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Session topic 30. Intrafamily and intergenerational transmission of health

Does transmission of cystic fibrosis between parents and children alter parental decision-making on family size and birth spacing, and thus impact population health? Emerging answers from the French "Cystic Fibrosis, Family, and Society" survey.

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Introduction

This study uses French administrative medical records matched to survey data on French families to investigate the probability and timing of a subsequent birth after a child is diagnosed with cystic fibrosis, commonly referred to as CF. CF is a rare disease that can only be transmitted by inheritance from both biological parents; in other words, individuals with CF inherit two deleterious gene mutations, one from each biological parent. Presently the estimated prevalence rate in the European population is 12 per 100,000 persons. Relevant to the conference venue, in Australia, as of 2022, 3,738 people were living with CF in Australia. And, the Australian state of Victoria reports that if two Australians carry the CF gene and have a child, each pregnancy will have a one-in-four chance that the child will have CF. One in every 2,500 Australian births produces a child who has CF. Meanwhile, in the United States, according to the American Cystic Fibrosis Foundation, approximately 1,000 new cases of CF are diagnosed each year. Presently in the United States, there are 40,000 children and adults living with cystic fibrosis.

This disease, which is the most frequently occurring serious genetic disease from paediatric age onwards in Western countries, can lead to devastating lifelong physical impairments and early death. Presently, there is no cure for CF. Meantime, current treatments are cumbersome, restrictive, and solely symptomatic. Although no cure is currently available for this chronic and debilitating disease, momentous advances have been made in understanding the genetic makeup of the disease; mapping its transmission pathways; and treating the resulting physical impairments with efficacious therapies.

While much is now known about the transmission of CF, physical impairments, and treatments, little is known about the impact that a child diagnosed with CF has on the odds of the parents having another child. Yet, in many families raising a child with CF, that child has at least one younger sibling born to the same biological parents. Some of the subsequent younger siblings will also be diagnosed with CF, like their older brother or sister, but not always; in fact, many of the younger siblings will not have contracted the disease.

Because the CF gene may not be transmitted from parents to the younger sibling of a child with CF it is often the case that a child with CF does indeed have a younger sibling. However, heretofore, no study has investigated the probability and timing of a subsequent birth after a child has been diagnosed with CF. This study addresses this stark gap in the research by describing and modeling whether or not a child is born to the same biological parents after the elder child has been diagnosed with CF and if so the timing of that subsequent birth. For the first

time, this study can exploit demographic and medical variables from a rich data source combining administrative medical records matched to survey data on families that raised a CF individual to more accurately assess the probability and timing of a subsequent birth after the birth of a child with a confirmed CF diagnosis.

Pursuing this line of family-related CF research will not only provide vital new information to researchers about the demography of families who raised children with CF, but more broadly the research will address the issue of whether families make decisions to limit their family size, thereby potentially reducing the intergenerational transmission of this genetic disease which has severe health implications.

Background

As noted, CF is a rare disease, yet it is the most common genetic disease from paediatric age onward in Western countries. Transmission is through autosomal recessive inheritance, meaning affected individuals are those who have inherited two deleterious mutations from each of their biological parents. The gene responsible (CFTR gene) was identified in 1989. CF contains almost 2,000 mutations, the most frequent of which is F508del. This chronic disease usually manifests itself in early childhood, including at birth, and results in acute damage to respiratory and digestive organs. These visceral impairments are responsible for early mortality as well as lifelong physical impairments, thereby also impacting affected individuals' emotional well-being, family lives, and social relationships. There is no cure for CF and current treatments are cumbersome, restrictive, and solely symptomatic. What is known about the effects of CF on patients' family structures and lives comes from small and selective clinical and epidemiological studies. Thus, this study adds much to understanding the family demography of patients with CF because the findings are based on nearly all French CF patients' medical records matched to an in-depth survey of their families and their social lives.

Theoretical Focus

The theoretical question posed by this study is whether family size and birth spacing reflect the reproductive decision-making of parents at risk of transmitting a genetic autosomal recessive disorder. The specific autosomal recessive disorder under investigation is CF. We hypothesize that parents at risk of transmitting CF to their offspring face more difficult reproductive decision-making than parents not at risk of transmitting a hereditary disease, like CF. We theorize that besides family size reflecting the challenges of reproductive decision-making among parents carrying the CF gene, birth spacing between siblings also reflects the challenges for these parents. The study tests several new hypotheses generated from our theoretical focus, one of the most significant being that the rank of the CF child in the birth order determines the timing and probability of any subsequent birth. Evidence supporting our theoretical conjectures has significant health implications for families with CF children and the provision of health services.

Data

These data come from the French "Cystic Fibrosis, Family, and Society" survey conducted from April 2017 to April 2019 among a sample of patients aged 14 or over who were included in the "French Cystic Fibrosis Registry". The registry is a national scheme that has been collecting health data every year since 1992 from almost all (about 95%) patients diagnosed with CF in France. The aim of the "Cystic Fibrosis, Family, and Society" survey was to match patients' socio-demographic data with their biomedical data from the aforementioned registry.

The data used for this study, extracted from the "Cystic Fibrosis, Family, and Society" survey, contains 280 CF patients for whom personal and medical information is available (date of birth,

age at diagnosis of CF, circumstances of diagnosis, i.e. at the antenatal or neonatal stage, and health status indicators) and information on their families, notably the situation of their parents and biological siblings (patients, brothers, and sisters from the same biological parents). For parents: dates of birth and eventual deaths of father and mother, employment status, nature of union, start and end dates of union, and dissolution of union including if that dissolution was due to CF in their children. For siblings: the number of brothers and sisters, their birth rank in relation to the patient's birth rank, dates of birth and death, any diagnosis of CF, and circumstances of diagnosis in the case of CF, i.e. at the antenatal or neonatal stage. Hence, these data are ideally suited to examine births after the births of CF patients.

Methods

Because the "Cystic Fibrosis, Family, and Society" survey collected many dates on key events in the lives of each CF patient, we could reshape our data to use survival time analysis methods. As the data description noted, information on each CF patient includes dates of births and deaths of family members, what age and dates CF diagnoses were confirmed for CF patients, and dates of union formations and dissolutions among parents of CF parents.

In the reshaped data, a major date recorded in the lives of CF patients was the birth of a younger sibling following the birth of a CF patient, if such a birth occurred. Therefore, we could investigate the time until the event of a subsequent birth after the birth of a CF patient using nonparametric and parametric survival analyses. We employ both nonparametric and parametric survival time methods to investigate the time until a subsequent birth after the birth of a CF patient occurs and if no subsequent birth occurs what factors might explain that outcome.

The survival time methods include a Kaplan-Meier curve, (see Figure 1 below), to graphically show the time until a subsequent birth; a semi-parametric Cox proportional hazards model to investigate hypothesized relationships between the time until a subsequent birth and explanatory variables; and lastly, parametric survival time regression models to predict the hazard of a CF patient experiencing a subsequent sibling birth. The survival time models also examine the probability that parents may choose not to have another child after learning of the CF diagnosis in their child.

For this submission to the 2025 International Population Conference in Brisbane, we only present here summary statistics on the sample, (Table 1), and several nonparametric results, (Table 2). The results shown in this submission strongly support our proceeding with developing both a semi-parametric Cox proportional hazards model and other parametric survival time regression models, such as a discrete-time proportional hazards model. At the conference in Brisbane in 2025 we will present additional results based on methods that provide the first insights into the timing of births in families raising children with CF.

Preliminary Results

The following preliminary results provide summary statistics on the sample of CF patients (Table 1) and the time until the next birth after the birth of the CF patient (Table 2). Further results from parametric survival time models will be presented at the conference in Brisbane.

Starting with summary statistics for the sample of 280 CF patients, Table 1 shows that CF patients were on average about 32 years of age when they responded to the "Cystic Fibrosis, Family, and Society" survey. Notably, more females, (58.9%, N = 165), responded to the survey than males, (41.1%, N = 115). The table shows that they were quite young when diagnosed with

CF, about six years of age on average. The CF patients' mothers were about 29 years of age when they gave birth to them. Over 81% of the CF patients were either the firstborn or secondborn (47.5% and 33.9%, respectively). Interestingly, when these survey data were collected, 8.2% of the CF patients reported having no younger siblings; in other words, they were the first and only child of their biological parents. This fact will be considered in survival models because this group of 23 CF patients who did not have any siblings might suggest that their parents chose to have no more children after learning of the CF diagnosis in their firstborn child. Besides this group without siblings, another 46% had one sibling only; that one sibling might have been older or younger. A cross-tabulation will be shown at the conference as to the birth order of CF patients relative to the number of siblings.

Other results in Table 1 show that nearly 30%, (28.9%) of CF patients had two siblings. Few of the CF patients grew up in very large families, meaning families of four or more siblings were rare, (see Table 1). Consistent with their average age of six years, most, i.e., 72.1%, were born during the 1980s or 1990s, (38.2% and 33.9%, respectively). The majority, 59.6%, were born after the breakthrough CF diagnostic test was established in 1987. Over 93% of CF patients stated that their families of origin had no history of the CF disease. This response is consistent with the disease's mode of transmission, which is autosomal recessive inheritance. Probably related to the use of the diagnostic test for CF which started after 1987, about 73% of the CF patients in the survey were diagnosed with CF either just before birth, at birth, or within 12 months of their birth. Among those CF patients with brothers and/or sisters, N = 254, just over 17%, (n = 49), state they have a sibling who also had CF.

These are some of the first statistics available on CF patients' families and lives that go beyond findings reported by small clinical or epidemiological studies.

TABLE 1 INSERT ABOUT HERE

The descriptive statistics shown in Table 1 are new contributions to the field. Likewise, the nonparametric survival time results, described in Table 2, are also new. Before discussing Table 2, however, we note again that many CF patients, (N = 126), did not have a younger sibling. In other words, they were either the first and only child, if born first, (N = 23), or the last child born following the births of their older sibling or siblings. Thus of the 280 CF patients, 126 did not have a younger sibling. Also, one CF patient was 'top-coded' at 167 months for the survival time analyses due to a suspect reporting time of 311 months. (This one particular patient might be deleted in future analyses if the months for a subsequent birth cannot be reconciled.) Table 2's results are based on 154 CF patients who had at least one younger sibling after their birth.

Based on the total number of months at risk for all 154 CF patients, (8,115), Table 2 shows that the mean and median number of months until a subsequent birth after their birth are 52.7 and 43 months, respectively. The mean measure of central tendency is less useful than the median measure as the mean is driven by outliers in very delayed subsequent births. Also, both of these global measures of central tendency for the 154 CF patients do not consider the birth order of the CF patient. (Regression analyses do control for birth order, otherwise called in this study, «Rank».)

Furthermore, among these 154 CF patients who would eventually find themselves having a younger sibling, 25% of them had a younger sibling by 30 months, 50% by 43 months, and 75% by 69 months, or for the latter a little over 5 years later. Though not shown in the table, by 98 months, about eight years after the CF patient's birth, there were only 9 CF patients still to have

a younger sibling, which is possible depending on their mother's age. All these subsequent births were to the same biological parents of the CF patient.

TABLE 2 INSERT ABOUT HERE

Besides two preliminary tables, we also present the baseline survival time curve for the time until a subsequent birth. In Figure 1, the survival curve shows the steady progression until a subsequent birth after the birth of the patient who contracts the CF disease from their parents who have both carried the CF gene. By 120 months, which is around 10 years, essentially all 154 CF patients had a younger sibling.

FIGURE 1 INSERT ABOUT HERE

At the conference, we will build on these foundational results to investigate the factors that change the timing until a subsequent birth. We will use well-suited survival time regression models, starting with the semi-parametric Cox proportional hazards model. A «Table 3» will contain estimated coefficients from the Cox proportional hazards regression. Those coefficients, based on *no* assumptions about the functional form of the hazard function, will then be compared with coefficients from a model or models that will make assumptions about the hazard's functional form. The outcome will be a table, Table 3, that will present and compare estimated hazard ratios, (or estimated coefficients) from the semi-parametric Cox proportional hazards regression model and two alternative parametric survival time regression models, one arguing for a log-logistic distribution and another arguing for a Weibull distribution. Then we will continue in our study to report on the other 126 CF patients who did not have a younger sibling. Table 4 will display estimated hazard ratios from a discrete-time proportional hazards regression model that will include these 126 patients who will be treated in the regression analyses as right-censored study participants.

To the best of our knowledge, this will be the first time that regression results like these will be presented, interpreted, and compared. We hypothesize that there are differences in the timing of subsequent births by birth order; cohort composition, availability of the 1987 CF diagnosis test, family history of CF, and mothers' ages. In other words, the regression models will assess whether any one of these measures influences the time until a subsequent birth holding other covariates constant. Between September 2024 and April 2025, we will conduct this additional research on the modeling.

Preliminary Conclusion

Our preliminary conclusion is that birth order, or more precisely that rank in the sibling birth order, is a crucial factor in determining whether or not another child is born after the birth of the CF patient and the timing of that subsequent birth as well. Also, factors related to the family and medical advances affect the timing and probability of subsequent births. We look forward to breaking this new ground, presenting our results in Brisbane at the IUSSP in 2025, and discussing the significant implication of this research that if families decide to limit their family size as they grapple with raising a child with CF, that decision could potentially reduce the intergenerational transmission of this genetic disease and inhibit the extend of its health consequences. Finally, our forthcoming results for CF patients have implications for studying and comparing the reproductive decision-making of couples confronting many other autosomal recessive diseases where morbidity is very high.

Table 1. Selected Descriptive Statistics of Sample of CF† Patients

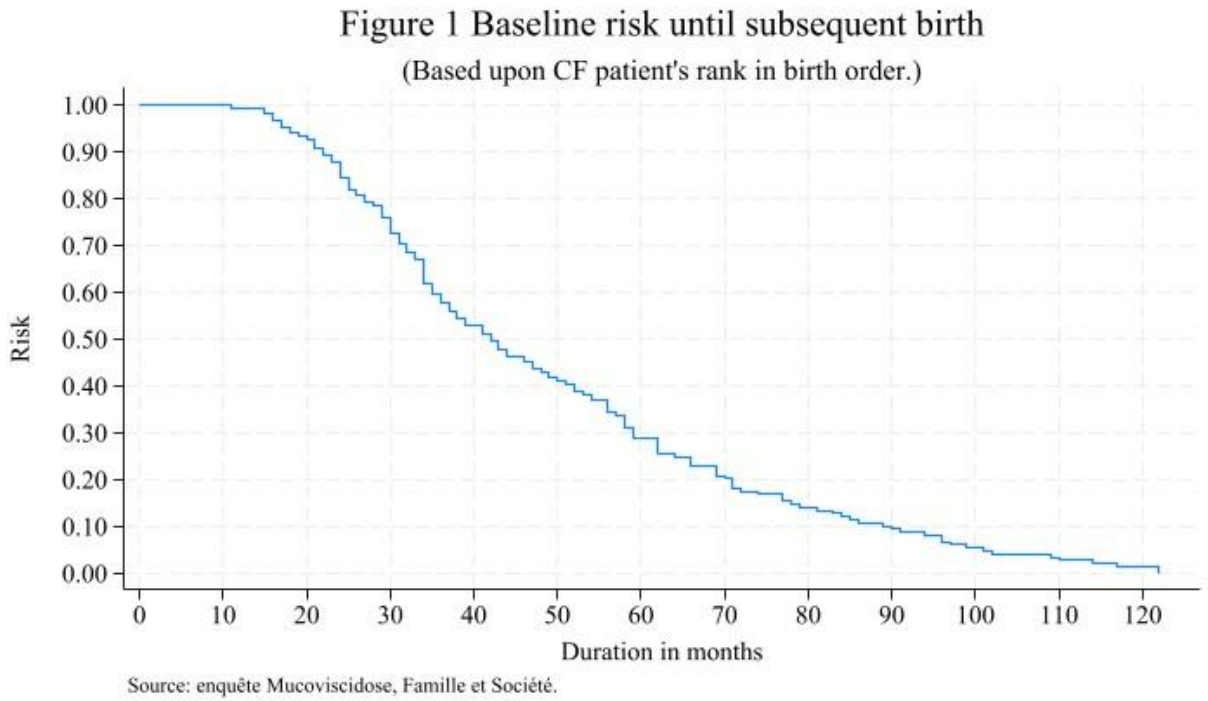
	Mean/n	sd/%
Age in years of CF patient at the time of survey	31.8	(10.0)
Age in years diagnosed with CF if not before or at birth	6.2	(11.0)
Age in years of mother when CF child born	28.7	(4.7)
Gender of CF patient		
Male	115	(41.1%)
Female	165	(58.9%)
Rank of CF patient in family based on birth order		
1st born/eldest	133	(47.5%)
2nd born/2nd eldest	95	(33.9%)
3rd born/3rd eldest	35	(12.5%)
4th born/4th eldest	11	(3.9%)
5th born/5th eldest	5	(1.8%)
7th born/7th eldest	1	(0.4%)
Number of siblings in CF patient's family		
None	23	(8.2%)
One	129	(46.1%)
Two	81	(28.9%)
Three	35	(12.5%)
Four or more siblings	12	(4.3%)
Decade in which CF patient was born		
1960s	21	(7.5%)
1970s	42	(15.0%)
1980s	107	(38.2%)
1990s	95	(33.9%)
2000s	15	(5.4%)
Born before or after CF test available		
Born before CF test	113	(40.4%)
Born after CF test	167	(59.6%)
History of CF in patient's family		
No family history of CF	262	(93.6%)
Yes family history of CF	18	(6.4%)
Diagnosis of CF within 12 months of birth		
No	61	(21.8%)
Yes	203	(72.5%)
Missing on complete month and year	16	(5.7%)
Sibling diagnosed with CF#		
No	206	(73.8%)
Yes	49	(17.2%)
No silbling	23	(8.2%)
N =	280	

Source: "Cystic Fibrosis, Family, and Society" survey; † = cystic fibrosis; **#** = two respondents state don't know.

Table 2: Survival time statistics on months until another birth after birth of CF† patient

Incidence rate of a subsequent birth‡	Average months until next birth	Median months until next birth	CF-Person-months records
0.0190	52.7	43.0	8,115
		Survival time	
Time at risk	25%	50%	75%
8,115	30.0	43.0	69

Source: Source: "Cystic Fibrosis, Family, and Society" survey. Notes: Summary statistics from survival analyses; measured in months; †CF = cystic fibrosis; ‡incidence rates = subsequent births per CF patient-month.



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