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Advanced Paternal Age and Risk of Fetal Death: A Cohort Study

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A possible detrimental paternal age effect on offspring health due to mutations of paternal origin should be reflected in an association between paternal age and fetal loss. The authors used data from a prospective study of 23,821 pregnant women recruited consecutively to the Danish National Birth Cohort from 1997 to 1999 to assess the association between paternal age and fetal death. Fathers of the pregnancies were identified by record linkage to population registers. The paternal age-related risks of fetal death and its components, early and late fetal loss, were estimated using survival analysis. Pregnancies fathered by a man aged 50 or more years (n = 124) had almost twice the risk of ending in a fetal loss compared with pregnancies with younger fathers (hazard ratio = 1.88, 95% confidence interval: 0.93, 3.82), after adjustment for maternal age, reproductive history, and maternal lifestyle during pregnancy. Various approaches to adjustment for potential residual confounding of the relation by maternal age did not affect the relative risk estimates. The paternal age-related risk of late fetal death was higher than the risk of early fetal death and started to increase from the age of 45 years. It should, however, be interpreted cautiously because of the restricted number of fetal deaths.

abortion, spontaneous; fetal death; maternal age; paternal age; pregnancy

While there is a general agreement that advanced maternal age is a strong risk factor for fetal death (1, 2), controversy still exists regarding the influence of advanced paternal age on fetal survival. A major reason for the association between maternal age and fetal loss is an increased risk of aneuploid conceptions with increasing maternal age and the fact that aneuploid conceptions are more likely to result in a fetal loss (3). The increased risk of aneuploid conceptions has been explained as a consequence of the long period of meiotic arrest of the primary oocyte between the first meiotic prophase in the fifth month of fetal life to the eventual development of the oocyte several decades later (4).

However, as early as 1955, Penrose (5) suggested that the high number of divisions in the male germ line might result in a higher probability of spontaneous mutations in the spermatozoa, leading to an increase in conditions associated with single gene mutations. A variety of rare diseases have been shown to be caused by point mutations of paternal origin, and it has been suggested that a search for conditions that show a paternal age effect would provide new insight into causal factors behind disease development (6). Recently, advanced paternal age has been associated with a short life span of the offspring (7), acute lymphatic leukemia (8), and schizophrenia (9) among offspring and with preeclampsia during pregnancy (10).

A possible detrimental paternal age effect on offspring health due to mutations of paternal origin should be reflected in an association between paternal age and fetal loss, analogous to the propensity of fetal death in aneuploid conceptions (11). Few studies have, however, investigated this association, and the outcomes under study, the study designs, and the findings are heterogeneous (12–19). Most of the studies are restricted to fetal loss in the latter half of pregnancy, which includes only a very small proportion of fetal losses. Only three studies examine early fetal loss (15, 17, 19), and none of these is prospective in design. A few large-scale studies are based on register data (13, 14, 18), which have very sparse information on potential confounding factors.

The objective of this study is to describe the associations between high paternal age and risk of fetal death in a cohort study, by using survival analysis and taking maternal age,

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reproductive history, and lifestyle factors into account. We describe the paternal age-related risk of overall fetal loss and report the risk of spontaneous abortion and stillbirth separately.

MATERIALS AND METHODS

The study is a cohort study, using data from the Danish National Birth Cohort, which is an ongoing nationwide study of pregnant women and their offspring (20). Recruitment to the Danish National Birth Cohort took place after the first antenatal care visit to the general practitioner, which is scheduled as early as possible after recognition of the pregnancy. The pregnant woman received written information about the Danish National Birth Cohort at the antenatal visit and was included as a participant in the cohort when a signed informed consent form from the woman was received at the Danish Epidemiology Science Centre. Participants contributed with information on exposures during the first part of pregnancy by means of a computer-assisted telephone interview, scheduled to take place during pregnancy weeks 12–16. In the case of fetal death prior to completion of this interview, the participants were offered a similar interview. The interviews covered questions on exposures in the first trimester of pregnancy, including alcohol consumption, smoking, coffee intake, reproductive history, and occupation.

For this particular study, we used interview data from all pregnant women recruited to the Danish National Birth Cohort from October 1, 1997, to March 31, 1999. These data are described in detail elsewhere (21). A total of 24,038 women were included in the Danish National Birth Cohort during that time period and subsequently interviewed. Of these, 217 women entered the cohort with two pregnancies, and only the first pregnancies were included in this study, leaving 23,821 pregnancies for analysis.

The data from the Danish National Birth Cohort did not include information on the father of the pregnancy. The identity of the presumed father was established as follows. All citizens in Denmark, including liveborn children, are registered in the Civil Registration System and given a unique number, which is used in all national registers to identify the person. The first six digits in the Civil Registration System number describe the person's birthday, and the number can thus serve as key for record linkage between registers, as well as for calculation of age. The Civil Registration System comprises information on persons living in the same household, links among mother, father, and child, and links between married couples.

We identified 22,443 males registered as fathers of a liveborn child in the study population by record linkage with the Civil Registration System. For 1,135 pregnancies, a presumed father was assigned, defined as the sole adult male cohabiting with the mother at the date of conception who was not a child of the mother or the father of the mother. For the remaining 243 pregnancies, either no adult male was cohabiting with the mother or more than one adult male lived in the same household. These were evaluated manually, and an additional 60 were assigned a presumed father, if the woman had a registered husband at the date of conception or if a sole adult male were cohabiting with the mother after exclusion of fathers of the mothers. It was not possible to assign a father to a total of 183 pregnancies.

TABLE 1. Key information on the pregnancies of all women for whom interview information was available and who were first-time participants, Danish National Birth Cohort, 1997–1999

	No.	%
Paternal age (years)		
≤19	64	0.3
20–24	1,421	6.0
25–29	7,151	30.0
30–34	9,222	38.7
35–39	4,130	17.3
40–44	1,213	5.1
45–49	313	1.3
≥50	124	0.5
Missing	183	0.8
Outcome of pregnancy		
Livebirth	22,593	94.8
Spontaneous abortion	1,039	4.4
Stillbirth	90	0.4
Induced abortion on indication	64	0.3
Other pregnancy outcome*	9	0.0
Loss of follow-up†	26	0.1
Pregnancy week at recruitment		
≤6	883	3.7
7–8	3,449	14.5
9–10	6,071	25.5
11–12	5,574	23.4
13–16	5,742	24.1
17–28	2,102	8.8
Total	23,821	100.0

* Ectopic pregnancy and hydatidiform mole.
† Including 11 women who emigrated during pregnancy.

The outcome measure of interest was fetal death, that is, a nondeliberate loss or death of an intrauterine product of conception irrespective of the duration of the pregnancy. By record linkage with the Civil Registration System, we identified liveborn offspring from all pregnancies in the cohort. From the National Discharge Registry, which contains information about all citizens diagnosed or treated in a hospital setting, we obtained information about other pregnancy outcomes: ectopic pregnancy, induced abortion on indication, hydatidiform mole, and spontaneous abortion and stillbirth. According to national standards, a stillbirth is defined as the birth of a child showing no signs of life and with a gestational age of 28 weeks or more. Spontaneous abortion is defined as a nondeliberate fetal death of an intrauterine pregnancy before 28 completed weeks of gestation. In case we could not identify an outcome of pregnancy by these two procedures, we used information about the outcome of preg-

TABLE 2. Distribution of maternal and paternal characteristics among 23,821 pregnancies, Danish National Birth Cohort, 1997–1999

	Total		Paternal age (years) at conception*								
	No.	%	≤19	20–24	25–29	30–34	35–39	40–44	45–49	≥50	Missing
Maternal factors											
Maternal age (years)											
≤19	218	0.9	51.6	8.0	0.7	0.1	0.0	0.0	0.3	—†	4.4
20–24	2,917	12.2	45.3	60.6	19.7	5.3	2.1	1.3	1.9	4.0	9.3
25–29	9,544	40.1	1.6	25.8	63.5	39.9	17.0	11.1	14.1	9.7	33.9
30–34	8,507	35.7	1.6	4.7	14.7	48.5	53.5	40.6	35.8	38.7	30.6
35–39	2,402	10.1	—	0.8	1.4	5.9	26.1	38.9	38.3	37.1	18.0
≥40	233	1.0	—	—	0.0	0.3	1.3	8.0	9.6	10.5	3.8
Parity (previous births)											
0	10,443	43.8	89.1	76.6	60.1	36.4	25.5	25.5	36.7	41.9	59.0
≥1	13,375	56.2	10.9	23.4	39.8	63.6	74.5	74.5	63.3	58.1	41.0
Missing	3	0.0	—	—	0.0	0.0	—	—	—	—	—
No. of previous spontaneous abortions											
0	19,238	80.8	90.6	87.1	86.1	80.4	73.9	70.9	70.6	72.6	82.5
1	3,448	14.5	7.8	10.7	11.0	14.9	18.7	19.9	19.8	18.5	13.7
2	818	3.4	1.6	1.5	2.0	3.4	5.4	6.1	7.7	4.8	3.8
≥3	297	1.2	—	0.6	0.7	1.2	1.9	3.1	1.9	4.0	—
Missing	20	0.1	—	0.1	0.1	0.1	0.1	0.1	—	—	—
Occupational status											
High-grade professional	1,992	8.4	—	1.3	4.9	9.8	12.1	11.0	13.4	22.4	4.9
Low-grade professional	5,768	24.2	3.1	8.1	21.0	26.2	29.2	30.7	26.5	21.8	23.0
Skilled worker	5,439	22.8	12.5	16.2	23.0	24.6	22.0	20.9	21.1	17.7	19.7
Unskilled worker	4,292	18.0	18.8	27.7	19.8	16.5	16.0	16.0	14.1	15.3	15.3
Student	3,140	13.2	29.7	26.5	18.1	10.3	8.3	7.3	8.9	11.3	16.4
Economically inactive	2,603	10.9	32.8	18.2	10.9	9.8	9.9	11.4	12.8	8.9	19.7
Unclassifiable	587	2.5	3.1	2.2	2.2	2.7	2.5	2.6	3.2	1.6	1.1

Table continues

nancy obtained from the mother and registered with the Danish National Birth Cohort Study. The date of conception was calculated as the first day of the last menstrual period plus 14 days, and gestational age at fetal loss or birth was likewise calculated from the last menstrual period, which was reported in the informed consent form. Permissions from the Danish Data Protection Board and the National Scientific Ethics Committee were obtained before initiation of the study.

The statistical analyses are described as follows. The relative risk (hazard ratio) of fetal loss according to paternal age was estimated by using survival analysis. Paternal age was calculated from the Civil Registration System number as paternal age at the date of conception. Paternal age was categorized in 5-year groups for analysis: 24 years or less, 25–29 years, 30–34 years, 35–39 years, 40–44 years, 45–49 years, and 50 years or more.

Several covariates were included in the multivariate model: maternal age, parity (nulliparity, parity with ≥1 previous births), previous spontaneous abortions ($n = 0, 1, 2, \geq 3$), and maternal and paternal occupational status (professional, skilled worker, unskilled worker, economically inactive, student, unclassifiable). The following variables describing maternal health-related behaviors during pregnancy were included: smoking (0, 1–10 cigarettes/day, ≥11 cigarettes/day), maternal alcohol consumption (0, ½–1½ drinks/week, 2–3½ drinks/week, ≥4 drinks/week), and maternal coffee consumption (0, 1–6 cups, ≥7 cups/day; 1 cup = ~150 ml). The women were asked whether or not their partner was a smoker. This information was entered into the model as paternal smoking status (smoker, nonsmoker).

To capture a possible confounding effect of maternal age, this variable was entered into the model in three different ways: in 5-year groups (≤24 years, 25–29 years, 30–34 years, 35–39 years, and ≥40 years), in 1-year groups (≤19, 20, 21, …, 40, 41, ≥42 years), and by modeling the effect of maternal age by restricted cubic splines with knots at 22, 27, 32, 37, and 42 years and entering this function into the model.

The statistical approach applied to estimate the hazard ratio of fetal loss (i.e., spontaneous abortion and stillbirth) was a Cox regression model with gestational days (days

TABLE 2. Continued

	Total		Paternal age (years) at conception*								
	No.	%	≤19	20–24	25–29	30–34	35–39	40–44	45–49	≥50	Missing
Alcohol consumption during pregnancy (drinks/week)											
0	13,269	55.7	76.6	71.6	61.2	53.3	48.7	49.0	49.8	43.5	52.5
½–1½	7,686	32.2	20.3	24.0	30.6	34.3	34.3	31.2	28.1	30.6	30.6
2–3½	2,262	9.5	3.1	3.2	6.8	9.9	13.2	14.6	14.1	21.0	10.4
≥4	540	2.2	0.0	0.8	1.2	2.2	3.4	5.1	7.3	4.8	6.6
Missing	64	0.4	0.0	0.3	0.2	0.3	0.4	0.2	0.6	0.0	0.0
Smoking during pregnancy (cigarettes/day)											
0	17,363	72.9	32.8	57.9	71.6	75.3	76.2	74.5	70.0	75.0	49.7
1–10	4,814	20.2	43.8	31.9	21.6	18.5	17.1	18.5	21.7	16.1	33.3
≥11	1,563	6.6	20.3	10.1	6.4	5.8	6.4	6.3	8.0	8.9	16.4
Missing	81	0.3	3.1	0.1	0.3	0.3	0.4	0.7	0.3	—	0.5
Coffee consumption during pregnancy (cups‡/day)											
0	12,854	53.9	59.4	66.3	60.0	53.3	45.7	42.0	42.2	41.9	45.4
1–6	10,148	42.6	37.5	31.5	37.4	43.4	49.7	52.5	51.4	50.8	48.6
≥7	808	3.4	3.1	2.3	2.4	3.3	4.6	5.4	6.4	7.3	6.0
Missing	11	0.1	—	—	0.1	0.0	0.0	—	—	—	—
Paternal factors											
Occupational status											
High-grade professional	4,499	18.9	—	2.7	12.9	21.7	25.8	26.9	28.8	31.5	8.2
Low-grade professional	4,127	17.3	1.6	6.8	14.6	19.0	20.3	22.1	24.3	24.2	12.0
Skilled worker	8,152	34.2	21.9	39.0	40.0	33.5	29.4	25.3	19.5	18.5	13.1
Unskilled worker	3,644	15.3	15.6	25.1	16.0	14.1	14.4	13.4	11.5	8.9	14.2
Economically inactive	1,675	7.0	20.3	15.9	10.5	4.8	3.6	4.8	4.8	6.5	10.6
Unclassifiable	1,329	5.6	9.4	6.5	5.2	5.9	5.2	5.5	5.4	3.2	6.6
Missing	395	1.7	31.2	3.9	0.8	1.0	1.3	2.0	5.8	7.3	35.0
Smoking											
Nonsmoker	7,422	31.2	26.6	55.0	67.5	69.7	67.3	61.9	58.1	55.6	33.3
Smoker	15,898	66.7	39.1	40.1	31.5	28.9	30.9	35.4	33.9	35.5	29.0
Missing	501	2.1	34.4	4.9	1.0	1.3	1.7	2.7	8.0	8.9	37.7

* Characteristics according to paternal age at conception shown as percentages.
† —, no persons in this cell.
‡ One cup = approximately 150 ml.

since last menstrual period) as the underlying time variable. The model allowed for delayed entry at the day of recruitment to the cohort. Follow-up ended at the day of fetal loss, livebirth, other pregnancy outcome (ectopic pregnancy, induced abortion, and hydatidiform mole), or day of loss to follow-up.

When hazards for early fetal death were analyzed, follow-up ended at the gestational day of spontaneous abortion, gestational day of other pregnancy outcomes (e.g., induced abortion on indication), or gestational day 139 (>20 weeks), whichever came first, in order to have a precise assessment of "time at risk." Likewise, entry time was 140 gestational days in the analysis of risk of late fetal death. An additional analysis, with a combination of early fetal death and induced abortion as the event of interest and with entry and exit times equal to those of the early fetal death analysis, was carried out as a sensitivity analysis. Finally, we made an analysis of the paternal age-related risk of fetal death of a restricted material after exclusion of all pregnancies preceded by infertility treatment according to information from the interview.

The proportional hazards assumptions were evaluated for all variables using cumulative baseline hazards plots and smoothed martingale residuals (22, 23). Likelihood ratio tests were used to test for homogeneity. The Cox regression model was analyzed using the SAS procedures software package PROG PHREG (24) and the survival library in the software package R (25).

RESULTS

Of the 23,821 pregnancies included in this study, a total of 1,129 ended in a fetal death. Only 64 ended in induced abortion on indication due to fetal abnormality. About two thirds of the pregnancies entered the cohort during the first

TABLE 3. Outcome among 23,821 pregnancies according to parental age group at conception, Danish National Birth Cohort, 1997–1999

Maternal age	Paternal age (years) at conception*							
	≤24	25–29	30–34	35–39	40–44	45–49	≥50	Missing
≤24 years								
Livebirths	993	1,396	482	81	15	6	4	12
Fetal deaths	40	57	19	5	1	1	1	12
Other†	4	3	1	1	0	0	0	1
25–29 years								
Livebirths	349	4,340	3,549	677	131	42	11	28
Fetal deaths	18	186	119	23	4	2	1	31
Other	1	17	11	1	0	0	0	3
30–34 years								
Livebirths	65	1,003	4,254	2,091	474	104	43	20
Fetal deaths	2	44	197	108	19	7	5	30
Other	1	3	19	11	0	1	0	6
35–39 years								
Livebirths	11	89	506	1,003	441	113	44	12
Fetal deaths	1	9	30	72	30	7	2	18
Other	0	1	5	4	1	0	0	3
≥40 years								
Livebirths	0	3	25	46	87	29	11	3
Fetal deaths	0	0	5	7	9	1	2	4
Other	0	0	0	0	1	0	0	0

* Characteristics according to paternal age at conception shown as numbers.
† Induced abortion on indication, ectopic pregnancy, hydatidiform mole, or loss of follow-up.

trimester (table 1). We succeeded in assigning a presumed father to 23,638, corresponding to 99.2 percent of all pregnancies. The percentages of identified fathers according to outcome of pregnancy were 99.7, 91.7, and 95.6 for livebirth, spontaneous abortion, and stillbirth, respectively. A cross-check of the identity of the 22,144 fathers assigned by

TABLE 4. Crude and adjusted hazard ratios of fetal death according to paternal age at conception among 23,821 pregnancies, Danish National Birth Cohort, 1997–1999*

Paternal age	No. of events	Risk of fetal death							
		Crude		Adjusted†					
				Maternal age in 5-year groups		Maternal age in 1-year groups		Maternal age modeled using restricted cubic splines	
		Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval	Hazard ratio	95% confidence interval
≤24 years	60	1.01	0.76, 1.32	1.09	0.81, 1.47	1.11	0.82, 1.51	1.09	0.80, 1.49
25–29 years	294	1	Referent	1	Referent	1	Referent	1	Referent
30–34 years	367	1.02	0.87, 1.20	0.87	0.74, 1.04	0.90	0.76, 1.07	0.89	0.75, 1.05
35–39 years	213	1.38	1.15, 1.64	0.98	0.80, 1.21	0.99	0.80, 1.23	0.97	0.79, 1.21
40–44 years	62	1.35	1.03, 1.77	0.82	0.60, 1.12	0.79	0.58, 1.09	0.79	0.57, 1.08
45–49 years	18	1.54	0.96, 2.48	1.03	0.63, 1.70	1.02	0.61, 1.68	1.00	0.60, 1.65
≥50 years	11	2.65	1.45, 4.84	1.69	0.91, 3.15	1.71	0.91, 3.21	1.62	0.86, 3.03

* Three different types of adjustment for maternal age.
† Adjusted for maternal age, parity, number of previous abortions, alcohol and coffee consumption during pregnancy, maternal and paternal smoking, and maternal and paternal occupational status.

TABLE 5. Adjusted* hazard ratios of early fetal death (<20 weeks of gestation) and late fetal death (≥20 weeks of gestation) according to paternal age at conception among 23,821 pregnancies, Danish National Birth Cohort, 1997–1999

Paternal age	Risk of early fetal death			Risk of late fetal death		
	No. of events	Hazard ratio	95% confidence interval	No. of events	Hazard ratio	95% confidence interval
≤24 years	51	1.17	0.84, 1.63	9	0.88	0.40, 1.94
25–29 years	254	1	Referent	39	1	Referent
30–34 years	309	0.86	0.72, 1.03	57	1.21	0.76, 1.92
35–39 years	186	0.99	0.79, 1.25	27	1.04	0.58, 1.88
40–44 years	54	0.77	0.55, 1.09	8	0.98	0.42, 2.33
45–49 years	15	0.97	0.56, 1.69	3	1.40	0.40, 4.85
≥50 years	8	1.38	0.66, 2.88	3	3.94	1.12, 13.8

* Adjusted for maternal age (1-year groups), parity, number of previous abortions, alcohol and coffee consumption during pregnancy, maternal and paternal smoking, and maternal and paternal occupational status.

linkage with the Civil Registration System and for whom we identified one sole male cohabiting with the mother at the date of conception showed agreement in 98.3 percent of the fathers.

Selected characteristics of the mothers and the fathers and the distribution of these according to parental age are shown in table 2. Maternal age and paternal age were correlated, but for each level of maternal age we found some variation in paternal age. Maternal obstetric history was generally related to paternal age in the expected fashion; however, the lowest proportion of nulliparous mothers was found for fathers between 35 years and 44 years of age. Maternal smoking and maternal coffee and alcohol consumption were related to paternal age differently. The highest proportion of both maternal and paternal smokers was found in pregnancies with the youngest fathers, while maternal coffee and alcohol consumption during pregnancy was positively related to paternal age. The maternal and paternal occupational status increased with increasing paternal age. The outcome of pregnancy in relation to paternal and maternal age is shown in table 3.

In table 4, we present the hazard ratio of fetal death according to paternal age. The apparent increased risk of fetal death when fathers were aged 35–49 years was essentially abolished after adjustment for maternal age. The risk of fetal loss was, however, substantially increased when paternal age was 50 years or more.

The risk estimates were similar in the three models where maternal age was entered in 5-year groups and in 1-year groups and modeled using restricted cubic splines. The results indicate that residual confounding by maternal age does not account for the positive association found between high paternal age and fetal losses and that controlling for maternal age in 1-year groups provides a noninflated estimate. The three ways of adjustment for maternal age were made for all the analyses presented, but only the results of adjustments for maternal age in 1-year groups are presented, since the estimates were unaffected by the manner of controlling for maternal age.

We tested for interaction between maternal and paternal age with respect to the risk of fetal death, and this revealed no strong evidence of such an interaction ($p = 0.3$). The risk estimates for all age groups below the age of 50 years were very close to 1, and the test for homogeneity allowed the collapse of all age groups less than 50 years of age ($p = 0.4$). After this was done, the relative risk of fetal death in offspring with fathers aged 50 or more years was 1.88 (95 percent confidence interval: 0.93, 3.82) compared with that for fathers aged less than 50 years.

To protect against the possibility that the effect of paternal age seen was due to confounding from subfertility, we restricted the analysis to pregnancies probably not being a result of infertility treatment. This was done by excluding all observations in which the couple was treated for sub- or infertility prior to the pregnancy, which occurred in 1,431 of the pregnancies. The relative risk of fetal death in pregnancies fathered by a male aged 50 years or more compared with that for fathers aged less than 50 years was 1.95 (95 percent confidence interval: 0.91, 4.17).

The paternal age-related risks of early and late fetal death adjusted for potential confounders were analyzed separately (table 5). The risk of early fetal death was elevated slightly (hazard ratio = 1.38, 95 percent confidence interval: 0.66, 2.88) for fathers aged 50 years or more but was similar for all other levels of paternal age. The test for homogeneity allowed the collapse of all of the age groups less than 50 years of age ($p = 0.2$), and a second likelihood ratio test comparing the risk for early fetal death when the paternal age is less than 50 years with pregnancies where the father is aged 50 years or more yielded a p value of 0.025. We extended this analysis by looking at a combination of spontaneous abortion and induced abortion on indication in the first 20 weeks of pregnancy as the outcome, because pregnancies with detectable malformations have a high probability of resulting in a spontaneous fetal loss if carried on without intervention. The results were essentially the same as found for spontaneous abortion; that is, the risk was close to one in all paternal age groups below 50 years of age but

was elevated, although imprecisely estimated, for a father aged 50 years or more (hazard ratio = 1.31, 95 percent confidence interval: 0.63, 2.73).

The paternal age effect on late fetal death showed a tendency to increase from a paternal age of 45 years. However, the likelihood ratio test for homogeneity provided no evidence against homogeneity of groups below age 50 years ($p > 0.9$). The hazard ratio for fathers aged 50 years or more compared with those below 50 years was 4.56 (95 percent confidence interval: 1.39, 14.9).

To assess the impact of including lifestyle factors in the analyses of the relation between paternal age and fetal loss, we mimicked a register-based study by including only maternal age and paternal age in the model. Doing so, we found the relative risk of fetal death in the paternal age group of 50 years or more to be 1.70 (95 percent confidence interval: 0.91, 3.18).

DISCUSSION

In this follow-up study of almost 24,000 pregnancies, we found that pregnancies fathered by a male aged 50 years or more had an increased risk of ending in a fetal death compared with pregnancies in which the father was less than 50 years of age. The paternal age effect tended to be stronger for late fetal death, which showed a fourfold increased risk if the father was 50 years or more at conception, than for fetal death in the first half of pregnancy.

Maternal age is a very strong risk factor for fetal death (2), and maternal and paternal ages are correlated. This implies the possibility of residual confounding of the estimates by maternal age. It has been shown that an apparently significant positive association between paternal age and Down's syndrome after adjustment for maternal age in 5-year groups disappeared when the maternal age was modeled more precisely (26). By treating maternal age in three different ways in the regression model (5-year groups, 1-year groups, and describing the shape of the maternal age effect by fitting third degree polynomials around five preselected knots, i.e., restricted cubic splines), we explored the possible confounding effect of maternal age. Using 1-year groups or restricted cubic splines instead of 5-year groups did not, however, reveal any strong residual confounding effect by maternal age on the paternal age-related risk of fetal death.

In contrast to earlier prospective studies (13, 14, 18), we have been able to control for a variety of potential confounding factors. Maternal reproductive history might confound the relation between parental age and fetal loss and is, where possible, included in the statistical models (27). That lifestyle factors known to influence risk of fetal loss vary substantially with parental age is often ignored, however. Alcohol intake in pregnancy has been shown to increase with increasing maternal age in Denmark (28), and our data show that both maternal alcohol drinking and smoking during pregnancy are associated with paternal age, although in opposite directions. By including important lifestyle factors known or suspected to affect the risk of fetal death (29–31), we feel more confident that confounding by lifestyle factors does not account for the associations found, particularly as exclusion of these factors from the model did not substantially affect the risk estimates.

One very large study of parental age and fetal loss exists, that of Selvin and Garfinkel (14), who analyzed birth certificate data from more than 1.5 million pregnancies for the effects of maternal age, paternal age, and parity. They found a paternal age effect on risk of fetal loss that was almost as strong as the maternal age effect. The outcome was restricted to fetal losses after pregnancy week 20, when only a minority of losses occurs. The high risk estimates for late fetal death that we found for men aged 50 years or more in our data are comparable to the finding of Selvin and Garfinkel.

A recent study addressed the combined effect of maternal and paternal age on risk of miscarriage by using data on "last planned pregnancy" in a retrospective sample of 3,174 couples (17). Through an analysis of the risk of miscarriage in combinations of maternal and paternal age classes, it was found that the maternal age-related risk began to increase earlier if the man was more than 40 years of age. One explanation could be that the reported interaction is due to residual confounding by maternal age, since very broad categories of maternal age were used. Analogous to this finding, Slama et al. (19) reported an increased risk of spontaneous abortion with advanced paternal age when the female partner was less than 30 years of age. In this latter study, a substantial effort was made to avoid residual confounding by maternal age. Although we have no biologic reasons to expect such interactions, we tested whether we were able to replicate this finding, but we did not find evidence of an interaction between maternal and paternal age in our data.

In addition to the size of this study, the almost complete follow-up, and the possibility of control for potentially confounding factors, an additional strength of our study was the early recruitment to the Danish National Birth Cohort, which allowed us to analyze risk of early fetal death. A common problem in studies of early fetal death is the possibility that those who recognize their pregnancy early may have a higher baseline probability of fetal loss, and they may differ from others with respect to, for example, parental age. The present study is to our knowledge the first study of paternal age and pregnancy loss that has dealt with these problems by applying survival analysis techniques with left truncation to the data. We have a sufficient number of pregnancies at risk from pregnancy week 6 to suggest that our results apply to pregnancy losses from pregnancy week 6 and onward. However, the data do not allow us to estimate the effect of paternal age on risk of fetal loss in the very first weeks of pregnancy. To assess the selection to the study according to outcome, a fetal life-table analysis of these data has been made. From this, the overall risk of fetal loss from the beginning of pregnancy week 6 was estimated to be 11.5 percent (32). The rate of stillbirth was 0.4 percent. These percentages are similar to the national ones, which suggest that selection bias according to outcome in this cohort was negligible.

A possible bias arises from the suggestion that couples with infertility problems and consequently a higher probability of fetal death would be overrepresented in pregnancies with old fathers. The finding of a marginally higher paternal

age-related relative risk of fetal death in the subcohort, restricted to pregnancies not preceded by any kind of fertility treatment, speaks against this as an important source of bias in our analyses. As always, when paternal factors are to be studied, uncertainties about paternity exist (33), although misclassification of paternity is unlikely to produce the results that we observe. This study included only 124 fathers aged 50 years or more and, among these, 11 pregnancies resulted in fetal death, of which three were late fetal deaths; the results should be interpreted with caution.

One mechanism behind the paternal age association with fetal loss could be a direct effect on germ cells of accumulated detrimental exposures with age. In contrast to a recent study (34), ours did not, however, find that paternal smoking affected the risk of fetal loss in our data. Another interpretation of our finding could be that the increased risk of fetal loss in pregnancies where fathers are 50 years or more is a cohort effect, not an age effect. If so, fathers born before 1947 should have had specific exposures leading to increased risk of intrauterine death in their offspring, exposures that the cohort born after then should have avoided. We have no knowledge of such exposures, and the fact that other authors have found a similar paternal age effect in studies based on different birth cohorts speaks against this interpretation (14).

Although fetal death is a frequent adverse pregnancy outcome, the proportion of fetal deaths attributable to advanced paternal age is small. Our results may, however, have wider implications. If advanced paternal age constitutes a risk for spontaneous abortion and stillbirth, then it is plausible that high paternal age carries a risk not only for the fetus but also for surviving children, arising from mutations of paternal origin.

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