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Phototherapy and Risk of Type 1 Diabetes

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abstract

BACKGROUND AND OBJECTIVE: Increases in both phototherapy use and the incidence of type 1 diabetes mellitus (DM-1) have been reported. One large study has suggested a strong association between them. Our objective was to quantify any association between neonatal phototherapy and DM-1 in a northern California integrated health care system.

METHODS: This retrospective cohort study included 499 642 children born at ≥35 weeks' gestation in 15 Kaiser Permanente Northern California hospitals from 1995 to 2011 and followed until March 31, 2014. We ascertained phototherapy, bilirubin levels, and other covariates from electronic records. We identified DM-1 cases using a diabetes registry and inpatient and outpatient diagnoses. We used traditional and propensity-adjusted Cox models to quantify associations.

RESULTS: Phototherapy use increased from 2.7% in 1995 to 16.0% in 2011. DM-1 was diagnosed in 37 of 39 406 children who had received phototherapy (15.1 per 100 000 person-years; mean follow-up 6.2 years) and 712 of 460 236 who had not (18.8 per 100 000 person-years; mean follow-up 8.2 years). There was no evidence of increasing diabetes incidence. We found no association between phototherapy and DM-1 in either unadjusted analyses (incidence rate ratio 0.81; 95% confidence interval, 0.56 to 1.12) or analyses adjusted for hyperbilirubinemia and other covariates (hazard ratio 1.06; 95% confidence interval, 0.78 to 1.45). DM-1 incidence was most strongly associated with race and ethnicity, with whites at highest risk (25.6 per 100 000) and Asians at lowest risk (8.9 per 100 000).

CONCLUSIONS: We found no evidence of increased DM-1 risk in children who had received phototherapy.

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Dr Newman conceptualized, designed and led efforts to obtain funding for the study, analyzed data, and drafted the initial manuscript; Dr Wickremasinghe assisted with the analyses and reviewed and revised the manuscript; Ms Walsh coordinated the study and reviewed the manuscript; Dr Grimes assisted with data analyses and reviewed the manuscript; Dr McCulloch provided statistical and design consultation, assisted with obtaining funding, supervised propensity analyses, and reviewed and revised the manuscript; Dr Kuzniewicz assisted with obtaining funding, supervised data management and creation of Kaiser Permanente, Northern California data sets, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Use of phototherapy and the incidence of type 1 diabetes mellitus (DM-1) in children have been increasing. A large Swedish study found a strong association between phototherapy and childhood DM-1, not confirmed in a smaller study from Scotland.

WHAT THIS STUDY ADDS: In this large cohort, there was no association between phototherapy and DM-1. Phototherapy use increased, and DM-1 incidence was stable. The main risk factors for DM-1 were white race and high birth weight.

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Jaundice in newborns is commonly treated with phototherapy, with a goal of preventing the total serum bilirubin (TSB) from reaching dangerous levels.[1] However, most jaundice resolves even if untreated, so the number needed to treat with phototherapy to prevent 1 newborn from reaching potentially dangerous TSB levels can be in the hundreds or thousands.[2] For this reason, it is important to identify even rare potential adverse effects of neonatal phototherapy.

In a 1999 EURODIAB study of perinatal risk factors for childhood type 1 diabetes mellitus (DM-1), maternal–infant blood group incompatibility was associated with a higher risk of diabetes.[3] Following up on this association, Dahlquist and Kallen[4] linked 7343 children in the Swedish Childhood Diabetes Registry with the Swedish Medical Birth Registries and reported in a letter to *Diabetes Care* that treatment of jaundice was associated with an increase in the risk of diabetes (odds ratio [OR] 3.79; 95% confidence interval [CI], 3.13 to 4.59). However, they also reported evidence of heterogeneity of the association by county of birth. A case–control study of childhood DM-1 from Scotland[5] did not confirm this association (OR = 0.72; 95% CI, 0.31 to 1.68). Although phototherapy status was not known for 87% of the subjects in that study (those born before 1992), the 95% CI still excludes an association of the magnitude reported from Sweden. A recent meta-analysis[6] found a weak association (OR = 1.14; 95% CI, 0.99 to 1.32; $P = .07$) between neonatal jaundice and DM-1 that was statistically significant in the subgroup of studies that ascertained jaundice from medical records rather than maternal recall (OR = 1.25; 95% CI, 1.03 to 1.51; $P = .02$). However, that analysis did not address the impact of phototherapy.

Because both childhood DM-1[7–10] and phototherapy use[11–13] are increasing in incidence, investigating a possible link between the 2 is important. As part of the Late Impact of Getting Hyperbilirubinemia or photoTherapy (LIGHT) study,[13] we investigated the association between neonatal phototherapy use and subsequent diagnosis of diabetes in a large cohort of children born in northern California.

METHODS

Design, Subjects, and Human Subjects Approval

The Late Impact of Getting Hyperbilirubinemia or photoTherapy (LIGHT) study is a retrospective cohort study of 525 409 children born alive at ≥35 weeks' gestation from January 1, 1995 through December 31, 2011 at 1 of 15 Kaiser Permanente Northern California (KPNC) hospitals. For the current analyses we excluded 344 infants (0.07%) who died during their birth hospitalization, 891 (0.17%) whose birth hospitalization ended with a transfer out of the KPNC system, and 24 532 (4.7%) who were followed <60 days after birth. This left a cohort of 499 642 infants.

The institutional review boards for the protection of human subjects at the University of California, San Francisco and KPNC approved the study.

Predictor Variables

For children born before KPNC's implementation of HealthConnect, KPNC's electronic medical record system (80% of subjects), we identified those who received inpatient phototherapy by using hospital discharge procedure codes (99.82 and 99.83) for hospitalizations that began <30 days after birth. For children born after implementation of HealthConnect, information about phototherapy was available from both physician orders and nursing phototherapy flow sheets. Based on comparison with paper charts in previous studies and with electronic records for infants born after implementation of HealthConnect, we estimated that procedure codes for phototherapy before HealthConnect were about 92% sensitive and 99.6% specific. Home phototherapy was ascertained based on an order for a home phototherapy device. Because we did not have reliable data on the duration or intensity of phototherapy, the primary predictor variable for all analyses was a dichotomous variable for any phototherapy, whether delivered in the hospital, at home, or both. We ascertained exchange transfusion based on International Classification of Diseases, Ninth Revision procedure codes, confirmed by individual record review; we included 36 definite, 1 probable, and 3 possible exchange transfusions.

We obtained covariates from electronic records, including sex, parent-reported infant race and ethnicity, chromosomal or congenital anomalies, birth weight, gestational age, and TSB levels. We defined small and large for gestational age as birth weight less than the 10th or greater than the 90th percentile for week of gestational age in this cohort. To optimize control for confounding by indication, we assessed each TSB level in relation to the 2004 American Academy of Pediatrics (AAP) phototherapy guidelines[1] by using direct antiglobulin test results and gestational age to determine the neurotoxicity risk group, as previously described.[2] We determined whether each subject had ≥1 TSB level between −3 and +4.9 mg/dL from the appropriate AAP phototherapy threshold and, if so, created a variable equal to the difference (in 1-mg/dL categories) between the first such TSB level

TABLE 1 Crude IRRs for DM-1 by Demographic and Clinical Characteristics

	N at Risk	*N* With DM-1	Incidence per 100 000 Person-Years	Crude IRR	95% CI Lower	95% CI Upper	*P*
Total population	499 642	749	18.5				
Year of birth							
1995–2000	165 854	433	21.7	1.24	1.06	1.46	.006
2001–2006	178 286	248	17.5	Reference	—	—	—
2007–2011	155 502	68	10.9	0.62	0.47	0.82	.0003
Maternal age							
<30 y	249 663	356	17.5	Reference	—	—	—
≥30 y	249 979	393	19.6	1.11	0.96	1.29	.14
Gender							
Female	244 182	348	17.6	Reference	—	—	—
Male	255 460	401	19.5	1.11	0.96	1.28	.17
Race							
White	211 422	447	25.6	Reference	—	—	—
Black	39 064	68	19.9	0.78	0.59	1.00	.05
Asian	93 702	66	8.9	0.35	0.26	0.45	<.0005
Hispanic	120 494	131	13.6	0.53	0.43	0.65	<.0005
Other or missing	34 960	37	14.9	0.58	0.40	0.81	.0006
Gestational age							
<38 wk	59 787	89	18.5	Reference	—	—	—
≥38 wk	439 855	660	19.1	1.04	0.82	1.30	.74
Birth wt							
<2500 g	16 805	22	16.5	0.92	0.57	1.40	.71
2500–4199 g	449 761	654	18.0	Reference	—	—	—
≥4200 g	33 076	73	26.0	1.44	1.12	1.84	.004
Size for gestational age							
Small (<10th percentile)	49 358	63	15.7	0.86	0.65	1.11	.24
Appropriate	400 564	591	18.3	Reference	—	—	—
Large (>90th percentile)	49 720	95	23.1	1.26	1.00	1.57	.04
Direct antiglobulin test result							
Not done	311 358	514	18.8	1.05	0.90	1.24	.51
Negative	177 284	219	17.8	Reference	—	—	—
Positive	11 000	16	19.6	1.10	0.62	1.82	.70
Maximum TSB, mg/dL							
Not done or <10	348 401	587	19.8	Reference	—	—	—
10–14.9	79 843	89	16.1	0.82	0.64	1.02	.07
15–19.9	61 810	56	12.9	0.65	0.48	0.86	.001
≥20	9588	17	20.3	1.03	0.60	1.66	.88
Any phototherapy							
No	460 236	712	18.8	Reference	—	—	—
Yes	39 406	37	15.1	0.81	0.56	1.12	.20

—, no point estimates, 95% CI, or P value for the reference categories of each risk factor.

and the phototherapy threshold at that age for use in propensity score modeling.

Outcome Variable

We used the KPNC virtual data warehouse[14] and diabetes registry to identify incident diabetes cases. To meet the case definition, subjects needed either ≥2 encounters (inpatient or outpatient) with a diagnosis of DM-1 or 1 such encounter and either ≥2 hemoglobin A1c levels ≥6.5% or a pharmacy record indicating a prescription for insulin.

Follow-up Time

Length of follow-up varied widely in this study, both because some subjects left the KPNC health care system and because follow-up began at birth (1995–2011) but ended in 2014 for all subjects. For purposes of quantifying incidence rates and using proportional hazards models, follow-up for each member of the cohort began at age 60 days and ended at death, the date the diagnosis of diabetes was confirmed, or the last follow-up date, defined as the last day of the last calendar month of coverage by the KPNC health plan or the last encounter date through March 11, 2014, whichever came later.

Statistical Analysis

The variation in follow-up times required analyses that take follow-up time into account, so we calculated incidence rates, incidence rate ratios (IRRs), and hazard ratios (HRs). We calculated incidence rates and IRRs by dividing DM-1 cases by person-years of follow-up. Two-tailed exact significance tests were

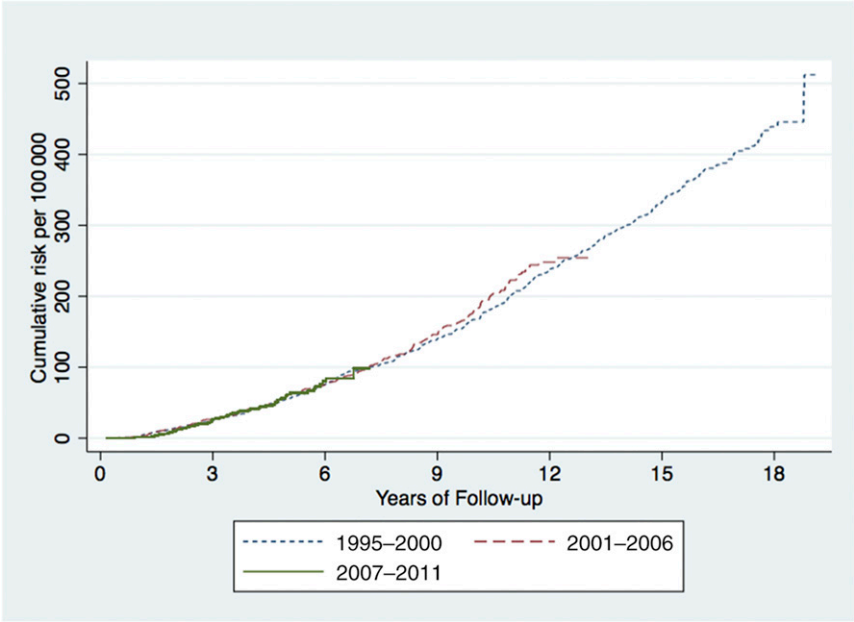

FIGURE 1
Cumulative incidence of DM-1 by birth cohort among children born in KPNC hospitals.

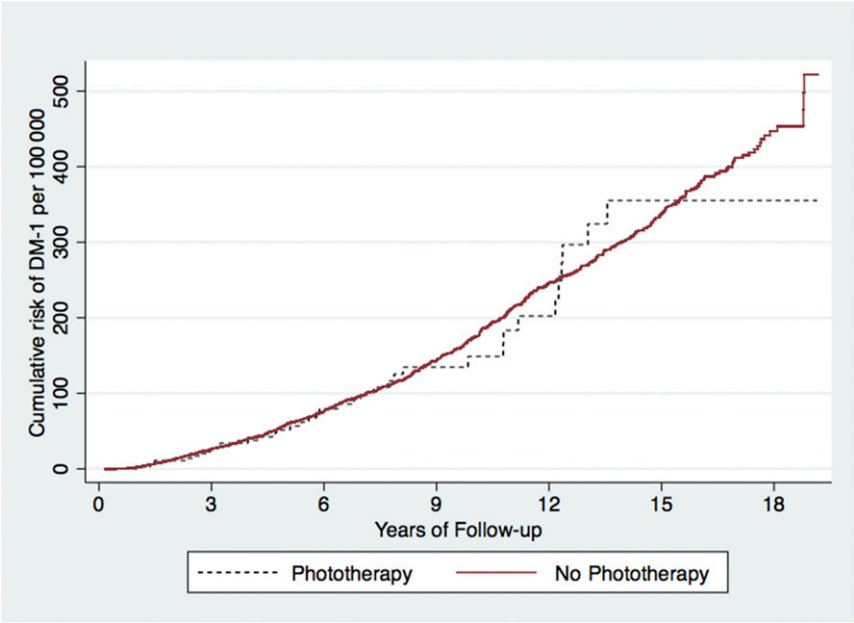

FIGURE 2
Cumulative incidence of DM-1 by phototherapy exposure among children born in KPNC hospitals.

used for comparisons. We used the multivariable Cox proportional hazards model to obtain HRs for phototherapy and covariates. In addition, we performed 2 sets of propensity-adjusted analyses: *restricted* propensity analyses that included only those with ≥1 TSB between −3 and +4.9 mg/dL from the appropriate AAP phototherapy threshold and *inclusive* propensity analyses that included all subjects and used a dichotomous variable for whether any TSB level had exceeded the AAP threshold. Propensity scores were used to control for the possibility of confounding by indication, that is, the possibility that an observed association between phototherapy and DM-1 could be confounded by a causal association between ≥1 indications for phototherapy (eg, hyperbilirubinemia, prematurity) and DM-1. We used a Poisson model to estimate the marginal excess risk per 100 000 person-years associated with phototherapy and its 95% CI. All multivariable analyses used robust standard errors to account for clustering by facility.

RESULTS

Cohort Description and Crude Incidence Rates

Of the 499 642 children in the cohort, 39 406 (7.9%) ever received phototherapy, of whom 5054 (1.0%) received home phototherapy only, 31 987 (6.4%) received hospital phototherapy only, and 2365 (0.5%) received both. As previously described,[15] use of phototherapy increased during the study period in this cohort, from 2.7% in 1995 to 16% in 2011.

Mean (SD) follow-up time was 6.2 (4.3) years among those who received phototherapy and 8.2 (5.2) years for those who did not, for a total of 4.04 million person-years at risk. DM-1 was diagnosed in 749 children (0.15%), or about 18.5 per 100 000 person-years. The mean (SD) age at diagnosis was 7.9 (4.3) years.

Characteristics of the study cohort and crude IRRs are shown in Table 1. The crude incidence per 100 000 person-years of follow-up appeared to decrease over time, from 21.7 for 1995 to 2000 births, to 10.9 for 2007 to 2011 births, but cumulative incidence curves for the 3 periods were nearly identical, at least up to about age 9 (Fig 1), suggesting that crude incidence differences were caused by the unequal follow-up time and greater incidence of DM-1 at older ages. There were crude associations between DM-1

TABLE 2 Crude and Multivariate Adjusted HRs for Phototherapy and Covariates

Variable	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Any phototherapy				
No	Reference		Reference	—
Yes	0.95 (0.68 to 1.32)	.75	1.06 (0.78 to 1.45)	.69
Year of birth				
1995–2000			Reference	—
2001–2006	1.05 (0.88 to 1.24)	.60	1.09 (0.95 to 1.26)	.23
2007–2011	1.02 (0.77 to 1.36)	.89	1.08 (0.72 to 1.63)	.71
Maternal age				
<20 y	0.67 (0.46 to 0.95)	.03	0.68 (0.49 to 0.95)	.02
20 to <25 y	0.83 (0.66 to 1.03)	.09	0.84 (0.71 to 1)	.05
25 to <30 y	0.87 (0.73 to 1.05)	.16	0.89 (0.74 to 1.07)	.22
30 to <35 y	Reference		Reference	—
35 to <40 y	0.85 (0.68 to 1.06)	.15	0.83 (0.65 to 1.07)	.15
≥40 y	1.01 (0.7 to 1.45)	.96	0.97 (0.66 to 1.42)	.88
Race or ethnicity				
White	Reference		Reference	—
Asian	0.35 (0.27 to 0.46)	<.0005	0.35 (0.29 to 0.42)	<.0005
Black	0.77 (0.59 to 0.99)	.04	0.79 (0.53 to 1.18)	.25
Hispanic	0.54 (0.45 to 0.66)	<.0005	0.56 (0.44 to 0.7)	<.0005
Other	0.63 (0.45 to 0.88)	.007	0.64 (0.47 to 0.87)	.01
Gestational age				
<38 wk			Reference	—
≥38 wk	1.07 (0.85 to 1.33)	.57	1.17 (1.01 to 1.35)	.04
Birth wt				
<2500 g	0.92 (0.6 to 1.41)	.72	0.89 (0.57 to 1.41)	.63
2500 to <4200 g	Reference		Reference	—
≥4200 g	1.4 (1.09 to 1.78)	.007	1.29 (1.04 to 1.61)	.02
Direct antiglobulin test				
Not done	0.93 (0.79 to 1.09)	.37	0.94 (0.82 to 1.07)	.35
Negative			Reference	—
Positive	1.05 (0.63 to 1.74)	.85	1.13 (0.69 to 1.86)	.63
Maximum total serum bilirubin, mg/dL				
Not done or <10			Reference	—
10–14.9	0.9 (0.72 to 1.13)	.36	0.92 (0.8 to 1.05)	.20
15–19.9	0.72 (0.55 to 0.94)	.02	0.74 (0.53 to 1.02)	.07
≥20	1.03 (0.63 to 1.66)	.92	1.05 (0.7 to 1.59)	.81

—, no point estimates, 95% CI, or P value for the reference categories of each risk factor.

and race and ethnicity (whites at highest risk), high birth weight, and large weight for gestational age. Compared with subjects who never had a TSB measured or whose TSB levels were all <10 mg/dL, those with moderate elevations of TSB (10–19.9 mg/dL) were at lower risk. There was no crude association between phototherapy and DM-1 (IRR = 0.81; 95% CI, 0.56 to 1.12; *P* = .20). However, the smaller sample size and shorter follow-up of the phototherapy group led to increasingly imprecise incidence estimates in that group after about age 8 (Fig 2). None of the 40 subjects treated with exchange transfusion received a diagnosis of DM-1.

Multivariate Analyses

Multivariate HRs were similar to crude HRs (Table 2). The lack of association between phototherapy and DM-1 persisted in the Cox model (HR 1.06; 95% CI, 0.78 to 1.45). Propensity-adjusted Cox models confirmed the lack of association between phototherapy and DM-1 (HR 0.95; 95% CI, 0.60 to 1.51 for the restricted model; HR 0.91; 95% CI, 0.66 to 1.25 for the inclusive model). In neither model was propensity score associated with DM-1, whether included as indicator variables for categories or with restricted cubic splines. The apparent protective effect of being born later in the study disappeared with use of the Cox model.

Compared with whites, multivariate HRs were <1 for other racial and ethnic groups, with the lowest hazards for Asians (HR 0.35; 95% CI, 0.29 to 0.42) and Hispanics (HR 0.56; 95% CI, 0.44 to 0.70). High (≥4200 g) birth weight was also associated with DM-1 risk (HR 1.29; 95% CI, 1.04 to 1.61), but being large for gestational age was not (HR 1.16; 95% CI, 0.95 to 1.41 in a model omitting the birth weight term; when both birth weight and weight for gestational age were included, neither was statistically significant). The association with moderately elevated TSB levels (10–19.9 mg/dL) and DM-1 (compared with those in whom a TSB was not measured or whose levels were all <10 mg/dL) was diminished and no longer statistically significant with use of the Cox model.

According to the Poisson model, the IRR (adjusted for the variables in Table 2) for phototherapy was 1.03 (95% CI, 0.76 to 1.41). This result corresponds to an estimated excess risk of 0.58 (95% CI, −4.7 to 5.9) per 100 000 person-years.

DISCUSSION

In this large retrospective cohort study, we found no evidence of an association between phototherapy and DM-1 and, in contrast with other studies,[7–10] no evidence of an increase in early DM-1 incidence. The incidence of DM-1 in the current study is higher than the latest, highest rates reported by authors reporting increasing incidence, suggesting that an increase may have happened earlier in northern California. For example, our overall incidence of 18.5 per 100 000 person-years in whites is higher than the 16.6 per 100 000 reported for DM-1 incidence at age 0 to 20 years in 2006 to 2010 in Colorado,[7] and our incidence of 8.9 per 100 000 person-years among Asian children is higher

than the most recent incidence of about 7 per 100 000 reported for 2009 to 2010 from Taiwan.[10]

Strengths of the study include its large, ethnically diverse population, availability of bilirubin levels to control confounding by indication, and a rigorous definition of DM-1 that included not only diagnosis codes but also laboratory and pharmacy data. Limitations include some potential misclassification of phototherapy exposure; lack of data on phototherapy wavelengths, intensity, and duration; and follow-up averaging only 6.2 years in those exposed to phototherapy.

The large sample size led to an upper limit of the 95% CI of 1.46 for the HR, far lower than the lower limit of 3.13 in the Swedish study,[4] effectively ruling out chance as the basis for the differing results. Although our data did allow excellent control for confounding by indication, the similarity of unadjusted and adjusted estimates and the lack of association of high TSB levels or propensity scores with DM-1 suggest that there was little or no confounding to control for. Therefore, better control for confounding in the current study cannot explain its much lower HR than was found in the Swedish study. Similarly, although there may be some misclassification of phototherapy exposure in the KPNC data, it is unlikely that this misclassification is much worse than in the Swedish study, in which exposure to jaundice treatment was obtained by linking with data from a nationwide birth registry. Jaundice treatment in that study included exchange transfusions, but subjects treated with exchange transfusion presumably represented only a small proportion of those treated: 0.1% in the current study but probably a bit higher in the Swedish study, which included births from the 1970s and 1980s, when exchange transfusions were done more often.[16,17] Our lack of data on phototherapy wavelengths and dose means we cannot specify from this study exactly what phototherapy doses or wavelengths were given to enough infants to allow confidence that they are unassociated with DM-1.

Perhaps the main difference between the current study and the Swedish study is duration of follow-up. The Swedish report included children born from 1973 to 1997 and was published in 2003, when the oldest subjects were 30 years old. The current study shows no evidence of an association up to about 10 years of follow-up, but the mean age at diagnosis of DM-1 was 7.9 years and the mean follow-up was only 6.2 years in the phototherapy group. Similarly, in the matched case–control study from Scotland, although the mean age at diagnosis of the cases was not provided, only those whose diabetes was diagnosed before age 15 were included. It is possible that with longer follow-up an increase in DM-1 might become apparent, but this would require the cumulative incidence curves to diverge dramartically at older ages, and there is currently no hint of such divergence.

CONCLUSIONS

In this northern California cohort we found no association between phototherapy and DM-1, and we ruled out an association of the magnitude previously reported from Sweden, at least up to about age 10 years. Nonetheless, phototherapy may have other subtle or delayed risks,[15,18] and these should be weighed against the estimated risk of hyperbilirubinemia in making treatment decisions.

ABBREVIATIONS

AAP: American Academy of Pediatrics
CI: confidence interval
DM-1: type 1 diabetes mellitus
HR: hazard ratio
IRR: incidence rate ratio
KPNC: Kaiser Permanente, Northern California
OR: odds ratio
TSB: total serum bilirubin

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