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An Analysis for Paternal-Age Effect in Ohio's Down Syndrome Births, 1970–1980

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SUMMARY

The purpose of this study was to analyze Down syndrome (DS) births during 1970–1980 in the State of Ohio for a paternal-age effect independent of maternal age. Birth certificates and chromosome analysis records were used to ascertain 1,244 white DS births, which by capture-recapture methodology were estimated to comprise two-thirds of all white DS births in Ohio for this period. The control data consisted of 1,667,210 white live births in Ohio during the same period. One method of statistical analysis was a case-control comparison, which for each single-year maternal age compares the mean paternal age for controls with each observed DS paternal age. No statistically significant paternal-age effect was found in nine of the 11 years. For two of the years, and for all years combined, the DS fathers were significantly *younger* than the fathers of controls. When the data were subdivided according to ascertainment, one subpopulation—those DS individuals obtained from birth certificates alone—also showed a statistically significant negative paternal-age effect. The Mantel-Haenszel test was also applied to these data. Assuming no paternal-age effect, a lower rate of DS births than expected was found at paternal ages ≥ 40, but not at ≥ 45, ≥ 50, or ≥ 55. These same methods were used to test for a maternal-age effect. In each of the 11 years and over all 11 years combined, a strong and statistically significant positive maternal-age effect was detected.

INTRODUCTION

Recent cytogenetic techniques have made it possible to determine in which parent and in what meiotic division nondisjunction occurred among cases of trisomy

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21. Results from studies using these techniques suggest that 20%–25% of the meiotic errors are of paternal origin [1, 2]. Sparked by these results, studies to determine whether there is an association between paternal age and Down syndrome (DS) have again been conducted recently. The results from these studies have not been in complete agreement. Among those reporting an increased risk for older fathers were Stene et al. [3], who found a higher rate of DS for fathers aged 55 and over in Copenhagen. Matsunaga et al. [4] confirmed an increased incidence of DS at paternal ages $\geq$ 55 in a Japanese study; however, they also found a decreased incidence at paternal ages 40–44. A British Columbia study [5] found the fathers of DS individuals to be slightly older than the fathers of controls during one of two time intervals studied, and a study in Norway [6] demonstrated an increased risk for DS among fathers $\geq$ 50. Analyzing DS cases ascertained from prenatal diagnoses in West Germany, Stene et al. [7] found a strong increased risk among fathers $\geq$ 41. Evidence for no paternal-age effect has also been reported. Three DS live-birth populations in the United States analyzed by Erickson showed no increased risk for older fathers [8, 9], nor did data from New York State analyzed by Regal et al. [10]. Additionally, a recent report on prenatal diagnosis studies from New York also found no paternal-age effect [11].

Some of the studies [3, 4] in which a paternal-age effect was found did not control for maternal age by single year, and thus have been reported to have statistical artifacts. The possibility of a spurious paternal-age effect due to a residual maternal-age effect was presented by Erickson [9] and Lamson et al. [12]. Some of the studies that found no paternal-age effect had ascertained DS cases only from birth certificates. Stene and Stene [13] claimed that data ascertained in this way may be inappropriate because of biases.

The main objective of this study was to analyze the effect of paternal age on DS incidence in Ohio during 1970–1980 using DS births ascertained through birth certificates and cytogenetic analysis. The methods used allowed control of maternal age by single year. Since mode of ascertainment has been implicated as a source of bias, three subpopulations of ascertainment were analyzed separately. This allowed a check for possible ascertainment biases. The methods were also applied to the same data to analyze the association between maternal age and DS.

METHODS

Ascertainment

DS individuals born to Ohio residents during 1970–1980 were ascertained from two separate sources: (1) cytogenetics laboratories located throughout the state, and (2) a birth certificate listing obtained from the Division of Data Services, Ohio Department of Health. Thirteen of the state's 15 cytogenetics laboratories permitted access to the records of the DS individuals who had been karyotyped. Two centers did not permit access; however, the number of DS individuals karyotyped by each of them was < 20 for the 11-year period. The data collected from these records (when possible) included name, date of birth, sex, maternal age, paternal age, and whether the karyotype showed the individual to be trisomy, translocation, or mosaic. With this information, the birth certificates of these individuals could be located at the Division of Vital Statistics, so that race, missing

data for above items, and whether or not the child was reported as DS on the birth certificate could also be obtained. Maternal and paternal ages were often available from both cytogenetic records and the birth certificate, and were generally in good agreement; the birth certificate was used when any discrepancy arose. (Further details on ascertainment of DS births by this method are provided in [14]).

The other source of ascertainment was the Division of Data Services, which lists all live births that were reported on birth certificates as having congenital anomalies. This list was used to locate the birth certificates of those reported as DS, some of whom had been karyotyped and some not. It is probable that some of those not karyotyped are false positives, and a study is currently being conducted to estimate the percentage of false-positive reporting on birth certificates.

From these two sources, the DS individuals ascertained could be classified into three subpopulations: (1) 324 individuals chromosomally analyzed and reported as DS on their birth certificates; (2) 569 individuals chromosomally analyzed but not reported as DS on their birth certificates; and (3) 351 individuals not chromosomally analyzed but reported as DS on their birth certificates. These 1,244 DS individuals were whites only, and of those chromosomally analyzed, only trisomy 21 individuals were included. They represent 63.5% of the estimated total number of white DS born in Ohio during 1970–1980 (see [15] for how this estimate was obtained). Not included in these figures were 76 DS individuals for whom no paternal age was obtained, 48 translocation DS, 11 mosaic DS, and six DS for whom race was unknown. Nonwhites were also excluded from the analysis because of statistically significant heterogeneity among the subpopulations when compared to whites [14].

Control data obtained from the Division of Data Services consisted of all white live births to Ohio residents during 1970–1980. There were appropriate data for 1,667,210 of these live births.

Statistical Analyses

Case-control comparison [5]. For the control live births, a mean paternal age was calculated for each single-year maternal age. These mean paternal ages were matched by single-year maternal age to each observed DS paternal age, and the difference between them was calculated. Specifically, the mean control paternal age was subtracted from the observed DS paternal age. This difference is termed a delta value. The frequency histograms of the delta values were observed to determine if statistical analysis based on the normal distribution was appropriate. If appropriate, a mean was calculated for the delta values and a 95% confidence interval constructed about this mean using ± 1.96 times the standard deviation of the mean. The null hypothesis of no paternal-age effect, or delta = 0, was supported at $P \geq .05$ if the confidence interval included 0.

This method was applied to each of the annual data sets, the overall 11 years combined, and the combined data divided into the three subpopulations of ascertainment. The mean paternal ages at each maternal age were calculated from control live births from each of the individual years when analyzing the annual data sets. The combined data were also divided into young and old paternal-age divisions, and the two categories were analyzed separately. The delta values for the old paternal-age categories were not normally distributed. One factor for the lack of normality is that the control mean paternal ages for the categories of older paternal age fluctuated very little across the maternal ages. Additionally, there are very few fathers over age 50, even though there is no biologic limit. Thus, there were no DS fathers with ages far above this constant mean control paternal age, which resulted in there being no large positive delta values and a truncation in the distribution. Therefore, a nonparametric test, Wilcoxon's signed rank test, was used to determine statistical significance. This method tests the null hypothesis that the paternal-age distributions for DS births and control births are the same, and was supported at $P \geq .05$ if $-1.96 \leq Z \leq +1.96$ (see [16], pp. 128–129, for how Z was calculated).

The case-control comparison was similarly applied to the same data to search for a maternal-age effect; that is, the mean maternal age of normal live births was compared with DS maternal ages for each single-year paternal age.

Mantel-Haenszel test. This method tests for an association between paternal age and DS by searching for an unusually high or low frequency of older fathers among the DS population. This test is less powerful than the case-control comparison but its advantage is that one can look at results independent of distribution in particular segments of the data set.

Births were classified according to two criteria: whether or not they were DS and whether paternal age was "young" or "old" according to four defined boundaries given below. Using this classification, a 2 × 2 table can be constructed with DS and not with DS on one axis and young paternal age and old paternal age on the other. Maternal age is controlled by constructing a 2 × 2 table for each single-year maternal age.

The expected number of DS births to older fathers was calculated for each 2 × 2 table on the assumption of no paternal-age effect. A summary statistic distributed as a χ^2 with 1 df was calculated. This summary χ^2 compared the observed with the expected number of DS births to older fathers cumulated over all 2 × 2 tables. The degree of association should be consistent at each maternal age before summarizing across all maternal ages. The summary statistic assesses the significance of the common degree of association between older paternal age and DS.

Older paternal age was defined by the following: ≥ 40, ≥ 45, ≥ 50, and ≥ 55. The Mantel-Haenszel test was also used to analyze the three subpopulations according to mode of ascertainment. Additionally, the data were analyzed for a maternal-age effect using this test, the definition of older maternal age being > 35.

RESULTS

To evaluate the presence of a paternal-age effect from the raw data, a distribution of case and control data by maternal and paternal ages was constructed. Specifically, the ratio percentage of DS births to the percentage of live births for each paternal age was calculated within each maternal age. In this way, maternal age is controlled and a paternal-age effect is suggested if the ratio increases as paternal age increases. These data are presented by parental-age quinquennia in table 1. They show that as paternal age increases horizontally, there is no trend of increasing ratios within each of the maternal-age quinquennia, even though such a trend is clearly shown in the bottom row when maternal age is not controlled.

TABLE 1

RATIO OF PERCENTAGE OF DS BIRTHS TO THE PERCENTAGE OF LIVE BIRTHS FOR EACH PATERNAL-AGE QUINQUENNIA CONTROLLING BY MATERNAL-AGE QUINQUENNIA, OHIO WHITE BIRTHS, 1970–1980

	PATERNAL AGE								
MATERNAL AGE	15–19	20–24	25–29	30–34	35–39	40–44	45–49	50–54	> 55
15–19	1.12	0.99	0.69	0.67	0.00	0.00	0.00	0.00	0.00
20–24	0.88	0.94	1.17	0.41	1.47	0.79	0.00	0.00	0.00
25–29	4.00	1.01	1.00	1.09	0.68	0.52	0.00	2.00	0.00
30–34	0.00	1.29	1.11	0.96	1.13	0.79	0.79	0.00	1.66
35–39	0.00	1.84	0.90	0.91	0.90	1.15	1.13	0.98	0.50
40–44	0.00	0.00	0.63	1.79	1.07	0.98	0.85	1.27	1.08
> 45	0.00	0.00	0.00	2.36	0.00	1.08	1.09	0.68	1.26
Maternal age not controlled	0.67	0.62	0.79	1.02	1.86	3.80	4.73	5.10	4.27

TABLE 2

MEAN PATERNAL AGES OVER ALL MATERNAL AGES FOR DS AND LIVE BIRTHS, AND ANNUAL AND OVERALL MEAN DELTA VALUES, STANDARD ERRORS, AND 95% CONFIDENCE INTERVALS FROM CASE-CONTROL COMPARISONS FOR WHITE AND NONWHITE PATERNAL-AGE EFFECT AMONG OHIO DS BIRTHS, 1970–1980

	MEAN PATERNAL AGE					
	DS	Live births	No. DS	MEAN DELTA VALUE	SE	95% CONFIDENCE INTERVAL
Whites:						
1970	31.6	27.6	124	−0.89	0.35	−0.19 to −1.58
1971	33.1	27.5	143	−0.03	0.35	−0.70 to +0.65
1972	32.3	27.5	117	−0.29	0.32	−0.92 to +0.34
1973	30.7	27.4	108	−0.67	0.39	−1.44 to +0.11
1974	30.9	27.2	83	−0.76	0.35	−1.45 to −0.07
1975	31.1	27.3	100	−0.29	0.36	−0.99 to +0.42
1976	31.3	27.4	113	−0.44	0.39	−1.22 to +0.32
1977	31.4	28.1	122	−0.56	0.29	−1.14 to +0.02
1978	30.9	27.5	109	−0.03	0.44	−0.90 to +0.83
1979	29.4	27.6	104	−0.38	0.38	−1.11 to +0.36
1980	30.2	27.6	121	+0.01	0.38	−0.74 to +0.76
1970–1980	31.3	27.5	1,244	−0.35	0.11	−0.56 to −0.13
Nonwhites:						
1970–1980	31.6	27.7	98	+0.47	0.57	−0.66 to +1.59

Case-control Comparison

Annual and 11-year totals for mean paternal ages of white DS fathers and control live-birth fathers, both uncontrolled for maternal age, are given in table 2. In every year, the DS mean paternal age is higher than the mean paternal age of controls. However, when maternal age is controlled through calculation of the mean delta values, also shown in table 2, this is reversed—DS fathers now being younger than control fathers on average in 10 of the 11 years. For nine of the 11 years, the confidence intervals include zero, indicating no paternal-age effect. For two of the years (1970 and 1974), the confidence intervals indicate that the DS fathers were significantly younger than the control fathers. The confidence interval for all 11 years combined was −0.56 to −0.13, also indicating a significantly negative paternal-age effect. Nonwhite totals for the 11 years are presented as well, and show no paternal-age effect. Nonwhite live births, 1970–1980, were used as controls for this analysis.

The DS births were also separated into young and old paternal-age categories and analyzed separately. Table 3 shows the results of the case-control comparison

TABLE 3

MEAN DELTA VALUES, STANDARD ERRORS, AND 95% CONFIDENCE INTERVALS FROM CASE-CONTROL COMPARISONS FOR OHIO WHITE DS BIRTHS, 1970–1980, FOR VARIOUS DIVISIONS OF YOUNG PATERNAL AGE

Definition of young paternal age	No. DS	Mean delta value	SE	95% confidence interval
≤ 39	1,027	−0.15	0.09	−0.33 to +0.03
≤ 44	1,146	−0.22	0.09	−0.41 to −0.04
≤ 49	1,217	−0.31	0.10	−0.50 to −0.11

TABLE 4

OVERALL MEAN DELTA VALUES, STANDARD ERRORS, AND 95% CONFIDENCE INTERVALS FROM CASE-CONTROL COMPARISONS AMONG SUBPOPULATIONS BY MODE OF ASCERTAINMENT, OHIO WHITE DS BIRTHS, 1970–1980

Mode of ascertainment*	Mean paternal age	No. DS	Mean delta value	SE	95% confidence interval
BC and CA	31.3	324	−0.17	0.20	−0.57 to +0.23
CA not BC	30.9	569	−0.32	0.17	−0.65 to +0.01
BC not CA	31.9	351	−0.55	0.20	−0.94 to −0.16
All BC	31.6	675	−0.37	0.14	−0.09 to −0.65
All CA	31.0	893	−0.27	0.13	−0.01 to −0.53

* BC and CA: those individuals reported on their birth certificates as DS, and chromosomally analyzed. CA not BC: those individuals chromosomally analyzed, but not reported on their birth certificates as DS. BC not CA: those individuals reported on their birth certificates as DS, but not chromosomally analyzed. All BC: those individuals reported on their birth certificates as DS, regardless of whether they were chromosomally analyzed. All CA: those individuals chromosomally analyzed regardless of whether they were reported on their birth certificates as DS.

applied to the young paternal-age categories. For two of the three definitions of young paternal age, ≤ 44 and ≤ 49, a statistically significant negative paternal-age effect was found, but not for those ≤ 39.

The older paternal age category of ≥ 40 was analyzed using Wilcoxon's signed test. A statistically significant negative paternal-age effect was found ($Z = 2.87$, $P = .002$). The older paternal-age categories, ≥ 45 and ≥ 50, were not analyzed since this test is not sufficiently powerful.

The three subpopulations of DS births classified by mode of ascertainment were analyzed separately using the case-control comparison, and the results are shown in table 4. The fathers of those DS individuals ascertained only from birth certificates were significantly younger than the fathers of control live births,

TABLE 5

MEAN MATERNAL AGES OVER ALL PATERNAL AGES FOR DS AND LIVE BIRTHS, AND ANNUAL AND OVERALL MEAN DELTA VALUES, STANDARD ERRORS, AND 95% CONFIDENCE INTERVALS FROM CASE-CONTROL COMPARISONS FOR MATERNAL-AGE EFFECT AMONG OHIO WHITE DS BIRTHS, 1970–1980

Year	Mean maternal age		No. DS	Mean delta value	SE	95% confidence interval
	DS	Live births				
1970	29.9	24.8	124	+2.39	0.38	+1.64 to +3.13
1971	30.7	24.8	143	+2.36	0.34	+1.69 to +3.03
1972	30.2	24.7	117	+2.34	0.35	+1.66 to +3.03
1973	28.9	24.6	108	+2.02	0.33	+1.37 to +2.67
1974	29.3	24.5	83	+2.19	0.46	+1.29 to +3.08
1975	29.1	24.6	100	+1.66	0.34	+0.99 to +2.31
1976	29.4	24.7	113	+2.20	0.38	+1.45 to +2.96
1977	29.2	24.8	122	+2.00	0.34	+1.34 to +2.66
1978	28.8	24.9	109	+1.85	0.38	+1.10 to +2.60
1979	27.3	24.9	104	+0.99	0.39	+0.22 to +1.75
1980	28.0	24.9	121	+1.16	0.33	+0.52 to +1.81
1970–1980	29.2	24.8	1,244	+2.09	0.17	+1.76 to +2.43

TABLE 6

COMPARISON OF OBSERVED DS BIRTHS WITH EXPECTED USING THE MANTEL-HAENSZEL TEST

PATERNAL-AGE DIVISION	TOTAL		
	Observed	Expected	χ^{2}*
≤ 39 ...	1,027	1,007.46	4.33
≥ 40 ...	215	234.54	
≤ 44 ...	1,157	1,142.15	3.42
≥ 45 ...	87	101.85	
≤ 49 ...	1,217	1,213.58	0.33
≥ 50 ...	27	30.42	
≤ 54 ...	1,236	1,234.98	0.03
≥ 55 ...	86	9.02	

NOTE: Comparisons are by various paternal-age divisions for Ohio white births, 1970–1980.

* Calculated using equation of Mantel and Haenszel as provided by [16], p. 256.

while those ascertained from chromosome analysis and birth certificates showed no statistically significant paternal-age effect.

The case-control comparison was similarly used to test for a maternal-age effect by comparing mean maternal age of normal live births to DS maternal ages for each single-year paternal age. The results are given in table 5. A strong and statistically significant positive maternal-age effect was found in each of the individual 11 years, and also for the 11 years combined.

Mantel-Haenszel Test

The Mantel-Haenszel summary chi squares for the four divisions of young and old paternal ages are shown in table 6. One of the four paternal-age divisions (≤ 39 and ≥ 40) showed a statistically significant lower rate of DS to older fathers ($\chi^{2}_{1} = 4.33$, $P = .04$).

The subpopulations classified by mode of ascertainment were analyzed separately using the Mantel-Haenszel test. The results are shown in table 7. No paternal-age effect was found within any of the subpopulations. Maternal-age effect was also tested by the Mantel-Haenszel test. The summary chi square calculated was 297.72, indicating a strong positive maternal-age effect ($P < .001$).

DISCUSSION

Using the largest data set analyzed to date, these results clearly provide no evidence of a positive paternal-age effect. This suggests that other studies indicating a strong positive effect may be the result of statistical fluctuations and/or temporal and geographic fluctuation in rates. It also weakens the recent suggestion by Hook and Cross [17] that a weak positive effect is consistent with all studies to date.

TABLE 7

COMPARISON OF OBSERVED DS BIRTHS WITH EXPECTED USING THE MANTEL-HAENSZEL TEST

Mode of ascertainment*	Paternal age	Observed DS	Expected DS	χ^2†
BC and CA	≤ 39–≥ 40	53	56.35	0.38
	≤ 44–≥ 45	21	23.16	0.19
	≤ 49–≥ 50	7	6.72	0.01
CA and BC	≤ 39–≥ 40	93	99.17	0.86
	≤ 44–≥ 45	39	41.44	0.15
	≤ 49–≥ 50	14	11.85	0.16
BC not CA	≤ 39–≥ 40	75	81.04	1.17
	≤ 44–≥ 45	32	37.63	1.32
	≤ 49–≥ 50	7	11.78	1.93

NOTE: Comparisons by various paternal-age divisions within each subpopulation, Ohio white DS births, 1970–1980.

* BC and CA: those individuals chromosomally analyzed, and reported on their birth certificates as DS. CA not BC: those individuals chromosomally analyzed, but not reported on their birth certificates as DS. BC not CA: those individuals reported on their birth certificates as DS, but not chromosomally analyzed.

† Calculated using equation of Mantel and Haenszel as provided by [16], p. 256.

The Mantel-Haenszel test found a statistically significant lower rate of DS births to older fathers in one of the 13 tests in which it was used. This negative paternal-age effect was seen among the paternal-age category ≥ 40. However, no effect was seen at the older definitions of old paternal age (≥ 45, ≥ 50, and ≥ 55). The case-control comparison found the DS fathers to be significantly younger than the fathers of control live births in six of 17 tests when the DS population was not subdivided by mode of ascertainment.

Previous studies either reported a positive paternal-age effect or no paternal-age effect. Of five studies reporting a positive paternal-age effect [3–7], two did not control for maternal age by single year [3, 4]. When the data were reanalyzed by single-year maternal age, no significant positive paternal-age effect was found [8, 17]. All of the studies reporting a positive paternal-age effect were done with DS populations outside of the United States; no paternal-age effect was found in five DS populations in the United States. Three of these U.S. studies analyzed data ascertained from birth certificates. It is known that birth certificates provide a low ascertainment of DS, and it may be that this source obscures an existing paternal-age effect. Four of the five studies that reported a positive paternal-age effect analyzed data that were extensively ascertained. However, underascertainment would affect only the results if underascertainment also led to a bias.

The Ohio data were divided into three subpopulations according to ascertainment. This made it possible to test each of the subpopulations separately for a paternal-age effect. The Mantel-Haenszel test did not detect a significantly higher or lower rate of DS to older fathers among any of the subpopulations by determining that the *number* of DS births to old and young fathers was not significantly different from the expected. However, the case-control comparison found the *ages* of the fathers for DS births to be different from the fathers of the control births in one of the subpopulations. The fathers of DS individuals ascertained by birth certificates

only were younger than the fathers of control births. The DS individuals ascertained by chromosome analysis only and those ascertained from both chromosome analysis and birth certificates did not have fathers significantly younger or older than controls. The basis for the difference among these subpopulations is not known, although it could simply represent statistical artifact as all three subpopulations had negative mean delta values (table 4). There would appear to be little if any biologic meaning to attach to these or any of the negative values found in this study, particularly since only seven of 30 tests showed statistical significance.

Both statistical methods used in this study detected a strong positive maternal-age effect, which supports the validity of the methods. Given their power to reject the null hypothesis, and that two-thirds of the estimated DS births in Ohio during 1970–1980 were used in this study, the Ohio data are unequivocal in providing no evidence for an increased risk of DS for older fathers.

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