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Maternal age at birth and childhood type 1 diabetes: A pooled analysis of 30 observational studies

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Running title: Maternal age at birth and type 1 diabetes

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Abstract

Objective: To investigate whether children born to older mothers have an increased risk of type 1 diabetes by performing a meta-analysis using individual patient data to adjust for recognised 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 pre-specified analyses. Risk estimates of type 1 diabetes by category of maternal age were calculated for each included study, before and after adjustment for potential confounders. Meta-analysis techniques were used to derive combined odds ratios, and investigate heterogeneity between 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 between 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.

KEYWORDS: Diabetes Mellitus, Type 1, Epidemiology, maternal age.

In recent decades the age at which women give birth has been increasing in many western countries. For instance, between 1987 to 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 CNS tumors (6).

Childhood onset type 1 diabetes is caused by the autoimmune destruction of the pancreatic beta 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: ('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: ('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 (CRC and CCP) to establish if 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 cases (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 controls from uncompleted families and from amongst 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 if they were aware of any additional studies.

An author from each included study was contacted to provide raw data sets, or estimates from pre-specified 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 categorisations (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 (CRC) and agreed with the study author.

Statistical analysis

Odds ratios (ORs) and standard errors (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 varying length 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 cases and controls 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 (18). 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 standard error of the logarithm of the ORs .

Meta regression techniques (19) were used to investigate whether any association between maternal age and diabetes varied by year of publication or response rates in cases and controls (because young mothers may be less likely to respond, which could bias results if cases and control response rates differed). Subgroup analyses were conducted subdividing studies by type and including only studies with a reduced risk of bias (excluding case-control studies with non-population based or non-randomly selected controls or any study with a response rate of less than 80% in either the cases or controls). 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 (20) 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 only available after adjustment for number of abortions and gestational age. In another (21) 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 cases, eleven articles were excluded because they utilised family based designs. A full list of the papers identified by the searches is available from the authors.

The remaining 32 articles (9-15;20-44) contained information from 37 independent studies, as information from five centres was taken from one article (14) and information from two centres was taken from another (15). An investigator from each of the 37 studies was invited to provide raw data (or estimates from pre-specified analyses), but one author (21) 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;32;34) pre-specified estimates were calculated by the study authors (in one (9) the required data was extracted directly from the published report and in two others (20;21) the required data could only be approximated and so were only included 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 Figure 1. Overall, for each 5 year increase in maternal age at delivery the odds ~~risk~~ 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 over 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 risk compared with children whose mothers were 25 to 30 years and there was little evidence of heterogeneity between studies (I^2=20, heterogeneity P=0.16). Similarly, though not statistically significant (P=0.20), children whose mothers were under 20 had on average a 12% reduction (OR=0.88, 95% CI 0.74, 1.04) in type 1 diabetes odds risk compared with children whose mothers were 25 to 30 years, but there was evidence of marked heterogeneity between studies (I^2=64, heterogeneity P<0.001).

An additional analysis (in 26 studies with available data) indicated that, compared with children born to mothers aged 25 to 30 years, children born to mothers aged 35 to 40 years had a 12% increase in the odds of diabetes (OR=1.12 95%CI 1.02, 1.23; P=0.014) while children born to mothers over 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 risk 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.

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

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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 breastfeeding, 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 cases and controls (shown in Table 1). Figure 2 shows that studies in which controls had a lower response rate than cases were less likely to observe an increase in diabetes risk with maternal age, while studies in which cases had a lower response rate than controls 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 risk per 5 year increase in maternal age when the response rates in the cases and controls were equal (obtained from the intercept of the fitted meta-regression slope shown in Figure 2b). Similarly, the association between maternal age and diabetes varied by the response rate in the controls as studies with lower control response rates observed weaker associations with maternal age (meta-regression slope P=0.004). There was no evidence of any association between the odds risk of diabetes per 5 year increase in maternal age and publication year (meta-regression slope P=0.43) or the mid-year of case 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 non-population based or non-randomly selected controls and excluding studies with a response rate of less than 80% in either the case group 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 around 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.

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. under 5 years) and later diagnosed diabetes (i.e. between 5 and 15 years) in 23 studies where 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 ~~risk~~ 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 7 studies (20-25;28) which 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 (20;21). The inclusion of the Danish study (20) had little impact on the findings (overall OR=1.06, I^2=71). However the further addition of the Sardinian study (21) lead to a marked increase in the combined odds ~~risk~~ 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 (21) were markedly different from every other study in the review as they observed an approximate 4.5 fold increase (OR 95%CI 3.85, 5.31) in diabetes odds ~~risk~~ per 5 year increase in maternal age primarily because over 89% of cases in Sardinia had mothers over 32 at birth, compared with less than 31% in the 30 studies in the main analysis.

There were five studies (22-25;28) from which data could not be obtained from authors (or extracted from the published reports). One from Colorado (22) (including 268 cases) observed a similar proportion of mothers of cases and controls over 30 years (25% versus 22%, respectively) whilst another from Colorado (25) (containing 221 cases some of whom may have been in the earlier study) observed a similar mean maternal age in cases compared with controls (26 years versus 27 years, respectively). A Hungarian study (24) (containing 163 cases) also showed a similar mean maternal age in cases

compared with controls (26 versus 27 years). A Finnish study (including 750 cases) (28) reported 'no difference between the diabetic subjects and the control subjects in any of the … neonatal variables [which included age of the mother (<30 vs. ≥ 30 years)]'. Finally, an Australian study (including 217 cases) (23) also showed a similar median maternal age in cases and controls (26 versus 27 years, respectively).

Conclusions

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 controls. In studies with a low risk of bias, there was a more marked increase in diabetes risk of around 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 cases from 30 studies, of which 29 supplied individual patient data or conducted pre-specified analyses, allowing a unified analytic approach and additional analyses to investigate potential sources of bias. Although no data were available from five (22-25;28) 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

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identified. However, such 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 non-participation of younger mothers in studies of maternal age and childhood disease can induce bias if case and control response rates differ (45). For studies with a low control and high case response rate (right side of Figure 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 and low case response rate (left side of Figure 2) resulting in a true positive association being overestimated. This non-response bias explains some of the variation in the association between maternal age and diabetes between studies. However, even in studies with a lower risk of this and other biases (due to higher response rates and randomly selected controls) 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;46) have shown that older maternal age at delivery can lead to preterm births and low birth weight babies but as 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;26;42). The offspring of older mothers may also be less likely to be breastfed, or may be breastfed for a shorter period, which may increase diabetes risk but adjustments for breastfeeding 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;20;29;35). Alternatively, previous studies have suggested that maternal age may be a marker for accumulated exposures such as infections or environmental toxins (13). Another speculated that older age at delivery may be associated with increased maturation of the immune system in their offspring potentially increasing predisposition to type 1 diabetes in later life (47). It is also possible that maternal weight, which increases with age, could be involved. 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 diabetes 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 partly be explained by increases in maternal age (47) although there were methodological problems in their analysis which

lead their original estimate of the influence of maternal age to be revised downwards (49). However, using the overall estimate from this meta-analysis, in England and Wales there would only be approximately a 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 around 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 under 5 and between 5 and 15 years old. However, we did not include studies of older type 1 diabetes 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 around a 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.

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

First author, year* (reference)	Design	Country	Type 1 diabetes Ascertainment method (year cases diagnosed)	Age at dx (years)	n†	Resp. rate (%)	Controls Source (matching criteria)	n†	Resp. rate (%)	BO	BW	GA	MD	CS	BF (mths)
Dahlquist, 1992 (9)	C-C	Sweden	Swedish childhood diabetes register (78-88)	0-14	2757	98	Medical birth registry (birth year, unit)	8271	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)	1340	100	✓	✓	✓	✓	✓	✓(any)
Wadsworth, 1997 (26)	C-C	UK	British Paediatric Association Surveillance Unit (92)	0-5	213	89	Health Authority Immunization Register	318	70	✓	✓		✓		✓(4)
Gimeno, 1997 (27)	C-C	Brazil	Diabetes association / Hospital admission (95)	0-19	344	91	Unclear (neighborhood, sex, age)‖	333	100	✓	✓				✓(3)
McKinney, 1999 (29)	C-C	England	Yorkshire Childhood Diabetes Register (93-94)	0-15	220	94	General practitioner's records (age, sex)	423	82	✓	✓	✓	✓	✓	✓(any)
Rami, 1999 (30)	C-C	Austria	Vienna Type 1 diabetes register (89-94)	0-14	103	86	Schools (age, sex)	373	80	✓	✓	✓	✓§	✓	✓(any)
Bache, 1999 (20)**	C-C	Denmark	Hospital admission (78-95)	0-14	857	100	Medical birth registry (month, sex, district)	1,404	100				✓		
Eurodiab, 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	Pre-schools and schools (age)	172	95	✓	✓	✓	✓§	✓	✓(any)
	C-C	Romania	Bucharest Type 1 diabetes register (89-94)	0-14	81	74	Pre-schools 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 (31)	C-C	Italy	Lazio Type 1 diabetes register (89-95)	0-14	139	100	Schools (age)	703	91		✓	✓	✓		✓(3)
Stene, 2004 (32)	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	S.E. Sweden Type 1 diabetes register (95-00)	0-15	442	100	Population register	1084	73	✓	✓	✓	✓§		✓(3)
	C-C	Lithuania	Lithuanian Type 1 diabetes register (96-00)	0-15	281	100	Outpatient clinic‖	807	95	✓	✓	✓	✓§		✓(3)
Sumnik, 2004 (33)	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 (34)	C-C	England	Morecambe Bay / E. Lancashire diabetes clinics (98)	0-15	196	83	Health Authorities (sex, birth date)	381	53	✓	✓	✓	✓§		✓(any)
Cardwell, 2005 (35)	Cohort	N. Ireland	N. Ireland Type 1 diabetes register (71-01)	0-14	990	92¶	Northern Ireland Child Health register	439,647	NA	✓	✓	✓	✓	✓	✓(any)
Sipetic, 2005(36)	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(37)	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 (21)**	C-C	Sardinia	Hospital diagnosis	?	189	?	Consecutive births in northern Sardinia	5460	?						
Polanska,2006 (38)	C-C	Poland	Upper Silesia Diabetes Register (89-96)	0-14	394	87	Central Bureau for Statistics	994,460	100	✓	✓				
Wei, 2006 (39)	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 (40)	C-C	Italy	Pavia Type 1 diabetes register (88-00)	0-19	99	85	Hospital (age, sex, week)	194	?	✓					
Haynes, 2007 (41)	Cohort	Australia	W. Australian Children's Diabetes Register (80-02)	0-14	926	99¶	W. Australia Midwives' Notification System	≈557,707	NA	✓	✓	✓	✓		
Ievins, 2007 (42)	Cohort	England	Hosp. admission [ICD diabetes code] (63-99)	0-14	410	-	Oxfordshire/W. Berkshire maternity records	266,665	NA	✓	✓	✓	✓	✓	✓(any)
Borras Perez, 2007 (43)	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 (44)	Cohort	Austria	Austrian diabetes register (89-05)	0-5	444	85¶	Birth certificate registry	1,435,385	NA	✓	✓	✓			

BF, Breastfeeding (in months); BO, birth order; BW, birth weight; C-C, case-control; CS, cesarean section; GA, gestational age; MD, maternal diabetes.

* 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 cases identified in cohort. # Duration of breastfeeding used in adjusted analysis shown in brackets. ** Only included in sensitivity analyses.

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 (in years)	Nos. of cases	Combined OR (95%CI)	P	Heterogeneity χ2 (P)	I²
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. cat.)			
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. Cat.)			
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. Cat.)			
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. Cat.)			
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. Cat.)			
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. Cat.)			
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

[*] Only includes 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: 1st, 2nd or 3rd born or later) could be made.

[†]Excluding case-control studies which have controls which are not randomly selected (or population based) or studies in which the response rate in either the cases or controls was less than 80% (or unknown) as shown in Table 1.

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

Figure 2. Scatterplot of odds ratio for diabetes per 5 year increase in maternal age by: difference in response rates between cases and controls (size of plotting symbol proportional to precision of study, line taken from meta-regression).