Interbirth Interval Is Associated With Childhood Type 1 Diabetes Risk

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Short interbirth interval has been associated with maternal complications and childhood autism and leukemia, possibly due to deficiencies in maternal micronutrients at conception or increased exposure to sibling infections. A possible association between interbirth interval and subsequent risk of childhood type 1 diabetes has not been investigated. A secondary analysis of 14 published observational studies of perinatal risk factors for type 1 diabetes was conducted. Risk estimates of diabetes by category of interbirth interval were calculated for each study. Random effects models were used to calculate pooled odds ratios (ORs) and investigate heterogeneity between studies. Overall, 2,787 children with type 1 diabetes were included. There was a reduction in the risk of childhood type 1 diabetes in children born to mothers after interbirth intervals <3 years compared with longer interbirth intervals (OR 0.82 [95% CI 0.72–0.93]). Adjustments for various potential confounders little altered this estimate. In conclusion, there was evidence of a 20% reduction in the risk of childhood diabetes in children born to mothers after interbirth intervals <3 years. ***Diabetes*** **61:702–707, 2012**

Childhood type 1 diabetes is caused by the autoimmune destruction of the pancreatic β-cells. The marked increases in incidence in recent decades (1) suggest a role for environmental exposures. Researchers have been particularly interested in environmental exposures in early life, and associations, although weak in magnitude, have been observed with caesarean section delivery (2), maternal age (3), and birth weight (4).

It has long been recognized that short interbirth interval (the time since the immediately preceding birth) is associated with increased risk of adverse pregnancy outcomes such as preterm birth and low birth weight (5). Recently, studies have shown associations between short interbirth interval and an increased risk of diseases in the offspring including childhood autism (6) and schizophrenia (7) and a reduced risk of childhood leukemia (8). The mechanism behind these findings is unknown, but researchers have suggested that short interbirth intervals may not allow complete restoration of maternal micronutrients at the time of conception (7,9), may lead to increased maternal stress (7), and may increase exposure to childhood infections from immediately older siblings (7). These mechanisms are of potential relevance to childhood type 1 diabetes because associations with type 1 diabetes have been observed with maternal micronutrient levels during pregnancy (such as vitamin D [10]), stressful life events during pregnancy (11), and day care attendance (a surrogate for infections in early life) (12). The aim of this study was to conduct the first investigation into the association between interbirth interval and childhood diabetes risk.

RESEARCH DESIGN AND METHODS

The authors of 29 studies who previously contributed to a meta-analysis of the association between birth order and type 1 diabetes (13) were contacted and invited to participate in this study if they could calculate interbirth interval for their study participants (usually from the date of birth or ages of other siblings). Authors of 14 of these studies (14–22) had recorded the dates of birth of older siblings and provided raw datasets or calculated estimates of the association between interbirth interval and diabetes before and after adjustments for potential confounders (if available). Interbirth interval was calculated as time since last live birth and was categorized based upon predefined categories used in a study of autism (6) (<21, 21–32, 33–44, and ≥45 months) and in a study of leukemia (8) (firstborns, <36 months, and ≥36 months).

Statistical analysis. Odds ratios (ORs) and SEs were calculated for the association between each category of interbirth interval and type 1 diabetes for each study. Unconditional and conditional logistic regression was used to calculate the ORs and SEs for unmatched and matched case-control studies, respectively. In one cohort study with varying length of participant follow-up, Cox regression analysis was used to estimate hazard ratios and their SEs as a measure of association (which are approximate ORs for rare diseases such as type 1 diabetes [23]). A year of birth term was added to Cox regression analysis models to adjust the hazard 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 (24). Tests for heterogeneity were conducted, and the I^2 statistic was calculated (25). A subgroup analysis was conducted by age at diabetes diagnosis, and pooled estimates were compared by age at onset using standard tests for heterogeneity (26). All statistical analyses were performed using Stata 9.0 (Stata, College Station, TX).

RESULTS

The characteristics of the 14 contributing studies are shown in Table 1. The associations between interbirth

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TABLE 1
Characteristics of studies contributing data to the pooled analysis of interbirth interval and type 1 diabetes, ordered by publication date

			Type 1 diabetes				Control subjects			Confounders‡			
First author, year (reference no.)*	Design	Country	Ascertainment (year diagnosed)	Age at dx (years)	*n*†	Response rate (%)	Source (matching criteria)	*n*†	Response rate (%)	MA	BW	MD	CS
Wadsworth, 1997 (14)	C-C	U.K.	British Pediatric Association Surveillance Unit (1992)	0–5	215	89	HA immunization register	321	70	✓	✓	✓	
McKinney, 1999 (15)	C-C	England	Yorkshire childhood diabetes register (1993–1994)	0–15	220	94	GP's records (age, sex)	433	82	✓	✓	✓	✓
Rami, 1999 (16)	C-C	Austria	Vienna type 1 diabetes register (1989–94)	0–14	104	102	Schools (age, sex)	369	80	✓	✓	✓§	✓
Eurodiab, 1999 (17)	C-C	Bulgaria	W. Bulgaria type 1 diabetes register (1991–1994)	0–14	125	73	Schools and policlinics (age)	439	79	✓	✓	✓§	✓
	C-C	Latvia	Latvian type 1 diabetes register (1989–1994)	0–14	140	99	Population register (age)	321	79	✓	✓	✓§	✓
	C-C	Lithuania	Lithuanian type 1 diabetes register (1989–1994)	0–14	117	94	Policlinics (age)	268	73	✓	✓	✓§	✓
	C-C	Luxembourg	Luxembourg type 1 diabetes register (1989–1995)	0–14	59	100	Preschools and schools (age)	172	95	✓	✓	✓§	✓
	C-C	Romania	Bucharest type 1 diabetes register (1989–1994)	0–14	81	74	Preschools and schools (age)	275	81	✓	✓	✓§	✓
	C-C	Northern Ireland	Northern Ireland type 1 diabetes register (1989–1994)	0–14	189	78	GP register (age)	464	62	✓	✓	✓§	✓
Sadauskaite-Kuehne, 2004 (18)	C-C	Lithuania	Lithuanian type 1 diabetes register (1996–2000)	0–15	283	100	Outpatient clinic	759	95				
Svensson, 2005 (19)	C-C	Denmark	Danish register of childhood diabetes (1996–1999)	0–14	477	81	Danish population register (age, sex)	679	48	✓	✓	✓	✓
Tenconi, 2007 (20)	C-C	Italy	Pavia type 1 diabetes register (1988–2000)	0–19	96	85	Hospital (age, sex)	187	?	✓			
Waldhoer, 2008 (21)	Cohort	Austria	Austrian diabetes register (1989–1905)	0–5	444	85	Birth certificate registry	1,435,247	NA	✓	✓		
Algert, 2009 (22)	Cohort	Australia	Hosp. admission, ICD diabetes code (2000–2005)	0–6	237	93	Midwives' database	502,040	NA	✓	✓	✓§	✓

BW, birth weight; C-C, case-control; CS, caesarean section; dx, diagnosis; GP, general practitioner; HA, health authority; Hosp, hospital; MA, maternal age; MD, maternal diabetes. ‡Data recorded in the study and available for analysis. *Year: year of publication. †No. included in analysis of interbirth interval. §Maternal type 1 diabetes used in analyses.

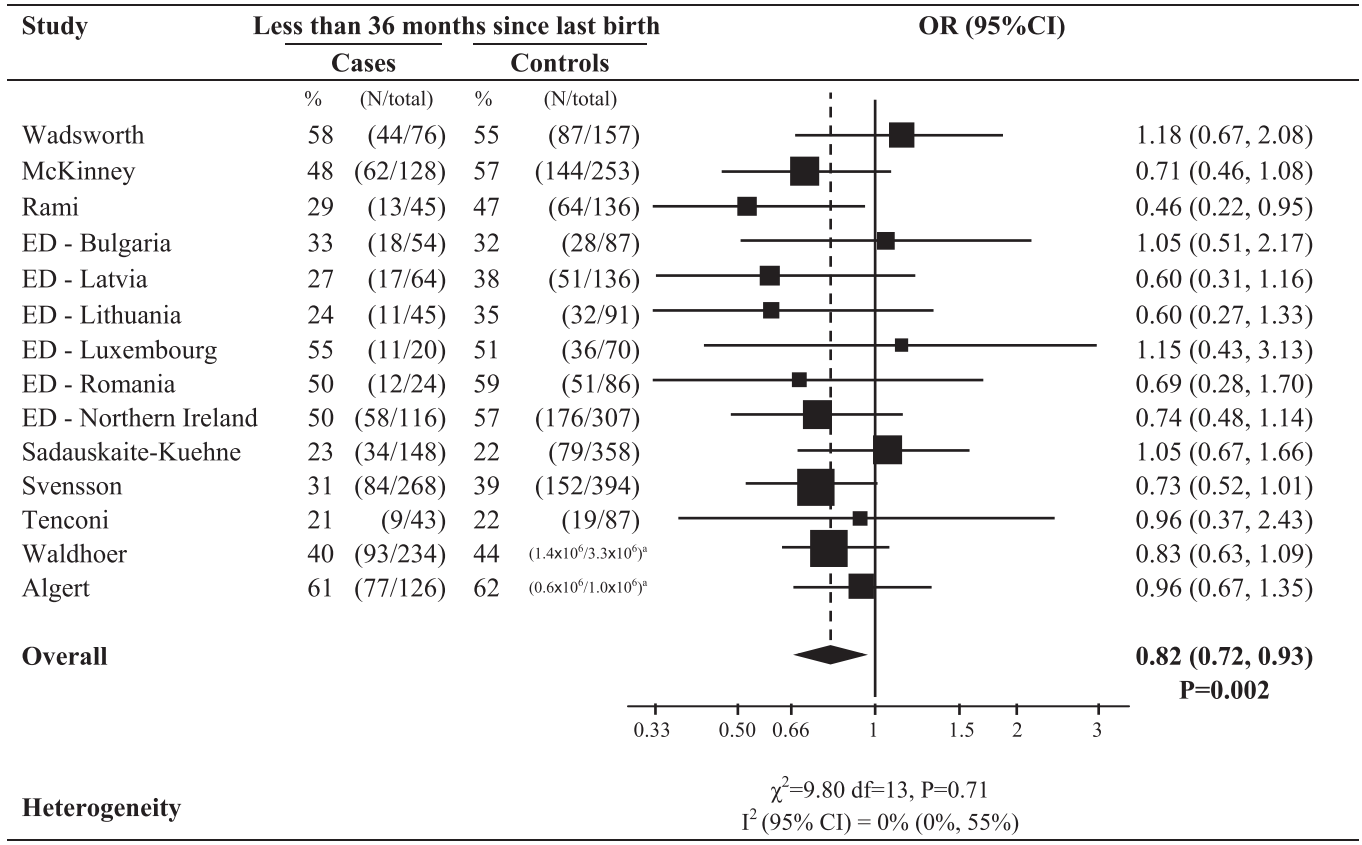
interval and type 1 diabetes (with 2,787 cases of type 1 diabetes) are shown in Fig. 1 and Table 2. Overall, children born to mothers with a short time since last birth (<3 years) had a significant 18% reduction in their subsequent risk of developing type 1 diabetes (OR 0.82 [95% CI 0.72–0.93]; $P = 0.002$) compared with children born to mothers with a long time since last birth (≥3 years). There was little evidence of heterogeneity between study centers in this association ($I^2 = 0\%$; heterogeneity $P = 0.71$). In contrast, there was little evidence of a difference in subsequent risk of type 1 diabetes in firstborns compared with children born with a long time since last pregnancy (OR 0.87; $P = 0.10$), although there was marked heterogeneity in this association between centers ($I^2 = 61\%$; heterogeneity $P = 0.002$).

Table 2 also shows evidence of a dose-response relationship with larger reductions in diabetes risk with shorter interbirth intervals (test for trend $P = 0.002$). Compared with the longest time since previous birth (over 45 months), the risk of type 1 diabetes was reduced by 20% (OR 0.80) in children with immediately preceding birth between 33 an 44 months, by 22% (OR 0.78) in children with immediately preceding birth between 21 and 32 months, and by 26% (OR 0.74) in children with immediately preceding birth <21 months. There was little evidence of heterogeneity in these associations across studies.

Table 3 shows maternal and child characteristics by interbirth interval. In the majority of studies, there was little evidence of a difference in birth weight, caesarean section delivery, or maternal diabetes, but maternal age was slightly lower by, on average, 3 years after interbirth interval <3 years compared with >3 years. Table 2 shows the findings for interbirth interval after adjustment for these potential confounders. In general, the associations between type 1 diabetes and interbirth interval were little altered after adjustment for maternal age, caesarean section delivery, maternal type 1 diabetes, birth weight, and gestational age in studies in which these variables were available (Table 1). Additionally, in 10 studies with data, adjustment for breast-feeding (at 1 month or similar) little altered the reduction in diabetes risk in children born to mothers with a short time (<3 years) since last birth (adjusted OR 0.75 [95% CI 0.63–0.90]).

Analysis was also conducted by age at diagnosis. The association between type 1 diabetes risk and time since last birth (<3 vs. ≥3 years) appeared slightly stronger in children >5 years old at diagnosis (in 11 studies with available data, OR 0.74 [95% CI 0.61–0.89]; $P = 0.002$) than in children <5 years old at diagnosis (in 13 studies with available data, 0.96 [0.76–1.21]; $P = 0.74$), but the interaction test was not significant (interaction test $P = 0.09$).

Additional sensitivity analyses were conducted. The risk of diabetes in children born to mothers with a short time since last birth (<3 years) compared with a long time since last birth (≥3 years) was similar to the overall association when restricted to second-born children only (in 12



ED, Eurodiab.

[a] Person years as calculated from cohort studies.

FIG. 1. Pooled analysis of risk of type 1 diabetes in children born after a shorter interbirth interval (<36 months since previous birth) compared with a longer interbirth interval (≥36 months since previous birth), excluding firstborns.

TABLE 2
Pooled analysis of association between interbirth interval and type 1 diabetes before and after adjustments for confounders

Interbirth interval	Studies (n)	Cases (n)	Pooled OR (95% CI)	P	Heterogeneity I^2 (95% CI)	Heterogeneity χ^2 (P)
Unadjusted analysis						
Time since last live birth (months)	14					
≥36		848	1.00 (ref.)			
<36		543	0.82 (0.72–0.93)	0.002	0% (0–55)	9.80 (0.71)
Firstborns		1,394	0.87 (0.73–1.03)	0.10	61% (29–78)	32.9 (0.002)
Time since last live birth, excluding firstborns (months)	12*					
≥45		526	1.00 (ref.)			
33–44		201	0.80 (0.61–1.06)	0.12	37% (0–68)	17.57 (0.09)
21–32		268	0.78 (0.65–0.92)	0.004	0% (0–58)	7.70 (0.74)
<21		153	0.74 (0.60–0.91)	0.001	0% (0–58)	3.17 (0.98)
Trend across categories		1,148	0.91 (0.85–0.97)	0.002	0% (0–58)	3.96 (0.97)
Adjusted analysis†						
Time since last live birth (months)	14					
≥36		826	1.00 (ref.)			
<36		531	0.83 (0.73–0.95)	0.006	0% (0–55)	6.79 (0.91)
Firstborns		1,347	0.90 (0.74–1.09)	0.27	59% (26–77)	31.97 (0.003)
Time since last live birth, excluding firstborns (months)	12*					
≥45		509	1.00 (ref.)			
33–44		190	0.76 (0.56–1.03)	0.07	39% (0–69)	18.2 (0.08)
21–32		261	0.77 (0.64–0.93)	0.005	0% (0–58)	4.12 (0.97)
<21		149	0.74 (0.59–0.92)	0.008	0% (0–58)	5.63 (0.90)
Trend across categories		1,109	0.90 (0.85–0.97)	0.003	0% (0–58)	4.79 (0.94)

*Based on 12 studies because two studies (the Italian 2007 study and Lithuanian 2004 study) did not record interbirth interval in detail sufficient for inclusion in these analyses. †Adjusted for maternal age (linear trend in 5-year categories), birth weight (in categories <2.5, 2.5–3.0, 3.0–3.5, 3.5–4.0, and ≥4 kg), maternal type 1 diabetes, Caesarean section delivery (yes or no), and year of birth (in categories) where available as shown in Table 1.

studies, OR 0.70 [95% CI 0.57–0.86]) and when also adjusted for birth order as well as maternal age (in 12 studies, 0.76 [0.65–0.88]). This association was also similar when participants were excluded if they had an older sibling with diabetes (in nine studies with available data, 0.71 [0.57–0.89]) and when stillbirths were included in the calculation of interbirth interval (in eight studies with available data, 0.73 [0.59–0.90]).

DISCUSSION

This study has identified a reduction in type 1 diabetes risk of ~20% in children born to mothers who gave birth in the previous 3 years. This reduction was consistent across the 14 study centers. This is, to our knowledge, the first study to investigate interbirth interval and type 1 diabetes.

The main strength of this study is that it contains data from 14 centers including 2,787 cases of type 1 diabetes with consistent categorization of interbirth interval (using previously specified categorizations from studies of leukemia [8] and autism [6]). A further strength was the use of population-based diabetes registers to identify cases (in 12 of the 14 studies) and the selection of control subjects from largely population-based sources. The study has various weaknesses. As with all observational studies, it is not possible to rule out residual confounding: that children born to mothers after shorter interbirth intervals also have other characteristics that could decrease their risk of type 1 diabetes. In our analysis, we were able to adjust consistently for maternal age, caesarean section, birth weight, maternal diabetes, birth order, and breast-feeding, but it is not possible to rule out the effect of other unknown confounders. One such candidate is miscarriage and abortion history, and it is possible that mothers with longer interbirth intervals may have been more likely to have had miscarriages or abortions; however, to our knowledge there is no evidence that miscarriage history affects childhood-onset diabetes risk and the reports of an association between abortion and childhood diabetes risk have been inconsistent (27–29).

Bias could have occurred if parents delayed pregnancy after the diagnosis of a child with type 1 diabetes because their next child, who would have an increased risk of type 1 diabetes, would tend to be born after a longer interbirth interval. However, it seems unlikely that this bias would have much influence because the incidence of diabetes is low in early life. Furthermore, in a subset of nine studies, children whose older siblings had diabetes could be removed and the main finding was similar. The main analysis was conducted on interbirth interval calculated after the removal of stillbirths (where possible), but an additional analysis was conducted including stillbirths and results were little altered. Half-siblings were excluded from the analysis in nine studies, as it was often unclear whether they had the same natural mother or whether the half-sibling was present in the house when the study participant was an infant. This may introduce some measurement error, but it would be expected that such error would dilute real associations rather than create spurious ones. The included studies were identified if they had contributed to a previous systematic review of birth order (13), instead of taken from literature searches, because to our knowledge data on interbirth interval and type 1 diabetes have not been published.

The cause of any reduction in the risk of childhood type 1 diabetes in children born after shorter interbirth intervals is unknown. Previous studies (9) showing increased risks of low birth weight after short interbirth intervals have suggested that incomplete restoration of maternal

TABLE 3
Maternal and child characteristics for children born after shorter interbirth interval (<36 months since previous birth) compared with longer interbirth interval (≥36 months since previous birth) by study, excluding firstborns

Study	*n**		Maternal age, mean (SD)			Birth weight in kg, mean (SD)			Maternal diabetes, *n* (%)			C-section delivery, *n* (%)		
	<36 months	≥36 months	<36 months	≥36 months	*P*†	<36 months	≥36 months	*P*†	<36 months	≥36 months	*P*‡	<36 months	≥36 months	*P*‡
Wadsworth et al.	160	129	29.0 (4)	30.7 (5)	0.01	3.42 (0.5)	3.29 (0.5)	0.06	1 (1)	2 (2)	0.58	NA	NA	NA
McKinney et al.	206	175	27.1 (4)	30.4 (5)	<0.01	3.35 (0.7)	3.41 (0.5)	0.39	2 (1)	1 (1)	1.00	26 (13)	13 (7)	0.13
Rami et al.	77	104	27.2 (5)	29.6 (5)	<0.01	3.37 (0.5)	3.32 (0.5)	0.57	0 (0)	1 (1)	1.00	8 (13)	7 (8)	0.41
ED Bulgaria	46	95	24.8 (4)	28.5 (4)	<0.01	3.43 (0.5)	3.60 (0.5)	0.19	2 (4)	0 (0)	0.10	8 (17)	16 (17)	1.00
ED Latvia	68	132	26.1 (5)	30.7 (4)	<0.01	3.50 (0.5)	3.60 (0.5)	0.21	1 (1)	1 (1)	1.00	4 (6)	9 (7)	1.00
ED Lithuania	43	93	26.1 (4)	29.8 (4)	<0.01	3.51 (0.5)	3.65 (0.5)	0.13	0 (0)	1 (1)	1.00	1 (2)	5 (5)	0.67
ED Luxemborg	47	43	28.3 (5)	31.3 (4)	<0.01	3.37 (0.6)	3.42 (0.5)	0.65	0 (0)	0 (0)		8 (17)	8 (19)	0.84
ED Romania	63	47	25.5 (5)	28.1 (4)	<0.01	3.22 (0.5)	3.22 (0.5)	0.98	0 (0)	0 (0)		4 (6)	4 (9)	0.72
ED Northern Ireland	234	189	28.1 (5)	31.0 (5)	<0.01	3.46 (0.5)	3.54 (0.5)	0.08	5 (2)	2 (1)	0.47	22 (10)	16 (9)	0.80
Sadauskaite-Kuehne et al.	113	393	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Svensson et al.	236	426	28.9 (4)	30.8 (4)	<0.01	3.58 (0.5)	3.56 (0.5)	0.63	7 (3)	12 (3)	1.00	23 (10)	51 (12)	0.44
Tenconi et al.	28	102	27.0 (5)	30.5 (4)	<0.01	NA	NA	NA	NA	NA	NA	NA	NA	NA
Waldhoer et al.	305,237	386,881	28.2 (5)	30.9 (5)	<0.01	3.42 (0.5)	3.41 (0.5)	<0.01	NA	NA	NA	NA	NA	NA
Algert et al.	148,196	93,061	30.3 (5)	31.9 (5)	<0.01	3.48 (0.5)	3.45 (0.5)	<0.01	383 (0.3)	339 (0.4)	<0.01	33,453 (22.6)	21,768 (23.4)	<0.01

C-section, caesarean section; ED, EURODIAB. *No. of individuals in the analysis of interbirth interval. †*P* value from *t* test. ‡*P* value from Fisher exact test.

micronutrients, particularly folate, at conception is responsible. However, as our study observed a reduced risk of type 1 diabetes after short interbirth intervals, this seems unlikely to be involved. Another potential mechanism behind the association is maternal stress. A Danish study previously demonstrated that children born after short interbirth interval were more likely to be unplanned (30), potentially increasing maternal stress. However, this also seems like an unlikely explanation, as previous studies have shown increased risks of type 1 diabetes with stressful life events during pregnancy (11), particularly bereavements and family stress (31).

Previous studies have shown that children who are second or higher in birth order have a reduced risk of type 1 diabetes (13). Authors have speculated that second or later birth order children may have increased exposure to sibling infections and that this may be protective through the hygiene hypothesis (which suggests that the immune system requires stimulation by infections and other immune challenges in early life to achieve a mature and balanced repertoire of responses [32]). It is possible that exposure to sibling infection may be greater in children born after short interbirth intervals, as their immediately older sibling will be of similar age. In our analysis, there were indications that the association between interbirth interval and childhood diabetes may be stronger for children diagnosed at older ages, perhaps because early-onset diabetes may have a stronger genetic component (33).

In conclusion, short interbirth interval is associated with a 20% reduction in type 1 diabetes risk. The magnitude of the association makes it difficult to rule out residual confounding. Confirmation of this finding in independent studies is necessary.

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