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Original article

# Parental age and the risk of isolated cleft lip: a registry-based study

Erik Berg MD [a,*], Rolv T. Lie PhD [a,b], Åse Sivertsen MD, PhD [a,c], Øystein A. Haaland PhD [a,d]

[a] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway
[b] Department of Health Registries, Norwegian Institute of Public Health, Bergen, Norway
[c] Department of Plastic Surgery, Haukeland University Hospital, Bergen, Norway
[d] Department of Pediatrics, Haukeland University Hospital, Bergen, Norway

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ABSTRACT

*Purpose:* An increasing number of children in high-income countries have older parents. Several studies have suggested that pregnancy outcomes including cleft lip (CL) are associated with high parental age. CL is a relatively common birth defect, and the prevalence is higher in Norway than in most high-income countries.
*Methods:* We studied the association of parental age with the risk of isolated CL (with or without cleft palate) in 2,449,218 births from the population-based Medical Birth Registry of Norway in the period from 1967 until 2010.
Individuals who had other birth defects or died before the age of three were excluded. Generalized additive models were used to estimate associations across the continuum of parent's age. A baseline risk was calculated, for births in the interquartile range for maternal age (24–31 years) and paternal age (26–34 years).
*Results:* The baseline risk of isolated CL was 1.15 per 1000. Several analyses were conducted for mother's and father's age. The risk increased with the age of both parents, with risk estimates of 1.27 per 1000 and higher for children of parents at an advanced age. In an interaction analysis, the risk was increased only when the age of both parents was high.
*Conclusions:* Our analyses suggest that the risk of fathering an infant with CL increases with advancing age. Additional analyses showed, however, that the risk was increased only when the age of both parents was high.



## Introduction

In high-income countries, more and more people are becoming parents at a higher age [1]. This may have consequences for reproductive health, and there is a large bulk of literature dealing with possible outcomes [2–4]. High maternal age is known to affect the risk of chromosomal aberrations, and high paternal age is known to increase the number of mutations in the sperm DNA and the risk of several types of genetic syndromes [5]. Less is known about the possible association of parent's age and the risk of nonsyndromic structural malformations. The age of parents may therefore be relevant both for counseling of future parents and for clinical follow-up.

One of the common birth defects that have been associated with higher parental age is cleft lip (CL) with or without cleft palate. CL is among the most common congenital anomalies, with a prevalence of 1.43 per 1000 live births in Norway [6]. This is one of the highest recorded rates of CL in the Western world. Because of the extensive need of clinical interventions, this group of congenital malformations poses both medical and economic challenges, in addition to the psychosocial impact on the patients and their families.

Several studies have attempted to measure the association between parental age and risk of oral clefts. However, the results of these studies are not consistent [7,8]. In 2005, a registry-based Danish study described an association between parental age and the risk of oral clefts, but only when both parents were at an advanced age [9].

The aim of this study was to estimate the effect of paternal and maternal age on the risk of CL without any sign of a genetic syndrome and to replicate the interaction reported from Denmark. Valid estimates may improve our understanding of possible reproductive health effects of advanced parental age.

## Material and methods

Since 1967, all births in Norway after 16 weeks of gestation have been compulsory reported to the nationwide Medical Birth Registry of Norway (MBRN). Midwifes have been responsible for recording

* Corresponding author. Department of Global Public Health and Primary Care, University of Bergen, Kalfarveien 31, 5018 Bergen, Norway. Tel.: +47-91520092; fax: +47-55586130.
*E-mail address:* Erik.Berg@igs.uib.no (E. Berg).

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diagnoses provided by pediatricians or obstetricians. We used MBRN data for the entire period from 1967 until 2010.

The MBRN has collected data according to the same basic routines since 1967. Information has been collected during the initial stay at the delivery unit and reported within 7 days after birth. The MBRN includes data on maternal age, paternal age, and health status of children born with gestational age 16 weeks or more. In a validation study, the proportion of CL cases recorded by the MBRN was found to be 83% to 94% depending on cleft type and severity [10].

A total of 2,581,612 births were registered in MBRN from 1967 to 2010, of which 3451 children had CL. Because of unknown paternal age, 28 949 births were excluded, and another 40 births were removed because of missing maternal age. Next, 11 cases were removed because the child had been given an ambiguous cleft diagnosis. We were left with 3353 CL cases among 2,552,612 births.

Nonsyndromic CL cases should be distinguished from syndromic cases [11]. Therefore, we excluded 68,940 children with other defects than clefts, hydroceles or hip dysplasia from the study. This included 375 CL cases. Among children who die before birth or within the first years of life (including stillborn, miscarriages, and terminated pregnancies), there is a higher frequency of clefts. Some of these deaths are likely to be caused by unknown accompanying birth defects or syndromes. Hence, we excluded all children who died before the age of 3 years, 34,454 births, including 88 cases of CL. The remaining study group comprised 2,449,218 children, with a total of 2890 cases. We denote these isolated CL (iCL) cases because they had no sign of other accompanying conditions. The selection process is outlined in Figure 1, and the characteristics of the study population are summarized in Table 1.

## Statistical analysis

The outcome variable in this study was iCL. The main explanatory variables were father's and mother's age, both treated as continuous variables. Birth year was used as a linear adjustment variable in all analyses. Generalized additive models (GAMs) were applied to conduct the analyses [12]. This is a powerful approach allowing flexible models to describe how the risk of iCL varies continuously by parental age. Categorization of exposure variables was avoided as it may lead to higher type I error rates, biased effect size estimates, residual confounding, and loss of power [13]. The loss of power is especially a problem when the association is stronger in the tail of the distribution of the exposure variable [14]. The interquartile range (IQR) for maternal age was 24 to 31 years, and for paternal age, it was 26 to 34 years. If both parents were aged in their respective IQRs, the child was said to belong to the IQR group ($n = 951{,}675$). This allowed for the estimation of an iCL risk that was not influenced by the most extreme values of parental age (baseline risk).

We first studied the effect of maternal age on the risk of iCL by using a GAM with cubic regression splines. Knots were set at $k_1 = 24$ (Q1 for women), $k_2 = 31$ (Q3 for women), and $k_3 = 40$ years of age. For paternal age, the analysis was similar, except that knots were set at $k_1 = 26$ (Q1 for men), $k_2 = 34$ (Q3 for men), and $k_3 = 50$. Next, a multiple regression analysis was conducted, in which both paternal age and maternal age were included as continuous variables in the model. The knots were the same as in the separate analyses. Finally, we used tensor product smooths to model interaction between paternal age and maternal age [12]. No knots were set in this model. All models were adjusted for birth year and parity (according to mother).

The fit of the different models was evaluated using Akaike's information criterion (AIC) [15]. The AIC is designed to balance accuracy and parsimony in a model. In this regard, a lower AIC indicates a better fit. Akaike weight was computed for each model (paternal only, maternal only, paternal and maternal, and interaction).

Multicollinearity may be a problem because there is a high correlation between maternal and paternal age. This may cause

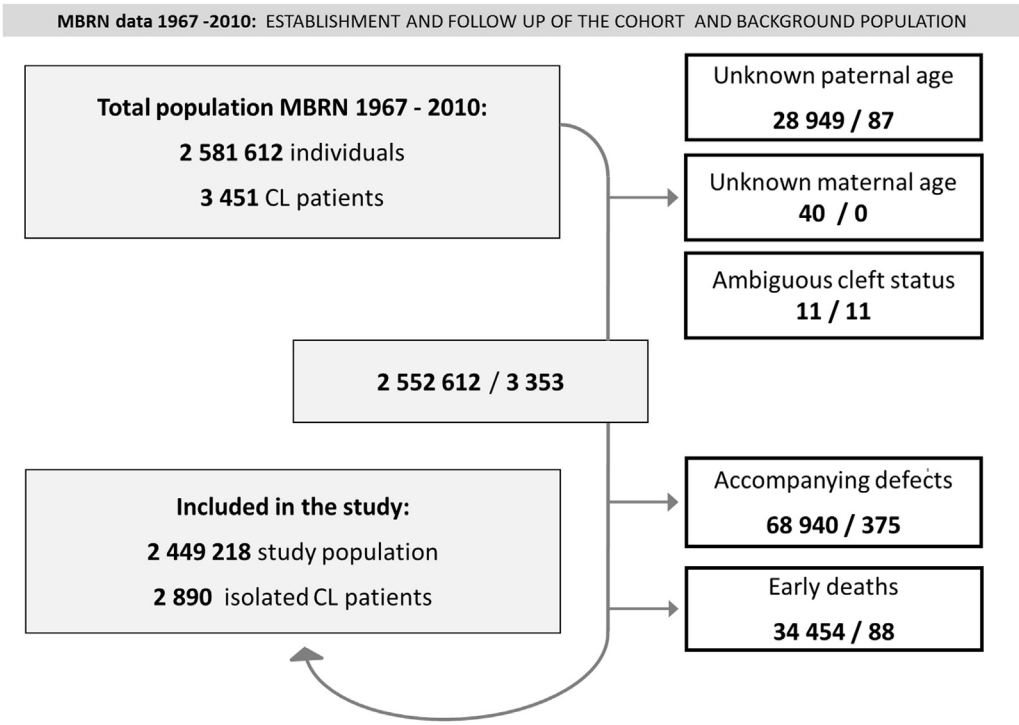


**Fig. 1.** Flowchart showing establishment of the population included in the study. "Total number/Number of iCL cases."