Maternal Age at Birth and Childhood Type 1 Diabetes: A Pooled Analysis of 30 Observational Studies

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OBJECTIVE—The aim if the study was to investigate whether children born to older mothers have an increased risk of type 1 diabetes by performing a pooled analysis of previous studies using individual patient data to adjust for recognized confounders.

RESEARCH DESIGN AND METHODS—Relevant studies published before June 2009 were identified from MEDLINE, Web of Science, and EMBASE. Authors of studies were contacted and asked to provide individual patient data or conduct prespecified analyses. Risk estimates of type 1 diabetes by maternal age were calculated for each study, before and after adjustment for potential confounders. Meta-analysis techniques were used to derive combined odds ratios and to investigate heterogeneity among studies.

RESULTS—Data were available for 5 cohort and 25 case-control studies, including 14,724 cases of type 1 diabetes. Overall, there was, on average, a 5% (95% CI 2–9) increase in childhood type 1 diabetes odds per 5-year increase in maternal age ($P = 0.006$), but there was heterogeneity among studies (heterogeneity $I^2 = 70\%$). In studies with a low risk of bias, there was a more marked increase in diabetes odds of 10% per 5-year increase in maternal age. Adjustments for potential confounders little altered these estimates.

CONCLUSIONS—There was evidence of a weak but significant linear increase in the risk of childhood type 1 diabetes across the range of maternal ages, but the magnitude of association varied between studies. A very small percentage of the increase in the incidence of childhood type 1 diabetes in recent years could be explained by increases in maternal age. ***Diabetes*** **59:486–494, 2010**

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Received 6 August 2009 and accepted 23 October 2009. Published ahead of print at http://diabetes.diabetesjournals.org on 29 October 2009. DOI: 10.2337/db09-1166.

In recent decades, the age at which women give birth has been increasing in many western countries. For instance, between 1987 and 2007, the age of mothers at delivery increased by on average 2.4 years in England and Wales (1), 2 years in Spain (2), and 2.3 years in Norway (3). There has been much research into the consequences of these older delivery ages for the offspring. In particular, studies have shown associations between maternal age and pregnancy complications, including preterm delivery and low-birth-weight babies (4), and various diseases in childhood such as asthma (5), leukemia (6), and central nervous system tumors (6).

Childhood-onset type 1 diabetes is caused by the autoimmune destruction of the pancreatic β-cells. The marked increases in incidence in recent decades (7) suggest the role of environmental factors and, partly because the peak incidence occurs in late childhood, it is thought that exposures in early life could play an important role. Research into the potential role of maternal age in childhood-onset type 1 diabetes began with a case series analysis as early as 1960 (8). In more recent decades, this association has received much attention using more informative case-control (and cohort) designs (9–11). However, this research is difficult to interpret due to the number of studies conducted, the different sizes (and power) of these studies, the seemingly conflicting results of some studies (for instance [10–12]), and the different ways in which associations have been reported.

The aim of this study was to perform a systematic review and meta-analysis to assess the evidence of an association between maternal age and type 1 diabetes, to

explore the shape of any association, and to assess the potential for confounding by relevant factors such as birth weight, gestational age, breast-feeding, and maternal diabetes (13–15).

RESEARCH DESIGN AND METHODS

Literature search. The main literature search was conducted using MEDLINE, through OVID ONLINE, and the strategy was as follows: ("Maternal Age" or maternal age) and ("Diabetes Mellitus, Type 1" or [diabetes and Type 1] or IDDM) using the terms in inverted commas as MEDLINE subject heading key words. Similar searches were conducted on Web of Science and EMBASE. Finally, to identify studies that investigated maternal age along with other risk factors, a more general search was conducted on MEDLINE using the following: ("Diabetes Mellitus, Type 1" and ["Case-Control Studies" or "Cohort Studies"[). The searches were limited to studies on humans published before June 2009. Abstracts were screened independently by two investigators (C.R.C. and C.C.P.) to establish whether the studies were likely to provide relevant data based on the following inclusion criteria: *1*) they identified a group with type 1 diabetes and a group without type 1 diabetes, and *2*) they recorded maternal age in these groups. Studies were excluded if they contained fewer than 100 case subjects (because adjustments for confounders may not perform well in these studies) or if they were family based (because the association between maternal age and type 1 diabetes could be distorted through selecting control subjects from uncompleted families and from among families with an increased genetic susceptibility). Citations generated from the more general MEDLINE search were initially screened to remove obviously irrelevant articles. Finally, the reference lists of all pertinent articles were hand searched and the corresponding author of each included article was asked whether they were aware of any additional studies.

An author from each included study was contacted to provide raw datasets, or estimates from prespecified analyses, for the association between maternal age (in categories: <20, 20–24, 25–29, 30–34, ≥35 years) and type 1 diabetes before and after adjustments for potential confounders (if available). Authors were contacted because categorizations (and adjustments) differed in published reports and some authors did not present any maternal age data, merely reporting findings.

Details of included studies (reported in Table 1) were extracted by one reviewer (C.R.C.) and agreed with the study author.

Statistical analysis. ORs and SEs were calculated for the association between each category of maternal age and type 1 diabetes for each study. Similarly, to investigate the trend across categories of maternal age, an OR (and SE) was calculated per increase in category (corresponding to an approximate 5-year increase in maternal age) using regression models appropriate to the design of the study. Unconditional and conditional logistic regression was used to calculate the ORs and SEs for the unmatched and matched case-control studies, respectively. In cohort studies with various lengths of participant follow-up, Poisson regression was used to estimate rate ratios and their SEs as a measures of association (which should be approximately equal to ORs for a rare disease such as type 1 diabetes [16]). A year of birth term was added to Poisson regression models to adjust the rate ratios for any differences in year of birth between case and control subjects resulting from this study design. Combinations of other potential confounders were added as covariates in the regression models for each study, before random-effects models were used to calculate pooled ORs (17). Tests for heterogeneity were conducted and the I^2 statistic was calculated to quantify the degree of heterogeneity between studies. This statistic measures the percentage of total variation across studies due to heterogeneity. Publication/selection bias was investigated by checking for asymmetry in funnel plots of the study ORs against the SE of the logarithm of the ORs. Rosenthal's "file drawer" method was used to estimate the number of studies averaging no effect that would be required to bring the overall result to nonsignificance (18).

Meta regression techniques (18) were used to investigate whether any association between maternal age and diabetes varied by year of publication or response rates in case and control subjects (because young mothers may be less likely to respond, which could bias results if case and control subjects' response rates differed). Subgroup analyses were conducted by subdividing studies by type and including only studies with a reduced risk of bias (excluding case-control studies with nonpopulation-based or nonrandomly selected control subjects or any study with a response rate of less than 80% in either the case or control subjects). Separate analyses were conducted by age at diagnosis of diabetes. A final sensitivity analysis was conducted including studies in which the required estimates could only be approximated from published reports. In one study (19), the odds ratio per 5-year increase in maternal age was extrapolated from the odds ratio per 1-year increase, combined between males and females, and was available only after adjustment for number of abortions and gestational age. In another (20), the odds ratio per 5-year increase was estimated from the following maternal age categories (15–21, 22–31, 32–41, 42–49, 50–55 years).

All statistical analyses were performed using STATA 9.0 (Stata, College Station, TX).

RESULTS

Search results. The searches identified 89 relevant articles. Thirty-four of these articles were excluded because they contained duplicate or overlapped information. Twelve articles were excluded because they contained information on fewer than 100 case subjects; 11 articles were excluded because they used family-based designs. A full list of the articles identified by the searches is available from the authors.

The remaining 32 articles (9–15,19–43) contained information from 37 independent studies, as information from five centers was taken from one article (14) and information from two centers was taken from another (15). An investigator from each of the 37 studies was invited to provide raw data (or estimates from prespecified analyses), but one author (20) could not be contacted. Table 1 contains the characteristics of 32 studies included in the analysis. In 25 of these studies, full datasets were obtained and in four (12,13,31,33) estimates according to prespecified models were calculated by the study authors from the full datasets (in one [9] the required data were extracted directly from the published report, and in two others [19,20] the required data could only be approximated and so were included only in sensitivity analyses, discussed later).

Overall findings. The associations between maternal age at delivery and type 1 diabetes from the 30 included studies (with 14,724 cases of type 1 diabetes) are shown in Fig. 1. Overall, for each 5-year increase in maternal age at delivery the odds of a child subsequently developing type 1 diabetes increased by on average 5% (OR 1.05 [95% CI 1.02–1.09]; $P = 0.009$). There was, however, marked heterogeneity between studies ($I^2 = 70$, heterogeneity $P < 0.001$). Table 2 shows the unadjusted association between maternal age at delivery and type 1 diabetes by category of maternal age. There was evidence of a fairly linear increase across the categories. Children whose mothers were older than 35 years had on average a 10% increase (OR 1.10 [95% CI 1.01–1.20]; $P = 0.03$) in type 1 diabetes odds compared with children whose mothers were 25–30 years, and there was little evidence of heterogeneity among studies ($I^2 = 20$, heterogeneity $P = 0.16$). Similarly, although not statistically significant ($P = 0.20$), children whose mothers were younger than 20 years had on average a 12% reduction (OR 0.88 [95% CI 0.74–1.04]) in type 1 diabetes odds compared with children whose mothers were 25–30 years, but there was evidence of marked heterogeneity among studies ($I^2 = 64$, heterogeneity $P < 0.001$).

An additional unadjusted analysis (in 26 studies with available data) indicated that, compared with children born to mothers aged 25–30 years, children born to mothers aged 35–40 years had a 12% increase in the odds of diabetes (OR 1.12 [95% CI 1.02–1.23]; $P = 0.02$), whereas children born to mothers older than 40 years had a 9% increase in the odds of diabetes (OR 1.09 [95% CI 0.98–1.21]; $P = 0.11$).

Funnel plots of the association between maternal age and odds of type 1 diabetes were investigated (not shown) and roughly conformed to the expected funnel shape, providing little evidence of asymmetry and therefore little evidence of publication bias. Applying Rosenthal's file

TABLE 1
Characteristics of included studies investigating the association between maternal age and type 1 diabetes, ordered by publication date

			Type 1 diabetic subjects				Control subjects			Available confounders‡					
First author, year* (reference)	Design	Country	Ascertainment method (year case subjects diagnosed)	Age at dx (years)	n†	Resp rate (%)	Source (matching criteria)	n†	Resp rate (%)	BO	BW	GA	MD	CS	BF# (months)
Dahlquist, 1992 (9)	C-C	Sweden	Swedish childhood diabetes register (78–88)	0–14	2,757	98	Medical birth registry (birth year, unit)	8,271	100						
Bock, 1994 (10)	C-C	Denmark	Hosp. admission from National Patient Registry (78–89)	<16	837	98	Birth registry (age, sex)	837	NA						
Patterson, 1994 (11)	C-C	Scotland	Hosp. admission/childhood diabetes register (76–88)	0–14	271	100	Maternal discharge records (age, sex, area)	1,340	100	√	√	√	√	√	√(any)
Wadsworth, 1997 (25)	C-C	U.K.	British Paediatric Association Surveillance Unit (92)	0–5	213	89	Health Authority Immunization Register	318	70	√	√		√		√(4)
Gimeno, 1997 (26)	C-C	Brazil	Diabetes association/ Hospital admission (95)	0–19	344	91	Unclear (neighborhood, sex, age)‖	333	100	√	√		√		√(3)
McKinney, 1999 (28)	C-C	England	Yorkshire Childhood Diabetes Register (93–94)	0–15	220	94	General practitioner's records (age, sex)	423	82	√	√	√	√	√	√(any)
Rami, 1999 (29)	C-C	Austria	Vienna type 1 diabetes register (89–94)	0–14	103	86	Schools (age, sex)	373	80	√	√	√	√§	√	√(any)
Bache, 1999 (19)**	C-C	Denmark	Hospital admission (78–95)	0–14	857	100	Medical birth registry (month, sex, district)	1,404	100			√			
Dahlquist, 1999 (14)	C-C	Bulgaria	W. Bulgaria type 1 diabetes register (91–94)	0–14	125	73	Schools and policlinics (age)	440	79	√	√	√	√§	√	√(any)
	C-C	Latvia	Latvian type 1 diabetes register (89–94)	0–14	140	99	Population register (age)	301	79	√	√	√	√§	√	√(any)
	C-C	Lithuania	Lithuanian type 1 diabetes register (89–94)	0–14	117	94	Policlinics (age)	266	73	√	√	√	√§	√	√(any)
	C-C	Luxembourg	Luxembourg type 1 diabetes register (89–95)	0–14	59	100	Preschools and schools (age)	172	95	√	√	√	√§	√	√(any)
	C-C	Romania	Bucharest type 1 diabetes register (89–94)	0–14	81	74	Preschools and schools (age)	277	81	√	√	√	√§	√	√(any)
Stene, 2001 (13)	Cohort	Norway	Norwegian Childhood Diabetes Registry (89–98)	0–14	1,810	100¶	Norwegian medical birth registry	1,382,602	NA	√	√	√	√	√	
Visalli, 2003 (30)	C-C	Italy	Lazio type 1 diabetes register (89–95)	0–14	139	100	Schools (age)	703	91		√	√	√	√	√(3)
Stene, 2004 (31)	C-C	Norway	Norwegian Childhood Diabetes Registry (98–00)	0–14	346	73	Norwegian population registry	1,626	56	√	√	√	√§	√	√(3)
Sadauskaite-Kuehne, 2004 (15)	C-C	Sweden	SE Sweden type 1 diabetes register (95–00)	0–15	442	100	Population register	1,084	73	√	√	√	√§		√(3)
	C-C	Lithuania	Lithuanian type 1 diabetes register (96–00)	0–15	281	100	Outpatient clinic‖	807	95	√	√	√	√§		√(3)

TABLE 1
Continued

First author, year* (reference)	Design	Country	Type 1 diabetic subjects: Ascertainment method (year case subjects diagnosed)	Age at dx (years)	n†	Resp rate (%)	Control subjects: Source (matching criteria)	n†	Resp rate (%)	Available confounders‡: BO	BW	GA	MD	CS	BF# (months)
Sumnik, 2004 (32)	C-C	Czech Republic	Czech Republic type 1 diabetes registry (95–00)	0–15	640	79	National Birth registry (age)	32,000	100	√					
Marshall, 2004 (33)	C-C	England	Morecambe Bay/E. Lancashire diabetes clinics (98)	0–15	196	83	Health Authorities (sex, birth date)	381	53	√	√	√	√§		√(any)
Cardwell, 2005 (34)	Cohort	N. Ireland	N. Ireland type 1 diabetes register (71–01)	0–14	990	92¶	Northern Ireland Child Health register	439,647	NA	√	√	√	√	√	√(any)
Sipetić, 2005 (35)	C-C	Serbia	Belgrade Hospital admission (94–97)	0–16	105	91	Hospital outpatients with skin disease‖ (age, sex, area)	210	100	√	√	√	√§	√	√(4)
Svensson, 2005 (36)	C-C	Denmark	Danish register of childhood diabetes (96–99)	0–14	602	100	Danish population register (age, sex)	1,459	100	√	√	√	√	√	√(4)
Bottini, 2005 (20)**	C-C	Sardinia	Hospital diagnosis	?	189	?	Consecutive births in northern Sardinia	5,460	?						
Polańska, 2006 (37)	C-C	Poland	Upper Silesia Diabetes Register (89–96)	0–14	394	87	Central Bureau for Statistics	994,460	100	√	√				
Wei, 2006 (38)	C-C	Taiwan	School-based urine screening program & questionnaire (92–97)	0–18	260	87	Randomly selected negatives from screening program	533	88	√	√	√	√		√(3)
Tenconi, 2007 (39)	C-C	Italy	Pavia type 1 diabetes register (88–00)	0–19	99	85	Hospital (age, sex, week)	194	?	√					
Haynes, 2007 (40)	Cohort	Australia	W. Australian Children's Diabetes Register (80–02)	0–14	926	99¶	W. Australia Midwives' Notification System	~557,707	NA	√	√	√	√		
Ievins, 2007 (41)	Cohort	England	Hosp. admission [ICD diabetes code] (63–99)	0–14	410	—	Oxfordshire/W. Berkshire maternity records	266,665	NA	√	√	√	√	√	√(any)
Borras Perez, 2007 (42)	C-C	Spain	Catalonia type 1 diabetes register (97–08)	0–14	626	72	Catalonia Public Health Birth Register	3,320	98		√	√			√(any)
Rosenbauer, 2008 (12)	C-C	Germany	Nationwide hosp. based surveillance (92–95)	0–4	747	71	Local registration offices (age, sex, area)	1,820	43	√	√		√§		√(4)
Waldhoer, 2008 (43)	Cohort	Austria	Austrian diabetes register (89–05)	0–5	444	85¶	Birth certificate registry	1,435,385	NA	√	√	√			

*Year of publication. †Number included in analysis of maternal age. ‡Tick denotes data recorded in study and available for analysis. §Maternal type 1 diabetes used in analyses. ‖Not randomly selected and population based. ¶Percentage of case subjects identified in cohort. #Duration of breast-feeding used in adjusted analysis shown in brackets. **Only included in sensitivity analyses. dx, diagnosis; Resp, response; BF, breast-feeding (in months); BO, birth order; BW, birth weight; C-C, case-control; CS, cesarean section; GA, gestational age; Hosp., hospital; MD, maternal diabetes; NA, not applicable.

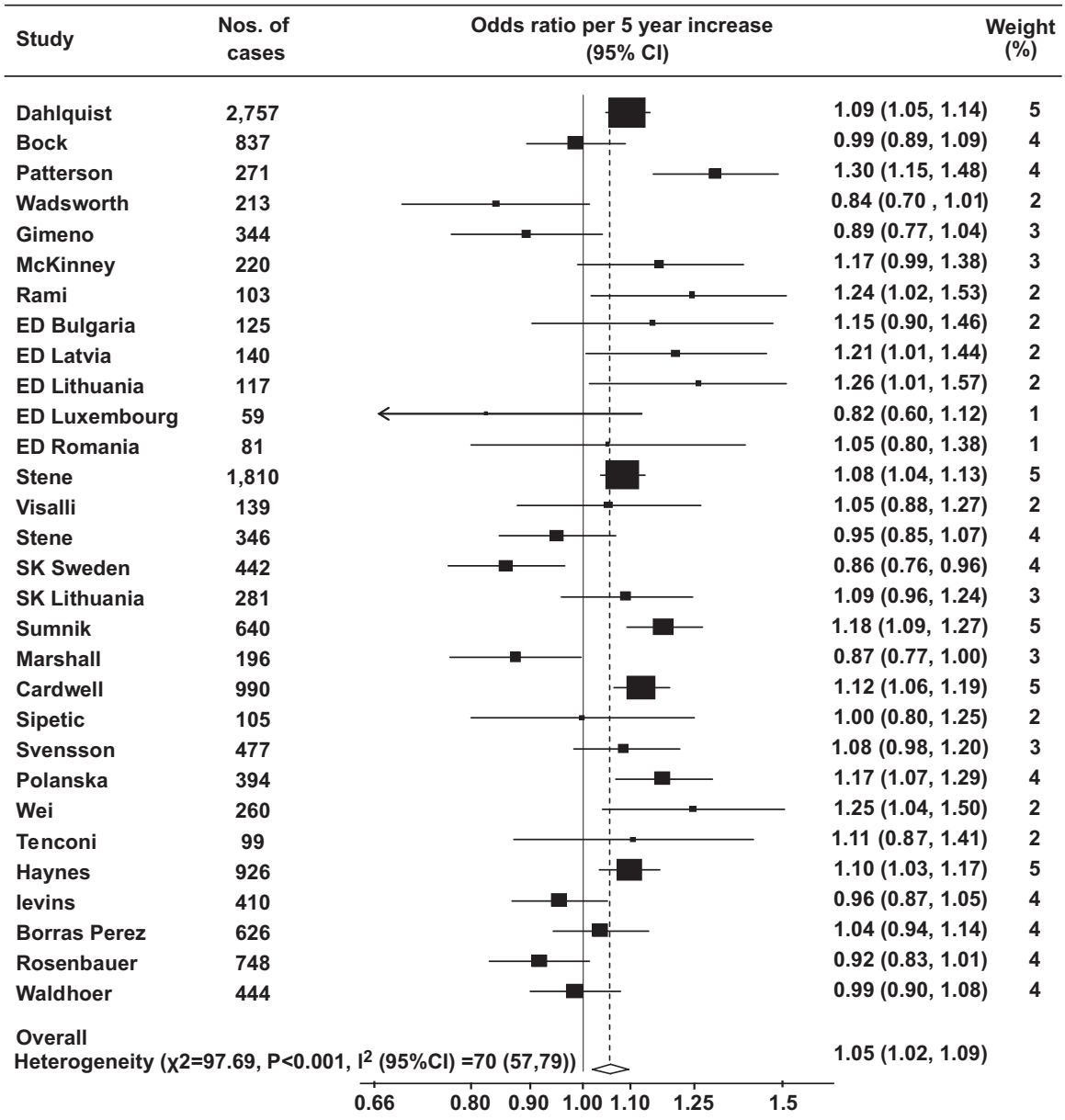

FIG. 1. Meta-analysis of the unadjusted association between maternal age (per 5-year increase) and type 1 diabetes (including 14,724 case subjects) using the random effects model; studies are ordered by publication date.

drawer method, ~205 studies averaging no association between maternal age and type 1 diabetes would need to have been conducted but not published (or identified by the searches) to bring the pooled OR, of 1.05 per 5-year increase, to nonsignificance.

Table 2 also shows the findings for maternal age analysis after adjustment for potential confounders. The association between type 1 diabetes and maternal age was little altered after adjustment for birth order, birth weight, and gestational age, in 20 studies in which these variables were available. In 30 studies, adjustments were made for all available confounders, which also included breast-feeding, cesarean section, and maternal diabetes for some studies (see Table 1 for information on the confounders available in each study), and again the findings were little altered.

Investigation of heterogeneity. There was evidence that some of the heterogeneity in the association between maternal age and diabetes could be explained by differences in response rates between case and control subjects (shown in Table 1). Figure 2 shows that studies in which control subjects had a lower response rate than case subjects were less likely to observe an increase in diabetes risk with maternal age, whereas studies in which case subjects had a lower response rate than control subjects observed more marked increases in diabetes risk with maternal age (meta-regression slope $P = 0.02$). There was an estimated 6% increase (OR 1.06 [95% CI 1.02–1.10]) in diabetes odds per 5-year increase in maternal age when the response rates in the case and control subjects were equal (obtained from the intercept of the fitted meta-regression slope shown in Fig. 2). Similarly, the association between maternal age and diabetes varied by the response rate in the control subjects as studies with lower control response rates observed weaker associations with

TABLE 2
Meta-analyses of 30 studies investigating the association between maternal age and type 1 diabetes before and after adjustments for recorded confounders and in subgroups defined by study type and quality

Maternal age (years)	Case subjects (n)	Combined OR (95% CI)	P	Heterogeneity χ^2 (P)	Heterogeneity I^2
Overall (n = 30 studies)					
<20	764	0.88 (0.74−1.04)	0.12	81.4 (<0.001)	64
20–25	3,919	0.95 (0.89−1.00)	0.05	36.1 (0.17)	20
25–30	5,433	1.00 (ref.)			
30–35	3,274	1.05 (0.97−1.13)	0.28	59.1 (0.001)	51
≥35	1,334	1.10 (1.01−1.20)	0.03	36.4 (0.16)	20
Per 5-year increase	14,724	1.05 (1.02−1.09)	0.006	97.7 (<0.001)	70
Adjusted for gestational age, birth weight, and birth order*(n = 20 studies)					
<20	403	0.95 (0.77−1.17)	0.65	42.7 (0.001)	56
20–25	1,846	0.90 (0.84−0.97)	0.003	20.9 (0.34)	9
25–30	2,826	1.00 (ref.)			
30–35	1,709	1.05 (0.93−1.19)	0.40	46.4 (<0.001)	59
≥35	737	1.12 (0.97−1.29)	0.14	33.0 (0.024)	42
Per 5-year increase	7,521	1.06 (1.00−1.12)	0.05	66.5 (<0.001)	71
Adjusted for all available confounders as shown in Table 1 (n = 30 studies)					
<20	736	0.89 (0.74−1.07)	0.22	88.9 (<0.001)	67
20–25	3,715	0.93 (0.87−0.99)	0.02	36.2 (0.17)	20
25–30	5,147	1.00 (ref.)			
30–35	3,105	1.08 (0.99−1.18)	0.10	62.4 (<0.001)	54
≥35	1,251	1.12 (1.02−1.24)	0.02	39.9 (0.09)	27
Per 5-year increase	13,954	1.06 (1.01−1.11)	0.01	116.9 (<0.001)	75
Cohort studies (n = 5 studies)					
<20	269	0.80 (0.65−0.99)	0.04	9.3 (0.06)	57
20–25	1,105	0.89 (0.82−0.96)	0.003	3.8 (0.43)	0
25–30	1,681	1.00 (ref.)			
30–35	1,057	0.99 (0.88−1.12)	0.93	8.7 (0.07)	54
≥35	468	1.08 (0.96−1.22)	0.21	5.2 (0.26)	23
Per 5-year increase	4,580	1.06 (1.01−1.11)	0.03	12.7 (0.01)	69
Case-control studies (n = 25 studies)					
<20	495	0.91 (0.73−1.14)	0.41	71.5 (<0.001)	66
20–25	2,814	0.97 (0.91−1.05)	0.47	28.9 (0.22)	17
25–30	3,752	1.00 (ref.)			
30–35	2,217	1.07 (0.97−1.19)	0.20	49.6 (0.002)	52
≥35	866	1.12 (0.99−1.25)	0.07	30.9 (0.16)	22
Per 5-year increase	10,144	1.05 (1.00−1.11)	0.04	84.6 (<0.001)	72
Studies with a low risk of bias† (n = 14 studies)					
<20	518	0.81 (0.70−0.94)	0.005	20.8 (0.08)	38
20–25	2,547	0.90 (0.86−0.96)	<0.001	9.3 (0.75)	0
25–30	3,648	1.00 (ref.)			
30–35	2,195	1.08 (0.99−1.18)	0.10	23.8 (0.03)	45
≥35	904	1.18 (1.06−1.32)	0.003	18.3 (0.14)	29
Per 5-year increase	9,812	1.10 (1.06−1.14)	<0.001	27.6 (0.01)	53

*Includes only studies for which adjustments for birth weight (in categories <2.5, 2.5−3, 3−3.5, 2−4.5, >4.5 kg), gestational age (in categories ≤ 37, 38−41, ≥42 weeks), and birth order (in categories first, second, or third born or later) could be made. †Excluding case-control studies that have control subjects who were not randomly selected (or population based) or studies in which the response rate in either the case or control subjects was less than 80% (or unknown) as shown in Table 1.

maternal age (meta-regression slope $P = 0.004$). There was no evidence of any association between the odds of diabetes per 5-year increase in maternal age and publication year (meta-regression slope $P = 0.43$) or the midyear of case subject recruitment in each study (meta-regression slope $P = 0.27$).

Subgroup analyses by type of study are also contained in Table 2. The main findings were similar in cohort and case-control studies, showing a 6 and 5% increase in type 1 diabetes odds per 5-year increase in maternal age, respectively, and both showing marked heterogeneity ($I^2 = 69$ and $I^2 = 72$, respectively).

A separate analysis, contained in Table 2, included only studies with a low risk of bias (excluding case-control studies with nonpopulation-based or nonrandomly selected control subjects and excluding studies with a response rate of less than 80% in either the case or control group). Overall, in the 14 studies with a low risk of bias there was a more marked increase in type 1 diabetes odds of ~10% (OR 1.10 [95% CI 1.06–1.14]) per 5-year increase in maternal age. There was also slightly less between-study heterogeneity, particularly when analysis was considered by category of maternal age.

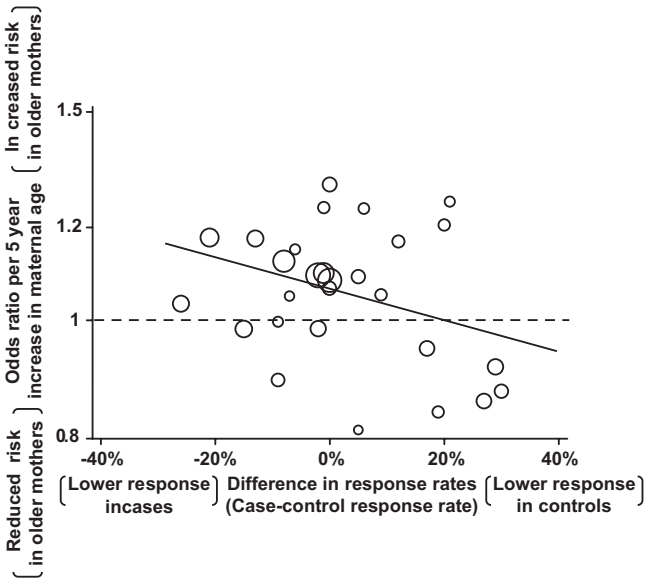

FIG. 2. Scatter plot of odds ratio for diabetes per 5-year increase in maternal age by difference in response rates between case and control subjects (size of plotting symbol was proportional to precision of study; line was taken from meta-regression).

Association by age at diagnosis and by birth order. There was little evidence of a difference in the association between childhood type 1 diabetes and maternal age in early diagnosed diabetes (i.e., younger than 5 years) and later diagnosed diabetes (i.e., between 5 and 15 years) in 23 studies in which these data were available. Specifically, for each 5-year increase in maternal age, there was on average a 5% (OR 1.05 [95% CI 1.00–1.10]) increase in early diagnosed disease and a 7% (OR 1.07 [95% CI 1.01–1.13]) increase in later diagnosed disease.

Also, there was little evidence of a difference in the association with maternal age by birth order in 21 studies for which these data were available. In first borns, there was an 8% (OR 1.08 [95% CI 0.99–1.17]) increase in diabetes odds for each 5-year increase in maternal age, in second borns there was a 12% (OR 1.12 [95% CI 1.03–1.22]) increase in odds for each 5-year increase, and in third or later borns there was a 9% (OR 1.09 [95% CI 1.00–1.19]) increase in odds for each 5-year increase.

Other studies. There were seven studies (19–24,27) that could not be included in the main analysis. A final sensitivity analysis was conducted, including two of these studies for which the required data could be approximated from published reports (19,20). The inclusion of the Danish study (19) had little impact on the findings (overall OR 1.06, $I^2 = 71$). However the further addition of the Sardinian study (20) led to a marked increase in the combined odds of diabetes per 5-year increase in maternal age (overall OR 1.11 [95% CI 1.04–1.18]) and a marked increase in the heterogeneity of the results ($I^2 = 92$). This was because the results of the Sardinian study (20) were markedly different from every other study in the review, as the researchers observed an ~4.5-fold increase (OR 4.5 [95% CI 3.85–5.31]) in diabetes odds per 5-year increase in maternal age, primarily because more than 89% of case subjects in Sardinia had mothers older than 32 years at birth, compared with less than 31% in the 30 studies in the main analysis.

There were five studies (21–24,27) from which data could not be obtained from authors (or extracted from the published reports). One from Colorado (21) (including 268 case subjects) observed a similar proportion of mothers of case and control subjects older than 30 years (25 versus 22%, respectively), whereas another from Colorado (24) (containing 221 case subjects, some of whom may have been in the earlier study) observed a similar mean maternal age in case compared with control subjects (26 vs. 27 years, respectively). A Hungarian study (23) (containing 163 case subjects) also showed a similar mean maternal age in case compared with control subjects (26 vs. 27 years). A Finnish study (including 750 case subjects) (27) reported "no difference between the diabetic subjects and the control subjects in any of the ... neonatal variables [which included age of the mother (<30 versus ≥30 years)]." Finally, an Australian study (including 217 case subjects) (22) also showed a similar median maternal age in case and control subjects (26 vs. 27 years, respectively).

DISCUSSION

This review provides evidence that children born to older mothers have an increased risk of childhood type 1 diabetes. On average, the risk of childhood diabetes increased by 5% for each 5-year increase in maternal age but this association varied between studies. Some of this variation could be explained by the response rates of included studies, possibly due to the lack of participation of younger mothers, particularly in control subjects. In studies with a low risk of bias, there was a more marked increase in diabetes risk of ~10% per 5-year increase in maternal age. The observed association between maternal age and diabetes could not be explained by birth order, birth weight, gestational age, cesarean section delivery, maternal diabetes, or breast-feeding.

This is, to our knowledge, the first systematic review and meta-analysis of the association between maternal age at birth and risk of type 1 diabetes in children. A major strength of this review is that it contains data from up to 14,724 case subjects from 30 studies, of which 29 supplied individual patient data or conducted prespecified analyses, allowing a unified analytic approach and additional analyses to investigate potential sources of bias. Although no data were available from 5 (21–24,27) of the 37 identified studies, most were relatively small and unlikely to alter the overall estimates by much. Furthermore, the results of these studies are largely consistent with the review findings. Despite little evidence from the funnel plots, there remains the possibility of publication bias (that studies showing no association were conducted but not published). Also, although our search strategy was comprehensive, studies containing relevant data may not have been identified. However, there would have to be many such studies or the studies would have to be large and to have observed markedly different associations to influence our overall findings.

The observed variation in the association between maternal age and childhood type 1 diabetes between studies could be due to real differences in different populations or biases specific to each study. It has previously been suggested that the nonparticipation of younger mothers in studies of maternal age and childhood disease can induce bias if case and control subjects' response rates differ (44). For studies with a low control subject and high case subject response rate (right side of Fig. 2), the age of control mothers included in the study will be artificially increased (biases upward) if young mothers tend not to

participate. Consequently, a true positive association between the disease and maternal age will be underestimated. The opposite bias occurs if there is a high control subject and low case subject response rate (left side of Fig. 2), resulting in a true positive association being overestimated. This nonresponse bias explains some of the variation in the association between maternal age and diabetes among studies. However, even in studies with a lower risk of this and other biases (due to higher response rates and randomly selected control subjects), there remained some heterogeneity. Interestingly, in studies with a low risk of bias there was a more marked increase in diabetes risk in older mothers of around 10% per 5-year increase.

The mechanism behind the increased risk of childhood type 1 diabetes in children born to older mothers is unclear. It is likely that maternal age is only a marker of some other factor more directly related to the risk of type 1 diabetes in children. Studies (4,45) have shown that older maternal age at delivery can lead to preterm births and low-birth-weight babies, but because we were able to adjust for these factors their involvement is unlikely. Higher maternal age may be a result of longer maternal education, and consequently higher social class, but previous studies have shown conflicting results for the association between type 1 diabetes risk and status (11,12,25,41). The offspring of older mothers may also be less likely to be breast-fed, or may be breast-fed for a shorter period, which may increase diabetes risk, but adjustments for breast-feeding had little impact on the observed association. Although children with older mothers are more likely to have older fathers, there is no clear association between paternal age at delivery and type 1 diabetes (10,11,19,28,34). Alternatively, previous studies have suggested that maternal age may be a marker for accumulated exposures, such as infections or environmental toxins (13). Another study speculated that older age at delivery may be associated with increased maturation of the immune system in the offspring, potentially increasing predisposition to type 1 diabetes in later life (46). It is also possible that maternal weight, which may increase with maternal age, could be involved, as a recent study found both maternal prepregnancy BMI and maternal weight gain during pregnancy to predict diabetes-associated islet autoimmunity in genetically susceptible children (47). Chromosomal aberrations are known to be more common in fetuses of mothers of advanced age, but such a mechanism is not known to operate in type 1 diabetes, and does not fit the apparent linear relation with risk of type 1 diabetes across the span of ages. It is possible to speculate that maternal microchimerism may be involved, as a recent study suggests that type 1 diabetic patients have higher levels of maternal microchimerism (48), but we are not aware of any data suggesting that maternal microchimerism is related to maternal age at birth.

A previous family-based study suggested that the observed increases in the incidence of type 1 diabetes in recent decades could be explained partly by increases in maternal age (46), although there were methodological problems in the researchers' analysis that led their original estimate of the influence of maternal age to be revised downward (49). However, using the overall estimates from this meta-analysis, in England and Wales there would be only an ~2% increase in childhood-onset type 1 diabetes between 1989 and 2003 due solely to increases in maternal age over this period (based upon national data [1]). As registry data indicate that childhood-onset type 1 diabetes in England and Wales increased by ~55% over this 15-year period (7), it is clear that maternal age explains hardly any of the increasing incidence and other factors must be responsible.

Our study suggests that the association between type 1 diabetes and maternal age is similar in children diagnosed younger than 5 and between 5 and 15 years. However, we did not include studies of older type 1 diabetic patients, and a previous study of maternal age in young adults with diabetes did not find much evidence of an association (50).

In conclusion, there is evidence of a weak but significant relation between age at birth and the risk of type 1 diabetes in children. Across the maternal age range, there is an ~20% difference in the risk of type 1 diabetes. Based upon these estimates, a very small percentage of the increasing incidence of children onset type 1 diabetes could be explained by increasing maternal age.

ACKNOWLEDGMENTS

We acknowledge support from the following: the Czech Republic Ministry of Education (Grant MSM 0021620814), Department of Health of Catalonia (C. Castell MD, PhD, Barcelona, Spain), Department of Health of Taiwan (DOH 90-TD1028), Fundacao de Amparo a Pesquisa do Estado de Sao Paulo (Grant 94/0943-0), the Centro Internazionale Studi Diabete (Italy, Rome), The Swedish Child Diabetes Foundation, the National Health Service (NHS) National Coordinating Centre for Research Capacity Development U.K., the Research Council of Norway, the German Research Foundation (Grant HE 234/1-1), the Ministry for Science and Technological Development of Serbia (no. 145084, 2006-2010), EUBIROD funded by the European Commission Health Information Strand (DG-SANCO 2005, contract no. 2007115), Diabetes U.K., and the Northern Ireland Department of Health and Social Services.

No potential conflicts of interest relevant to this article were reported.

We thank G. Soltész MD (University of Pecs, Pecs, Hungary) and G. Dahlquist MD, PhD (Umea University, Umea, Sweden), coordinators of the EURODIAB Substudy 2.

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