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Parental Rheumatoid Arthritis, Child Mortality and Case Fatality A Nationwide Cohort Study

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Abstract

Objective—We have reported increased long term morbidity in children of parents with rheumatoid arthritis (RA). Here we assess child mortality and case fatality in the same cohort.

Methods—All singletons born in Denmark from 1977 to 2008 were identified through linkage of Danish National registries. Cox proportional hazard model was used to calculate hazard ratios (HR's) of death from all causes among children exposed to parental RA, compared to unexposed

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children. Risk of death after infection or respiratory diseases was also assessed for children below the age of 5 years.

Results—1,917,723 new-borns were followed for an average of 16 years. Of these 13,556 were exposed to maternal RA and 6,330 to paternal RA. Overall mortality rates in children exposed to maternal or paternal RA did not differ from unexposed children: HR 0.98 [95% CI 0.84, 1.15] and 1.08 [95% CI 0.86, 1.36] and neither did the risk of death below the ages of 5 years, 3 years, or 1 year. Below the age of 5 years, 6,106 children of parents with RA were diagnosed with respiratory diseases and 3,320 with infectious diseases. Case fatalities in children with these diseases were not significantly higher than those for unexposed children: HR 1.11 [95% CI 0.74–1.66] and 0.84 [95% CI 0.52–1.35], respectively.

Conclusion—Children of parents with RA had similar mortality as other children, also after diagnoses of respiratory or infectious diseases.

Introduction

Rheumatoid Arthritis (RA) is a systemic inflammatory autoimmune disease with a prevalence of 1% and with a female predominance (1).

Maternal RA has been associated with a number of adverse pregnancy outcomes, including preterm birth and low birth weight (2–4). An increased risk of detrimental long term health in children of women with RA has also been suggested, including risk of type 1 diabetes and rapid catch up growth in the first year of life (5, 6), which may lead to an increased risk of cardiovascular diseases in early adulthood (7, 8).

In a nationwide cohort of all children born in Denmark from 1977 to 2008 we found that children of mothers with RA had excess morbidity during childhood and early adulthood in 8 diagnostic groups out of 11 examined (9). Similar results were found among children of fathers with RA [10]. These findings implied that genetic factors could be an important contributing factor to the increased child morbidity, besides a possible role of fetal programming.

It is possible that the mechanisms that lead to excess morbidity in these children also affect their prognosis i.e. an increased mortality compared to the general population of children. No study has been conducted on general mortality or case fatality in children of parents with RA. In the present study, we aimed to assess the overall child mortality and the risk of death after common childhood diseases i.e. respiratory and infectious diseases in the same cohort of children (9).

Materials and methods

Study population

We identified and followed all singletons born in Denmark between January 1, 1977, and December 31, 2008 (N= 1,927,343) from the Medical Birth Registry (10). This was possible due to the unique personal identification number assigned to all Danish citizens since 1968, which is recorded in the Civil Registration System and allows linkage between national

registries (11). The nationwide cohort of children has been described previously (2). Briefly, the identified children were further linked to other national registries e.g. to the Danish National Hospital Registry (12) and Social registries at Statistics Denmark. Children who could not be linked to their mother (n = 3), children who had missing information on maternal identification number (n = 71) and adopted children (n = 9,546) were excluded (2).

To assess case fatality, two sub-cohorts were followed over time: (1) children recorded with a first diagnosis of respiratory system diseases and (2) those with a first diagnosis of infectious or parasitic diseases in the Danish National Hospital Registry from January 1, 1977 until December 31, 2009. The *International Classification of Diseases, 8th Revision* (ICD-8) was used: 460–519 and the *ICD, 10th Revision* (ICD-10): J00-J99 i.e. respiratory diseases and ICD-8: 000-136 and ICD-10: 00-B99 i.e. infectious diseases. Respiratory and infectious diseases were the most common childhood diseases in the current study population, and children exposed to maternal RA was previously found to be at increased risk of these diseases (HR 1.23 [95% CI 1.19, 1.27] and HR 1.22 [95% CI 1.17, 1.27], respectively (9).

Exposure (Parents with rheumatoid arthritis)

Diagnoses on maternal or paternal RA were obtained in the years from 1977 until 2008 from The Danish National Hospital Registry by using ICD 8: 712.19, 712.39, 712.59 and ICD 10: M05 and M06 (except M06.1 Stills Disease)). Children were classified as “exposed” if their mother or father were diagnosed with a main or secondary discharge diagnosis of RA. The time of first hospitalization or first contact with the outpatient clinic associated with a diagnosis of RA was used as the date of clinically diagnosed parental RA, while the time before this date was considered time with parental ‘preclinical RA’. Exposure to parental RA was also assessed.

Outcome (Death from all causes)

Information on death of the children was obtained from the Danish Civil Registration System from January 1, 1977 until December 31, 2009.

Statistical analysis

Cox proportional hazards models were used to calculate hazard ratios (HRs) and associated 95% confidence intervals (95% CI) for mortality rates among children exposed to parental RA (maternal or paternal RA, respectively). Age of the children (in days) was used as the underlying time scale. Follow up started at birth and ended at the age at death, age at emigration or until age at end of follow-up; December 31, 2009, whichever came first. The reference group was children born in the same time period and not exposed to maternal or paternal RA, respectively. The risk of death was also calculated among children below the age of 5 years, 3 years and 1 year, since mortality in this age range is strongly age dependent.

In the “case fatality” analyses the children were followed from age at diagnosis (i.e. either respiratory or infectious diseases) and until age at death, age at emigration or until age at the end of follow-up, whichever came first. Analyses following the children until the age of 5

years were considered the main case fatality analyses, since mortality is very low after this age and the duration of the disease can be short.

The adjusted hazards models assessing exposure to maternal RA included: maternal age at birth (in years), maternal education (elementary, middle and high school), year of birth and paternal RA (yes/no). The models assessing exposure to paternal RA additionally included paternal age at birth (in years) and instead of paternal RA (yes/no) maternal RA (yes/no). In a sub-analysis among all the children who died during follow-up, we assessed whether dead children of mothers with RA had more comorbidities, than dead children not exposed to maternal RA, as in our previous study 11 diagnostic groups and three specific autoimmune-related diseases were assessed (9).

A number of sensitivity analyses were performed to test the robustness of the exposure definition. First, exposure to parental RA was restricted to RA diagnosed before birth. Second, exposure was restricted to those with parents having more than one recorded diagnosis of RA. Third, analyses were stratified on the year before and after 1995, where information on outpatients was included. Finally, additional censoring was made of the children at the time one of their parents turned 55 years. The latter was to explore a possible impact by a potential shorter survival time among parents with RA (13).

To explore potential confounding by prior pregnancy history and to take into account dependency between siblings, analyses were also conducted including only firstborn children. Adjustment for gestational age was additionally made to explore if differences in gestational age would mediate differences in mortality.

“Complete case analyses” were conducted by including only children with complete information in the fully adjusted models (up to 94% of the children). All statistical analyses were performed using SAS statistical software (version 9.2). The study was approved by The Danish Data Protection Agency (Jr. no. 2010-41-5535).

Results

In total, 1,917,723 singletons were included in the study and followed until end of 2009 with an average follow up of 16 years. Of these 13,556 children were exposed to maternal RA and 6,330 children exposed to paternal RA. Among 494,511 children with respiratory diseases 6,352 were exposed to parental RA (maternal RA: n = 4,442, paternal RA: n = 1,900 and both maternal and paternal RA = 20) while 3,484 of 271,164 children with infectious diseases were exposed to parental RA (maternal RA: n = 2,468, paternal RA: n = 1,006 and both maternal and paternal RA = 10) (Table 1).

Compared with unexposed children, children exposed to parental RA had mothers with shorter education at time of birth, whereas maternal and paternal age at birth was approximately similar for exposed and unexposed children (Table 1). The findings were similar in children diagnosed with either respiratory or infectious diseases (Table 1).

Child Mortality

From 1977 to 2009 17,757 deaths were reported in this cohort (0.9%). Compared to unexposed children, children exposed to either maternal or paternal RA had no overall significant increased risk of death from all causes: HR 0.98 [95% CI 0.84, 1.15] and 1.08 [95% CI 0.86, 1.36]. Nor was the risk increased at the ages below: 5 years, 3 years or 1 year (Figure 1).

After combining the children exposed to maternal or paternal RA into one group of exposed children, the risk was 1.00 [95% CI 0.88–1.14]. This estimate was based on 207 exposed deaths and 14,797 unexposed deaths (data not shown).

Results were similar after exposed children were restricted to those having a mother or father diagnosed with RA before birth. Results were also similar after exposed children were restricted to those having a mother or father diagnosed with RA more than once (data not shown). Among children born after the year 1995, we found a twofold increased risk of death among children of fathers with RA, but the estimate was based on only 13 exposed deaths (data not shown).

Case-fatality

Case fatality in children of parents with RA diagnosed with either a respiratory or infectious disease was similar to unexposed children with the same diseases. The hazard ratios of death below the age of 5 were HR 1.11 [95% CI 0.74–1.66] and 0.84 [95% CI 0.52–1.35], respectively (Table 2). When the children were followed until a mean age of 16 years, case fatality was also similar for children of parents with RA, compared to unexposed children (data not shown). Risks were neither statistically significantly increased in children of mothers or fathers with RA, respectively. However the results were based on few observations (data not shown). Exposure to parental RA diagnosed before birth (i.e. maternal or paternal RA) showed similar results, as did parental RA diagnosed more than once (data not shown).

Sensitivity Analyses

When restricting the analyses to firstborn children only, the estimates increased by up to 11%, but they were still not statistically significant. Adding paternal age to the models on children exposed to maternal RA did not change the estimates. Similarly, risk estimates remained similar after gestational age was added to the models. When restricting the analyses to children who died during follow-up, only diseases of the respiratory system and diabetes type 1 were more often seen among children of mothers with RA, than among children not exposed to maternal RA; out of 11 diagnostic groups and three specific autoimmune diseases examined (data not shown). However, number of exposed children with comorbidity were low, thus risk of Type II error is high.

Discussion

Mortality in children of parents with RA was similar to unexposed children. Children of parents with RA also had similar survival after respiratory and infectious diseases.

Our findings are reassuring since the same cohort of exposed children had excess morbidity for a large number of diseases [10]. No prior study has assessed mortality or case fatality in children exposed to parental RA. On the other hand, previous studies demonstrated that autoimmune diseases aggregates in families, especially in first degree relatives, suggesting shared genetic risk among autoimmune diseases (5, 14, 15) and perhaps increased susceptibility toward diseases in general. Even though children exposed to parental RA may have a possible higher risk of morbidity, the current study suggests that children of parents with RA are not at increased risk of death during childhood or early adulthood in a population with low child mortality. Our follow-up ended at a mean age of 16 years and up to 32 years for the oldest.

The number of exposed deaths was limited (i.e. 231 deaths among children of parents with RA), which was reflected in the wide confidence intervals. Furthermore, we do not know if these children will develop diseases with higher mortality later in life, since the children were followed for a maximum of 32 years of age.

Children exposed to ‘preclinical RA’ at time of birth were included in the group of exposed children. The identification of a preclinical state includes ‘conditioning upon the future’, which may cause bias, since the parent has to survive until RA is diagnosed sometime after birth (13). To eliminate this potential bias, we additionally censored children at the time one of their parents turned 55 years and the estimates remained unchanged. Furthermore, similar results were found, when exposed children were restricted to those having a parent diagnosed with RA before birth. Even though we adjusted for a number of potential confounders, unmeasured or residual confounding may still exist.

This is the first study to assess overall mortality in children of parents with RA. This nationwide cohort study has complete follow-up, which makes selection bias unlikely. We were able to include more than 19,000 children exposed to parental RA with a mean follow up of 16 years; of which 6,352 children were followed until 5 years of age after a diagnosis of respiratory disease and 3,484 after infectious disease.

In conclusion, neither overall childhood mortality, nor case fatality after a diagnosis of respiratory or infectious diseases were increased in children of parents with RA, compared to the general population of children. Future studies are needed in children of parents with RA to assess their health in adulthood.

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Significance

- Children of parents with RA had similar mortality as other children
- Children of parents with RA had similar mortality after diagnoses of respiratory or infectious diseases, compared to children of parents without RA.

Figure 1. Mortality relative rates in children exposed to maternal or paternal rheumatoid arthritis*

*RA, rheumatoid arthritis; HR, hazard ratio; CI, confidence interval; exp., exposed

^aNo. of children followed: 1,917,723. No of deaths: all ages: 17,757; < 5 years: 11,647; < 3 years: 10,956 and <1 year: 9,538.

^bAdjusted for maternal age, maternal education, birth year and paternal RA

^cAdjusted for maternal age, maternal education, birth year, paternal age and maternal RA

^dThe results were similar to the results among children exposed to maternal or paternal RA diagnosed before birth, respectively (maternal: HR = 0.92 95% CI, 0.51–1.65; paternal: HR = 1.20, 95% CI, 0.57–2.51).

Table 1Characteristics of children at time of birth^{*}

	Unexposed Children [†]	Children exposed to paternal RA	Children exposed to maternal RA	Children exposed to paternal RA
All children				
N (%)	1,897,894 (98.97)	19,829 (1.03)	13,556 (0.71)	6,330 (0.33)
Maternal age, mean $\pm$ SD years	28.35 $\pm$ 4.9	28.44 $\pm$ 5.1	28.46 $\pm$ 5.1	28.41 $\pm$ 5.1
Paternal age, mean $\pm$ SD years	31.14 $\pm$ 5.8	31.41 $\pm$ 6.1	31.10 $\pm$ 6.0	32.10 $\pm$ 6.4
Maternal education, %				
Low	36.3	43.4	43.2	43.6
Middle	30.9	29.3	29.3	29.3
High	30.4	24.9	25.0	24.8
Children with respiratory disease				
N (%)	494,511 (98.73)	6,352 (1.27)	4,462 (0.89)	1,910 (0.38)
Maternal age, mean $\pm$ SD years	27.79 $\pm$ 4.9	27.97 $\pm$ 5.2	28.04 $\pm$ 5.2	27.82 $\pm$ 5.1
Paternal age, mean $\pm$ SD years	30.66 $\pm$ 5.8	31.07 $\pm$ 6.3	30.82 $\pm$ 6.1	31.67 $\pm$ 6.6
Maternal education, %				
Low	40.6	46.9	46.7	46.9
Middle	30.1	28.4	28.2	29.2
High	26.9	21.8	22.1	21.0
Children with infectious disease				
N (%)	271,164 (98.73)	3,484 (1.27)	2,478 (0.90)	1,016 (0.37)
Maternal age, mean $\pm$ SD years	27.8 $\pm$ 5.1	27.95 $\pm$ 5.1	27.95 $\pm$ 5.1	27.96 $\pm$ 5.2
Paternal age, mean $\pm$ SD years	30.7 $\pm$ 5.9	31.09 $\pm$ 6.3	30.71 $\pm$ 6.1	32.03 $\pm$ 6.7
Maternal education, %				
Low	41.5	48.1	47.5	49.5
Middle	28.9	27.2	27.3	26.9
High	26.7	21.1	21.4	20.2

^{*} RA, rheumatoid arthritis; SD, standard deviation

[†] Includes children unexposed to parental RA. Children unexposed to maternal RA (N=1,904,167 (99.29%) and paternal RA (N=1,911,393 (99.67%)) showed similar estimates

Table 2

Mortality relative rates after respiratory or infectious diseases in children exposed to parental rheumatoid arthritis^{*}

Children < 5 years of age	N	No. of deaths	HR (95% CI) ^b
Diseases of the respiratory system			
Parental RA ^a	6,106	25	1.11 (0.74–1.66)
No parental RA	474,544	1,437	1 (Reference)
Infectious and parasitic diseases			
Parental RA ^a	3,320	16	0.84 (0.52–1.35)
No parental RA	258,513	1,315	1 (Reference)

^{*} RA, rheumatoid arthritis; HR, hazard ratio; CI, confidence interval

^a children exposed to either maternal or paternal RA are combined

^b adjusted for maternal age, paternal age, maternal education and birth year