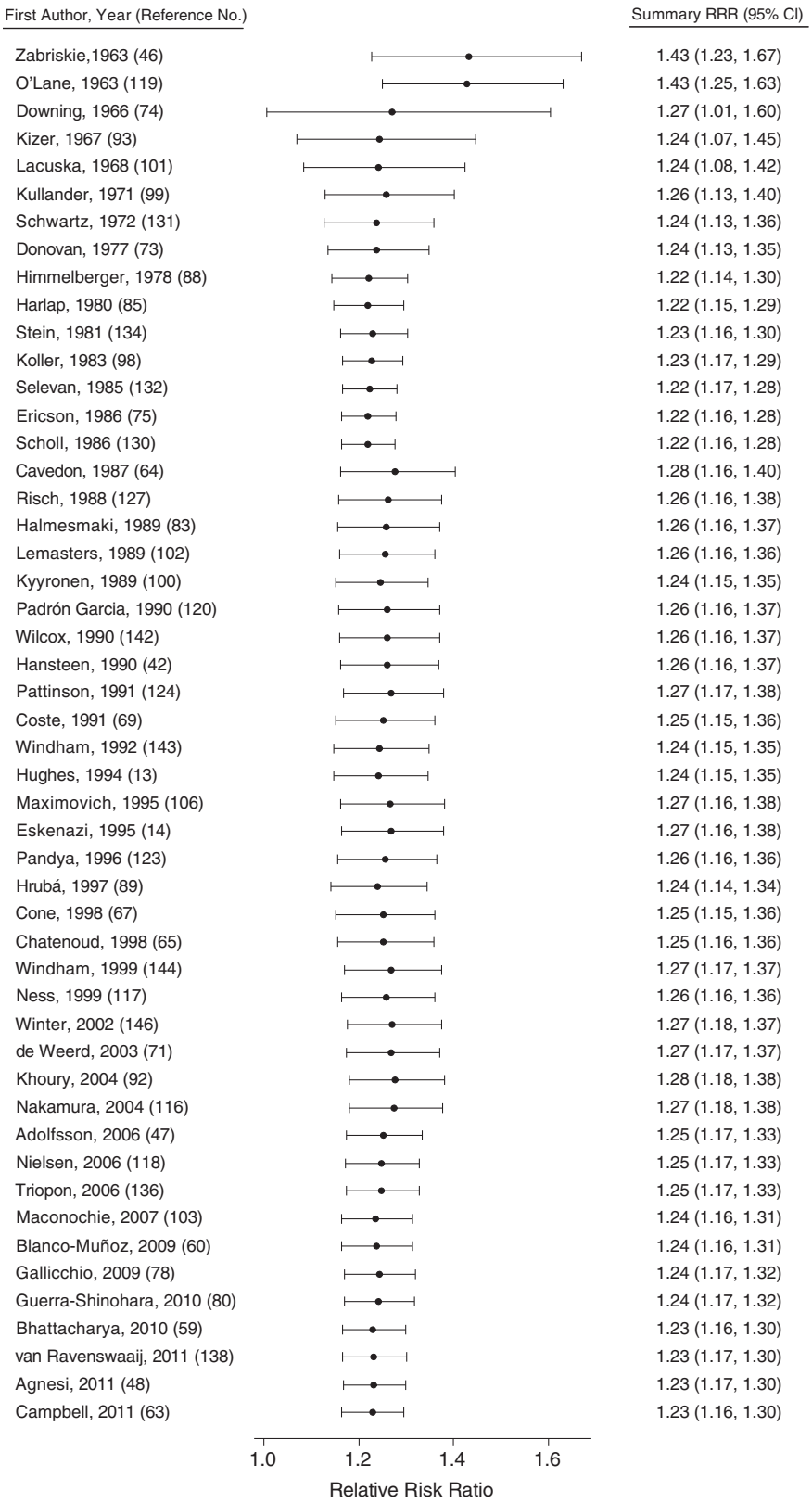

Figure 6. Forest plot for the cumulative meta-analysis of any active maternal smoking and risk of miscarriage (150). Studies are sorted chronologically in order of publication date, and each point represents the summary relative risk ratio (RRR) including all studies published before and including the study listed on the corresponding line. Bars, 95% confidence intervals (CIs).

of the conceptus. These data were not meta-analyzed because the largest such study had data on 10 times more cases than the next largest study. Using 2,305 cases, this study found a case-case odds ratio of 1.2 (95% CI: 0.8, 1.8) for the effect of smoking on miscarriage in normal versus chromosomally aberrant (nontrisomic) losses (41). The results of 2 smaller studies also had small and nonsignificant differences among the effects of smoking on karyotype groups (42, 43).

To examine why previous reviews did not generally conclude that the association between smoking and miscarriage was consistent, we conducted cumulative meta-analyses of the 50 studies that assessed the risk of miscarriage with a report of "any active smoking" (Figure 6). We iteratively combined the estimates from the 50 studies, plotting the cumulative estimate from the first 2 studies through the entire group. This analysis demonstrated that an increased risk of miscarriage has been consistently documented since the publication of the first 2 studies in 1963. The relative risk estimates in the cumulative meta-analysis were all statistically significant and ranged from 1.22 to 1.43.

Thus, the consistency of the pooled estimate has not changed significantly over the last 50 years. Why has consensus not yet been reached on smoking and miscarriage? Comparison of this systematic review with other reviews demonstrates that much of the relevant literature was not included in these earlier reports. For example, only 34 of the 112 articles included in this study were referenced by at least 1 of the US Surgeon General reports on the health effects of smoking published from 1964 to 2010. Many reviews of smoking and pregnancy, environmental exposures and reproduction, and causes of miscarriage have stated that the evidence is inconsistent without conducting systematic reviews. Multiple recent literature reviews that we found cited only 1 or 2 original articles on smoking and miscarriage (44, 45), and some limited their references to prior reviews (36). Despite the reviews that found the evidence to be unconvincing, we demonstrated that the association between smoking and miscarriage, first documented by Zabriskie (46) in 1963, has endured half a century of research.

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