

RESEARCH ARTICLE

The effects of being born with cystic fibrosis on the timing of subsequent births: Evidence from the French Cystic Fibrosis Registry

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Abstract

Cystic fibrosis is an autosomal recessive genetic disease for which there is currently no cure. This study investigated how the birth order of a child with cystic fibrosis influences both the likelihood and timing of subsequent births. We hypothesized that the position of the child with cystic fibrosis within the family birth order is more important than the mere occurrence of the affected birth in determining subsequent fertility behavior. Our results indicate that family characteristics and diversity are strongly shaped by the child's birth order. First, the birth order position of the child with cystic fibrosis significantly affected the timing of the next birth. Second, accurate estimation of sibling count and age spacing required the inclusion of children with cystic fibrosis whose data were right-censored. Excluding children with cystic fibrosis who were either only children or last-born children led to biased estimates. We conclude that the position of the child with cystic fibrosis within the birth sequence is a key determinant for understanding how the disease influences parental decisions about additional childbearing, as well as how it shapes sibling structure. Our findings have implications for understanding how families change when they face autosomal recessive genetic diseases, because parents must make difficult decisions about whether and when to have another child after the birth of an affected child.

Keywords: Genetic disease transmission; Cystic fibrosis; Birth order; Family change; Sibling numbers and spacing; Detailed cystic fibrosis histories

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1. Introduction

One of the most profound events for parents is the birth of a child with an autosomal recessive genetic disease. The child's birth can change the day-to-day functioning of the family, transform parents' reproductive choices and future family-planning decisions, strain household finances, multiply daily stresses, and compel society to allocate healthcare resources to find cures and develop therapies and medicines. One study estimated that average annual health care spending for a CF patient nearly doubled, from about \$67,000 in 2010 to approximately \$131,000 in 2016 (Grosse *et al.*, 2018). Another study found that nearly two-thirds of American cystic fibrosis (CF) families faced severe financial burdens (Seyoum *et al.*, 2023).

Studies have reported that compared to parents raising children without an autosomal recessive genetic disease, parents raising a child with an autosomal recessive genetic disease spend more time and resources ensuring their child's well-being, including consulting with specialist doctors, facilitating social interactions for their child, advocating at schools, and arranging medical interventions (Boettcher *et al.*, 2021; Gee *et al.*, 2017). Many studies have concluded that more societal support is needed to ameliorate the multi-layered challenges faced by these parents, advance genetic research and medical therapies, and expand healthcare programs and research (Cheema *et al.*, 2024; Daly *et al.*, 2022; Mlcoch *et al.*, 2025).

Research documenting the burdens that parents face when raising a child with an autosomal recessive disease and tools to lessen those burdens is important (Harris *et al.*, 2021), but equally important is understanding whether the birth of a child with this type of inherited disease changes the fundamental dynamics of family growth. In particular, the likelihood and timing of another birth after the birth of the child with the autosomal recessive gene. Whether the affected child has a younger sibling is a fundamental question that has not been addressed. Profound parental concerns arise after the birth of the child, such as: given uncertainties about the future prognosis of the child and the likelihood of great responsibilities ahead, do they decide not to have another child? Or do they decide to have another child so that their child with a genetic disease benefits from having a younger sibling? And if parents decide to have another child, how long do they wait before having that next child?

To gain new insights into this overlooked yet highly consequential subject, this study has the rare opportunity to investigate whether the birth of a child with CF, one type of recessive disorder, is associated with either ending parents' intentions for a larger family or moderating those intentions. Section A1 outlines the main aspects of CF.

Using French data containing retrospective information on the birth order of children with CF and their siblings, this study addresses the timing of the birth of a younger sibling after the birth of a child with CF. By pursuing this research, we showed that the birth order of a child with CF is critical for understanding the timing of the next sibling's birth. It can affect family size and alter sibling spacing. Thus, it is not just genetic science and medical advice that influences family change for those families raising children with a genetically inherited disease, such as CF. Our study suggests that a family feature, namely the birth order of the child with CF, is an additional driver.

Our study situates genetic research and medical science on CF within a broader social science context. We argued

that the research has implications for other autosomal recessive disorders, as the impact of the birth of a child with an inherited genetic disease on family structure is not restricted to just CF (Boardman, 2014; Schultz, 2014).

1.1. Background

Scientific advances in genetics have led to a deeper understanding of autosomal recessive conditions, including CF. The discovery in 1989 of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which is responsible for CF (Kerem *et al.*, 1989; Riordan *et al.*, 1989; Rommens *et al.*, 1989), and its 2,000 variants has meant better treatments and more efficacious medical interventions (Farrell *et al.*, 2001). Doctors can now diagnose CF at birth, and many countries offer nationwide neonatal screening for CF. Evidence suggests that advances in screening and early detection of CF have lowered morbidity and mortality rates and improved health outcomes for those living with CF.

An autosomal recessive condition is one that is inherited in families. There are different transmission pathways from parents to children, but for a child to be born with an autosomal recessive condition, such as CF, both parents must carry a mutated gene. Other autosomal recessive conditions include albinism, sickle cell anemia, Tay-Sachs disease, and phenylketonuria. The commonality among these conditions is that to inherit any one of them, both parents must be carriers of the mutated gene (Davies *et al.*, 2007). The science of recessive inheritance continues, marked by triumphs that advance the care and treatment of those living with genetic diseases.

Besides scientific and medical breakthroughs that have extended lives and improved health outcomes for individuals with CF, these achievements have also aided reproductive and family-planning decisions of couples who are carriers of the CF gene. Advances in neonatal screening for CF mean that parents can obtain genetic information and counseling promptly. Even if neonatal screening is not an option, advances in testing allow parents to learn their status as carriers of the disease soon after the birth of their child with CF. Nowadays, medical knowledge is channeled into specialized consultations between physicians and parents to help them understand CF transmission, the odds of having another child with CF, and the use of preimplantation genetic testing to avoid having another child with CF (Dudding *et al.*, 2000; Henneman *et al.*, 2001). Overall, advances have helped parents make more informed decisions about whether to conceive another child after having had a child with CF. Reproductive choices for parents caring for children with genetic diseases now go hand in hand with advances

in genetics and medicine (Boardman and Clark, 2022; Chudleigh *et al.*, 2024; Foil *et al.*, 2023).

Besides genetic and medical research, social science research has examined parents' future family-planning decisions after the birth of a child with CF. The theme emerging from social science studies is that these parents' future family planning and reproductive decisions are complex (Gee *et al.*, 2017). According to these studies, parents' future reproductive decisions depend on the prognosis for the child with CF, the condition's impact on parents themselves and siblings, and the availability of three key contexts: healthcare services, networks for social support, and experts in the genetic sciences and medicine (Gee *et al.*, 2017; Myring *et al.*, 2011; Sawyer *et al.*, 2006).

Other social science research reported that parents' future family-planning decisions are influenced by developments in the genetic sciences, medicine, and technology that might help them manage their child's condition. For example, advances in genetic counseling, enhancements in neonatal and newborn screening technologies, and innovations in reproductive technologies, e.g., intrauterine insemination or sperm retrieval, mattered to family planning decisions (Dudding *et al.*, 2000).

The social science studies, though insightful, shed no light on whether fundamental demographic characteristics of a child with CF affect parents' family planning decisions. One such characteristic of the child with CF for which there is no knowledge is the effect of their position in the birth order on the occurrence of another birth in the family. Nonetheless, we noted a study that examined the effect of birth order on parents' stress levels when raising a child with CF (Continisio *et al.*, 2020). We hypothesized that the birth order of such a child affects parents' decisions about whether to have another child and when. By investigating the role that the birth order of a child with CF could play in shaping parents' future family-planning decisions, new insights are gained into the timing of an additional child's birth and thus the dynamics of these families' expansion.

1.2. Hypotheses

More research is needed about parents' family-planning decisions after a child with a genetic disease, such as CF, is born. The present gap in this research area motivated us to formulate hypotheses, of which two are key to expanding our knowledge about the effect of the birth order of a child with CF on the timing of a younger sibling's birth if such a birth occurs. There is a literature on fertility intentions and parents' reproductive choices, for example, Cukrowska-Torzewska and Grabowska (2023), but no studies address the population we study or undertake an approach like ours.

The first key hypothesis was that the timing of a younger sibling's birth after the birth of a child with CF depended upon the birth order of the child with CF. The specificity of this hypothesis originated from our aim to replace the agreed-upon general idea—that parents' future family-planning decisions were affected by the birth of a child with CF—with a more precise testable hypothesis. Our precise hypothesis reflected the reality that parents' reproductive decisions considered whether their child with CF was the first-, second-, third-, or later-born child in the birth order. Theoretically, if the child with CF were further down in the birth order, the time it took until the next birth should lengthen. The time should increase because the next sibling's birth would create a larger family to support, and the younger sibling is at risk of inheriting the CF gene. Therefore, this hypothesis underscored that the discrete position in the birth order of the child with CF was critical for assessing if birth order influenced future family-planning decisions.

Our second key hypothesis was that to obtain an unbiased estimate of the effect of the birth order of a child with CF on the timing of the next birth, two groups of individuals must be included in analyses: (i) those with CF who were the first and only child born in the family; and (ii) those with CF who were the last-born child.

This hypothesis might appear perplexing, but its reasoning was sound. It recognized that the birth of a child with CF may have led some parents to entirely reassess their family planning. The reassessment may have led parents to decide not to have any more children or to experience prolonged ambivalence about having more. Deciphering the motives of these two groups of parents not to have another child after the birth of their child with CF was not possible with our data. However, what was possible with our data was testing whether the exclusion of these two groups from analyses would upwardly bias estimates of the timing of a subsequent birth after the birth of a child with CF.

Besides these two key hypotheses, we expected that other individual characteristics and advances in CF research and treatment could affect the timing of the next birth after a child with CF is born. We hypothesized that if the child with CF was born before the 1989 genetic test for CF was available, the time to the next birth would lengthen. Likewise, the time would lengthen if the individual were born into later birth cohorts or diagnosed with CF early in infancy. The former factor related to parents in later cohorts having more information about the disease, while the latter factor related to knowing individuals' CF condition sooner after birth.

We conjectured that mothers' ages at the time of the birth of the child with CF were associated with the timing of the next sibling's birth. A mother who was older when she gave birth to her child with CF would be more likely to delay the next birth because of the ensuing emotional, physical, and potential financial demands. These challenges, we argued, would outweigh the desire to have another child before her ability to do so ended. Lastly, we expected a family history of CF to delay the next birth as well, but the gender of an individual with CF would not affect the timing of the next birth. By testing these hypotheses, we believe that research on families raising children with CF will be broadened, and that the insights may be relevant to researchers studying families raising children with other genetic conditions.

2. Data and methods

2.1. Data description and sample selection

To test our hypotheses, we used data from the French Cystic Fibrosis, Family, and Society Survey conducted by the French Institute for Demographic Studies between April 2017 and April 2019 (Bellis *et al.*, 2023). The survey asked a range of family history questions to persons participating in the French Cystic Fibrosis Registry. The Registry is a national program that has collected health data on individuals diagnosed with CF in France every year since 1992. Bellis *et al.* (2012) estimated that by 2009, the Registry covered nearly all persons with CF in France. The present study successfully matched individuals' survey responses to their biomedical data in the Registry.

When the survey was conducted between 2017 and 2019, the Registry contained 3,617 individuals with CF aged 18 years or more. These individuals were invited to participate in the Cystic Fibrosis, Family, and Society Survey. Of the 3,617 individuals, 428 (11.8%) responded to the survey. Of these, 267 completed the entire family history questionnaire module.

To ensure the next child's birth after the birth of the individual with CF was to the same two biological, gene-carrying parents, thus not biasing findings on the timing of births to the same couple, we excluded certain individuals: those whose parents had separated, divorced, or died during the individuals' childhoods ($n = 20$); those whose siblings were adopted or step-siblings ($n = 26$); and those who had a biological sibling with CF, but whose sibling's birth order was undetermined ($n = 7$). Exclusions reduced the sample to 214 persons with CF aged 18 years and over who had complete family histories and in which all siblings were biological offspring of the same two parents. Those who were fourth or fifth in the birth order ($n = 18$) were also excluded. The final sample numbered 196. Section A2

details the construction of the final sample. In our study, birth order mapped perfectly onto parents' marriages or partnerships. In some studies, birth order changes with divorce, parental death, or repartnering, but not in this study.

For the 196 individuals, we had information on their past from both the Registry and the family history questionnaire. From the Registry, we retrieved data on their specific CF gene sequence, medical treatments from birth onward, and the date of CF diagnosis (Bellis *et al.*, 2023). From the questionnaire, we collected data on family of origin, family history of CF, place of birth, familial relationships, and past CF-related health events and medical interventions.

The family history questionnaire data informed whether individuals with CF had siblings, how many, when they were born, whether they were deceased, and whether they too had CF. Since the questionnaire collected siblings' birth dates, we could determine birth order relative to the birth date of the individual with CF. The family history data identified the exact nature of the sibling relationships: full, step, or adopted. Given our aims, these data were ideal.

2.2. Statistical approach

The data on dates of births for all family members and dates on other major past family events allowed us to transform these data into survival time data. The event of interest was the date of birth of the next sibling following the birth of a child with CF. The months that elapsed between the two birth dates were our dependent variable, labeled "Months until next sibling's birth." Transforming the data to survival time equivalents enabled us to examine the effect of our independent variable, "Position in the family birth order," on our dependent variable.

Our initial empirical approach used nonparametric survival-time methods to analyze the months elapsed between the birth of a child with CF, accounting for position in the birth order, and the birth of the next sibling.

Next, we fitted a semi-parametric Cox proportional hazard regression model (Cox, 1972). This model tested our hypothesis about the effect of "Position in the family birth order" on the number of months until the next sibling's birth, while controlling for mediating factors. Cox regression also had two advantages: first, estimated coefficients could be transformed into hazard ratios to compare with those from a parametric Royston–Parmar model; and second, this regression approach obviated the need to specify a functional form for the baseline hazard function.

The second regression approach was the parametric Royston–Parmar model (Royston, 2001; Royston and Parmar, 2002). We fitted this model to our data for several reasons. First, this model avoids having to impose an artificial functional form for the hazard underlying the timing of births in families raising children with genetic diseases. Presently, no empirical work exists to guide researchers as to the true functional form of that hazard. Second, given this fact, the model can accommodate a flexible functional form of the hazard rather than be constrained to a specific functional form. Third, the model offered greater flexibility by using restricted cubic spline functions as alternatives to linear functions of log time (Burke *et al.*, 2020; Royston and Parmar, 2002).

The Royston–Parmar model also included the two crucial groups of people with CF ($n = 72$), who never experienced the birth of a next sibling after their own. In survival time analysis, they were classified as “right-censored.” In survival time analyses (Hosmer *et al.*, 2008), right censoring means that the event under study has not occurred for the observation. In other words, the observation was at risk of the event, but the event did not occur by the end of the study period (Klein *et al.*, 2014). Here, the individual with CF could have experienced the event of a next birth, but that event did not happen before their mother became infertile (49 years of age). The time between the individual’s birth and when their mother turned 49 years of age was measured in months. Though approximate, we decided that the logical month for them to become right-censored was the month that coincided with their mothers’ 49th birthdays. That age is the age demographers use as a guide as to when females are considered no longer able to bear children (Leridon, 1973).

Both models estimated the effect of our main independent variable, “Position in the family birth order,” on the timing of the next sibling’s birth after the child with CF was born. Each model contained the same control variables: gender, when a diagnosis of CF was established, birth cohort, and whether born before or after the genetic test for CF was instituted.

3. Results

3.1. Findings

Table 1 provides descriptive statistics for the 196 individuals with CF. There were more females (58.2%) than males (41.8%), indicating a greater propensity of females to answer the online survey. The average age was 32 years at the time of the survey. When first diagnosed with CF, individuals were about six years of age. When they were born, their mothers were about 28 years of age. At birth, 166 of the 196 participants were either first- or second-born.

Most of them had only one sibling. Although not shown in Table 1, 49% of those with only one younger sibling were first-born. Furthermore, most of the 196 individuals were born in the 1980s and 1990s; born before the CF test was available; and had been diagnosed with CF within a year of their birth. Very few had a sibling diagnosed with CF, nor did many have a family history of CF. Among the participants, 124 had a younger sibling born after them to the same biological parents, while 72 had none.

Results shown in Table 2 pertained only to individuals with CF who reported a younger sibling born after their birth (restricted sample). Those who reported no birth following their birth were omitted but included later in the survival time regression models. Mean and median numbers of months until the next sibling births were stratified by the birth order for individuals with CF up to the birth order position of third-born. If individuals were the first-born, the mean and median months until a subsequent sibling’s birth (i.e., the second-born child) were 48 and 38 months, respectively. For the second-born, the mean and median months for the next birth (i.e., the third-born child) increased to 62 and 58 months, respectively. Considered cautiously due to the small sample size ($n = 9$), third-born individuals showed a decrease in the number of months until a fourth birth, as indicated by the mean and median. This decrease may indicate an unplanned pregnancy or a maternal desire for another child before fecundity ends.

Table 2 also shows the estimated quartiles for the next-younger sibling by birth order. The 25th percentiles for the months until the next birth for first-, second-, and third-born individuals were 30, 31, and 33 months, respectively, suggesting similar durations in the short-term until subsequent births. The 50th percentiles—the median number of months until the next birth—were already noted in the preceding paragraph. A comparison of the 50th percentiles indicated greater variability in the timing of subsequent births across birth-order groups. While 50% of first-borns had a younger sibling within 38 months, it took 58 months for 50% of the second-borns to have a younger sibling.

Lastly, incidence rates for subsequent births further underscore the variability in their timing by birth order. The incidence rate for first-borns with CF was 0.021 per one person-month, or 1 subsequent birth per person-4-year period. The incidence rate for first-borns was higher than that for second-borns (0.016 per one-person month), implying 1 subsequent birth per person-5-year period. Thus, a subsequent birth after the second-born occurred at least a year later than a subsequent birth after the first-born.

Table 1. Selected descriptive statistics of CF individuals (N = 196)

Parameters	Mean/ <i>n</i>	SD/Percentage
Age of the CF patient at the time of the survey (years)	32.0	9.2
Age when diagnosed with CF, if not before or at birth (years)	5.9	10.4
Age of the mother when the CF child was born (years)	28.3	4.4
Sex of the CF patient		
Male	82	41.8%
Female	114	58.2%
Position of the CF patient in the family birth order		
1st born (eldest)	89	45.4%
2nd born (2nd eldest)	77	39.3%
3rd born (3rd eldest)	30	15.3%
Number of siblings in the CF patient's family		
One	108	55.1%
Two	64	32.7%
Three	21	10.7%
Four	3	1.5%
Decade in which the CF patient was born		
1960s	14	7.1%
1970s	27	13.8%
1980s	81	41.3%
1990s	74	37.8%
Born before or after the CF test is available		
Born after the CF test	77	39.3%
Born before the CF test	119	60.7%
History of CF in the patient's family		
No	183	93.4%
Yes	13	6.6%
Diagnosis of CF within a year of birth		
No	33	16.8%
Yes	163	83.2%
Sibling diagnosed with CF ^a		
No	164	84.1%
Yes	31	15.9%
A next birth after an individual with CF birth		
No	72	36.7%
Yes	124	63.3%

Notes: ^aA respondent stated "don't know." Source: Cystic Fibrosis, Family, and Society Survey.
Abbreviation: CF: Cystic fibrosis.

Table 2. Survival time statistics until the next birth after the birth of CF individuals, by position in the birth order

Birth order position	Number of individuals	Incidence rate for subsequent birth ^a	Averaged months	Survival time		
				25%	50% ^b	75%
First	89	0.021	48	30	38	59
Second	26	0.016	62	31	58	101
Third	9	0.021	47	33	36	71

Notes: Source: Cystic Fibrosis, Family, and Society Survey. Time until next birth measured in months; based on 124 individuals who had a next birth. ^a

Incidence rates = next births per individual-month; ^b 50% survival time is also the median number of months.

Abbreviation: CF: Cystic fibrosis.

Statistics in Table 2 suggested that the timing of a subsequent birth after the birth of a child with CF varied by the birth order of the child with CF. However, these statistics could be misleading because individuals' demographic characteristics and historical circumstances at the time of their birth could have affected the timing of the next birth or the possibility of no birth. To account for the hypothesized effects of demographic and historical factors, we fitted two alternative survival time regression models. Both models yielded estimates confirming that the birth order of an individual with CF predicted the timing of the next sibling's birth even after accounting for demographic and historical factors. Estimated hazard ratios are in Table 3.

The first observation was that the relative risk of a next sibling birth for the second-born child with CF, compared with that of the first-born with CF, was lower, even after controlling for demographic characteristics and historical circumstances close to the time of birth. The estimated hazard ratios for the variable "Second-born" indicated that the second-born child had a lower risk of a next birth compared to the first-born child. All four estimated hazard ratios for this key demographic variable were moderate to highly significant at conventional statistical levels (restricted sample: Cox model: $e^{\beta} = 0.497$; $t = -3.14$; Royston-Parmer model: $e^{\beta} = 0.464$; $t = -3.15$; unrestricted sample: Cox model: $e^{\beta} = 0.133$; $t = -8.65$; Royston-Parmer model: $e^{\beta} = 0.134$; $t = -7.85$).

Besides the first remark about the position in the birth order of the child with CF, two other remarks can be made about the estimated coefficients for the variable "Second-born." First, the estimated hazard ratios highlighted the importance of including right-censored cases. Comparing the hazard ratios from the restricted and unrestricted samples suggested that excluding right-censored individuals from the models yielded biased hazard ratios that underestimated the effect of the birth order of a child with CF on the next births. The hazard ratios

of the restricted sample implied that the birth of a third-born child happened more quickly than it should have compared to the birth of a second-born child. By including the right-censored individuals (unrestricted sample), this upward bias in timing was corrected, as shown by the smaller hazard ratios, reflecting parental indecision about conceiving another child. As argued earlier, indecision due to the challenges of raising a second-born child with CF may extend the months until a third birth or preclude the birth.

Second, there is uniformity between the hazard ratios for "Second-born" across the restricted and unrestricted samples. Their comparisons indicated that the underlying baseline hazard was stable over time. The Cox model, which made no assumptions about the baseline hazard, appeared sufficient for reliable inference about the effect of the birth order of a child with CF on the timing of the next sibling birth in families with four or fewer children.

Although sample sizes were small for third-borns, findings from the unrestricted sample suggest that, if the child with CF was third-born, the time to a possible fourth birth was further extended compared to the timing of the next birth for first-borns. No significant difference was observed between the hazard ratios for second-born and third-born, indicating that the timing of births following second-borns and third-borns was indistinguishable, neither longer nor shorter.

Our focus was on estimating the effect of the birth order of an individual with CF on the next sibling's birth, while controlling for individuals' characteristics and historical circumstances at the time of birth. Interestingly, findings on the effects of individuals' characteristics and historical circumstances on the timing of subsequent births warrant further study. In the Royston-Parmer model of the unrestricted sample, for example, estimated hazard ratios for several control variables suggest that the timing of births in families raising children with CF is associated with early diagnosis, mothers' ages, shared

Table 3. Two alternative survival time regressions estimating the risk of a next sibling birth after the birth of a child with CF, by restricted and unrestricted samples

Predictors	Restricted sample ^a		Unrestricted sample ^b	
	Cox	RP	Cox	RP
Second-born	0.497** (–3.14)	0.464** (–3.15)	0.133*** (–8.65)	0.134*** (–7.85)
Third-born	0.709 (–1.06)	0.636 (–1.07)	0.0874*** (–5.03)	0.0800*** (–5.68)
Sex of the CF individual	0.927 (–0.40)	0.877 (–0.66)	1.026 (0.15)	0.996 (–0.02)
CF individual born in the 1970s	0.336* (–2.49)	0.306* (–2.47)	0.388* (–2.01)	0.270** (–3.01)
CF individual born in the 1980s	0.345** (–2.66)	0.260** (–3.09)	0.512 (–1.56)	0.352** (–2.68)
CF individual born in the 1990s	0.976 (–0.05)	0.316 (–1.95)	0.725 (–0.51)	0.178*** (–3.38)
CF diagnosed within a year of birth	0.931 (–0.27)	0.715 (–1.29)	0.538* (–2.26)	0.425*** (–3.48)
Born before 1989 CF genetic test	2.538*** (5.03)	0.897 (–0.26)	1.141 (0.26)	0.336** (–2.79)
A family history of CF	1.499 (1.40)	1.326 (0.75)	2.336** (3.27)	2.418** (2.65)
Mother's age at the birth of the individual	1.057* (2.09)	1.007 (0.32)	0.974 (–1.13)	0.919*** (–4.22)
Chi-square	136.88***	65.56***	126.08***	442.77***
Degrees of freedom	10	10	10	10
Log-likelihood	–469.51	–79.63	–536.87	–166.72
<i>n</i>	124	124	196	196

Notes: Source: Cystic Fibrosis, Family, and Society Survey. Data are estimated hazard ratios with *t*-statistics in parentheses. Cox: Cox proportional hazard model; RP: Royston–Parmar flexible parametric survival time model. ^aRestricted models: Only individuals with CF who had experienced a next birth. ^bUnrestricted models: All individuals. **p* < 0.05, ***p* < 0.01, ****p* < 0.001.

Abbreviation: CF: Cystic fibrosis.

cohort, and advanced CF testing. For each control variable measuring these factors, the timing or duration to the next birth increases. Also, the results confirmed our expectation that the sex of the individual with CF would not affect the next births. However, the puzzling effect of a family history of CF was unexpected. It accelerated the timing of subsequent births rather than delaying them. We expected the opposite. Further research is needed to decipher this result.

3.2. Bias in the estimates of timing until a subsequent birth

The Royston–Parmar regressions generated predicted survivor curves for the restricted and unrestricted samples (Figures 1 and 2).

Comparisons of the predicted survivor curves in Figure 1 (restricted sample) with those in Figure 2 (unrestricted sample) supported our second hypothesis, which predicted that excluding right-censored individuals would bias the

estimated effect of birth order on the timing of a subsequent birth after the birth of the individual with CF.

When we compared the survival curves of the unrestricted sample (Figure 2) with those of the restricted sample (Figure 1), it was clear that many months passed until the next sibling's birth after the birth of an individual with CF. In the unrestricted sample, the number of months until the birth of a second-born child was greater than that of the restricted sample. The difference in the number of months was due to including the right-censored individuals who were first-born in the unrestricted sample. Similarly, the number of months until the birth of a third-born was greater in the unrestricted sample than in the restricted sample for the same reason. Lastly, both samples suggested that the birth order of an individual with CF mattered to the timing of the next sibling's birth. Both samples showed that a second birth occurred in fewer months after the first than the months that would have passed before a third birth after a second.

For brevity and easier interpretation of the figures, we excluded survival curves for the third-born and truncated the time scale to 110 months. The patterns for third-born children paralleled those of higher birth-order children. The trends in the survival curves after 110 months stayed consistent with our arguments. Sensitivity analyses were conducted on the regressions. In particular, maternal age restrictions were modified to assess whether models' estimates became insignificant, changed direction, or differed statistically. As we expected, none of these changes occurred. Though the empirical estimates changed slightly, all estimates remained significant, standard errors remained comparable, and none differed statistically from the estimates reported in Table 3. Future work will build on these regressions, such as specifying more sophisticated stratified Cox models, as well as frailty and shared frailty models. We also intend to seek additional funding for such empirical activities, given the foundational findings of this study.

4. Discussion

This study was motivated by research suggesting that the birth of a child with an autosomal recessive genetic disease, such as CF, affected parents' future family-planning decisions. Whether the birth order of a child with a genetic disease influenced the timing of the next birth remained unknown. Having this knowledge can help explain the size of families raising children with genetic diseases and the birth spacing among siblings. The day-to-day functioning of these families, the needs of siblings, the stress levels of parents, and costs to society could depend on the birth order of the child with a genetic disease.

For one of these autosomal recessive genetic diseases, namely CF, we could begin to answer the question using a novel French dataset. Our study showed that the position of the child with CF in the birth order was significantly associated with the timing of the next birth after the birth of a child with CF. The relative risk of a next birth after the second-born child with CF, compared with that after the first-born child with CF, was lower, even after controlling for demographic characteristics and historical circumstances close to the time of birth. A similar effect was found for a birth after the third-born child. The finding for a child with CF who was second in the birth order suggests that that child's position influences French couples' family-planning decisions after that birth in the birth order. French couples who had a second-born child with CF were more likely than French couples after the first-born child with CF to decide between either no more children or a delay in the timing of another birth.

Our findings on the role of birth order in the family-

planning decisions of parents raising a child with CF add to the literature. Earlier studies on the family-planning decisions of couples who were carriers of genetic diseases were qualitative, using field research methods, especially in-person, intensive interviewing (Henneman *et al.*, 2001; Myring *et al.*, 2011; Sawyer *et al.*, 2006). The data from the interviews focused exclusively on the impact of the birth, not the impact of the birth order. Identifying birth order and its effect on parents' future family planning choices was not considered by these studies. Our study contributes for these reasons: (i) it is a quantitative complement to the qualitative studies; (ii) it fills a gap in the literature on families raising children with CF; and (iii) it provides new knowledge of the dynamics of family expansion among this population of families.

Despite the study's contributions, it has limitations. One was that responses to the survey may have been affected by recall bias. This type of bias could have occurred if survey respondents could not accurately recall when major family events occurred. For example, siblings' birth dates, parents' deaths or divorces, or when genetic testing and medical interventions happened. Hence, the inability to accurately recall when an event occurred would lead to measurement error. Because we expected some degree of recall bias, we acted during the initial phase of data collection to mitigate its effects (Jones *et al.*, 2015; Laborde *et al.*, 2007; Yeatman and Sennott, 2015). We speculated that the effect of this bias was small when respondents recalled the number of brothers and sisters, but greater when they recalled the dates of birth and death of siblings. We addressed the threat of recall bias during data collection by providing respondents with a graphical representation of their life course, a method aligned with life history calendars (Belli *et al.*, 2001). This approach enabled respondents to better recall and check the consistency of dates.

Another proviso was that survey data collection was completed before *CFTR* gene-modulating triple therapy was available (Dawood *et al.*, 2022). In the future, this new therapy may affect parents' reproductive decisions. Studies of families raising children with CF should ask parents if newly introduced therapies (e.g., the drug Kaftrio®) would affect their reproductive decisions. In France, the drug Kaftrio® (ivacaftor/tezacaftor/elixacaftor) was approved for use in 2022. The first compassionate programme was launched on May 19, 2022 (Burgel *et al.*, 2024). More generally, studies of families affected by genetic diseases must ensure that research designs account for breakthroughs in science and medicine. When data were collected for this study, such accounting was done.

We also acknowledge that parents' deliberations can change after the birth of a child with CF, or there could be

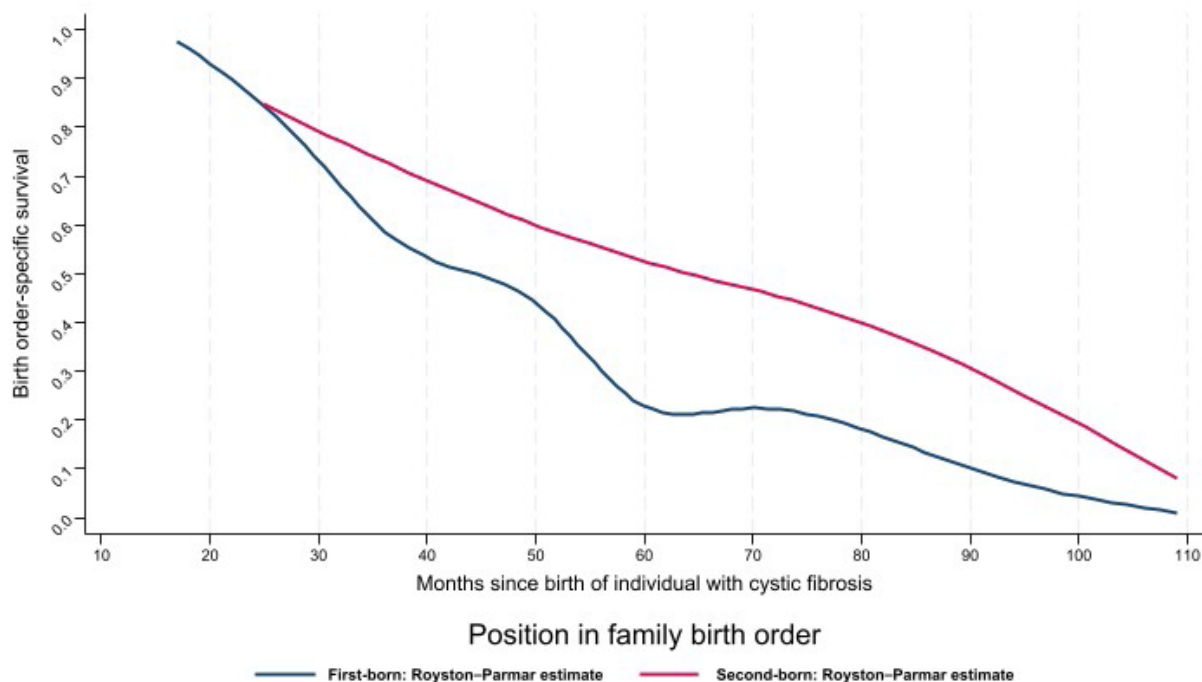


Figure 1. Survival time until the next birth after the birth of an individual with cystic fibrosis. By birth order in family (restricted sample).
Notes: Source: Cystic Fibrosis, Family, and Society Survey. All family members are biologically related; both parents are biological parents and carry the cystic fibrosis gene. $n = 124$.

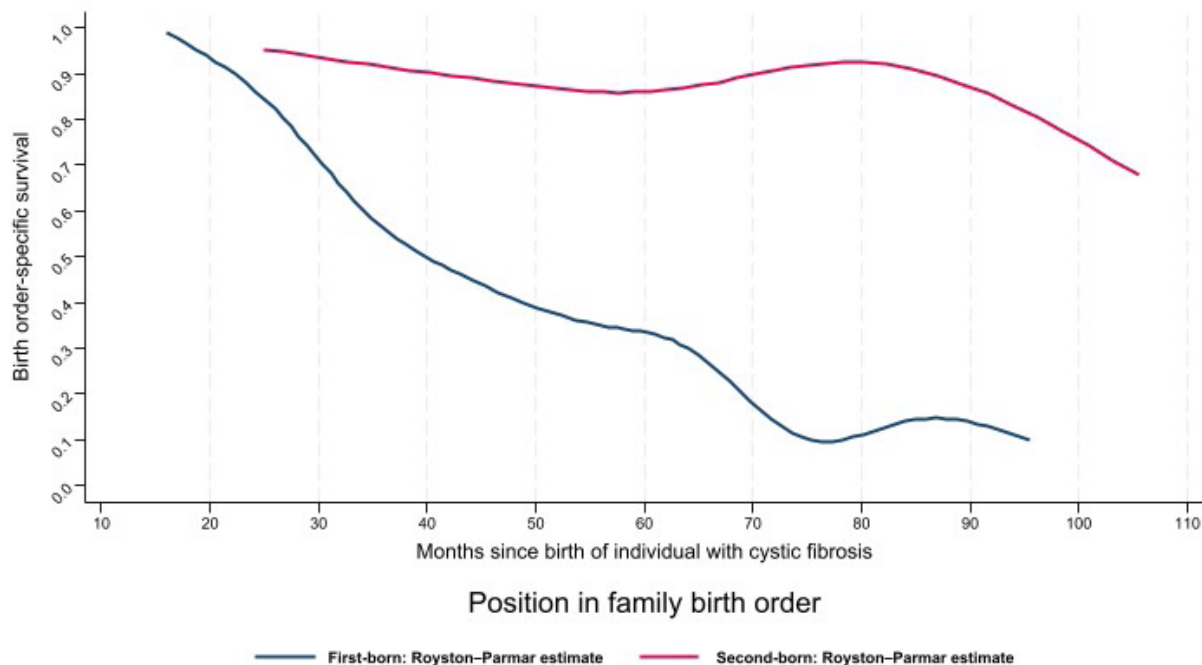


Figure 2. Survival time until the next birth after the birth of an individual with cystic fibrosis. By birth order in family (unrestricted sample).
Notes: Source: Cystic Fibrosis, Family, and Society Survey. All family members are biologically related; both parents are biological parents and carry the cystic fibrosis gene. $n = 196$.

delays due to the possibility of genetic counselling before another birth. Perhaps after absorbing the challenges of raising a child with a genetic disease, such as CF, there are no further births. In the current state of demographic research in this field, measures of parental deliberation after such a birth or of changes in parental preferences for having more children have not been measured. These limitations are ones we aim to address in future research and survey designs.

Another caveat is that we could not account for a terminated pregnancy that could have occurred later after the birth of a child with CF. A subsequent abortion or miscarriage might have caused parents to have no more children. However, collecting such highly sensitive family history data might have triggered emotional distress for survey participants while increasing survey non-response. It is reasonable to assume that delving deep into family-of-origin fertility histories, after already asking questions about CF and its consequences, could have created methodological issues and raised ethical concerns. Nonetheless, we anticipate that future studies can build upon our study and collect more in-depth fertility data if appropriate ethical and methodological procedures are followed.

Although not a shortcoming, the study did not aim to investigate the effects of a child with CF on siblings' well-being. Our data could not have supported such an inquiry due to the lack of measures of sibling effects. Nevertheless, more saliently, the question of whether parents still planned to have another child after the birth of a child with CF is a precursor to studying sibling effects. The question addressed here is foundational for studies of sibling effects since the impact of a child with CF on a sibling may depend on birth order and the time that passes between the birth of a child with CF and the next birth. While there is no literature addressing our question, there is literature available on sibling effects when raising a child with CF (Milo *et al.*, 2021; Li *et al.*, 2023).

Notwithstanding limitations, the study's findings add knowledge to understanding the dynamics of family change and diversity among families raising children with CF. We took a quantitative approach to understanding parents' family planning based on the past biographical events of individuals with CF. Moreover, our approach highlighted the importance of including right-censored individuals without younger siblings. As shown in [Table 3](#) and the figures, the coefficients for birth order and the predicted survival curves changed dramatically after models included right-censored individuals. Future studies of parents who are carriers of a genetic disease should consider whether the couple's declared final family size

reflects parental preferences to have no more children after the birth of a child with a genetic disease. Interpretations of epidemiological data and statistical profiles on CF, particularly in terms of the incidence and prevalence of this disease in the population, need to recognize that data sources and statistics reflect parents' decisions about whether to restrict or enlarge family size and, if enlarging, when to do so.

5. Conclusion

In conclusion, this study underscores that parents at risk of transmitting a genetic disease, such as CF, appear to make a conscious decision about the timing of a subsequent birth after a diagnosis of a genetic disease in their offspring. A parent's decision on whether to have more children and when, though a private one, is also informed by science and medical advances. Although a desire to have more children might exist, our study suggests that some parents revise their plans to have no more children after the birth of a child with CF. Others continue to have children, but the timing until another child is extended depends on the birth order of the child with CF. Given the limitations of our study's generalizability, similar studies should be conducted on other genetic diseases and in other contexts.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Gil Bellis, Peter Brandon

Formal analysis: Peter Brandon

Investigation: Gil Bellis

Methodology: Peter Brandon

Writing—original draft: Peter Brandon, Gil Bellis

Writing—review & editing: Gil Bellis, Peter Brandon

Ethics approval and consent to participate

The Cystic Fibrosis, Family and Society Survey was authorized by two regulatory authorities responsible in France for verifying the conditions under which personal data is collected and processed: "Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé" (CCTIRS), file number 15.605, and the "Commission Nationale de l'Informatique et des

Libertés" (CNIL), authorization request number 915443. Participants provided written consent to participate in the survey.

Consent for publication

Participants were informed in writing of the aims of the study and their rights. They gave their written consent for their data to be published anonymously.

Availability of data

The data are available on request from Gil Bellis (bellis@ined.fr) or Peter Brandon (pbrandon@albany.edu).

Further disclosure

Parts of the findings were presented at the 30th International Population Conference in Brisbane, Australia, on 15 July 2025, titled "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".

References

- Belli, R. F., Shay, W. L., & Stafford, F. P. (2001). Event history calendars and question list surveys: a direct comparison of interviewing methods. *Public Opinion Quarterly*, 65(1):45-74.
<https://doi.org/10.1086/320037>
- Bellis, G., Cazes, M. H., Lemonnier, L., Moreau, T., Rault, G., Ravilly, S., Scotey, V., & Sponga, M. (2012). *French cystic fibrosis registry. Annual data report 2009*. Available from: https://www.vaincrelamuco.org/sites/default/files/french_cf_registry_annual_data_report_2009.pdf [Last accessed on November 15, 2024].
- Bellis, G., Thauvin, P., Nait Abdallah, K., Ragazzi, S., Baril, E., Daudré, L., & Taillandier, L. (2023). Parcours et qualité de vie des patients atteints de mucoviscidose. Premiers résultats de l'enquête "Mucoviscidose, famille et société" [Life trajectories and quality of life of patients with cystic fibrosis. First results of the "Cystic Fibrosis, Family, and Society" Survey]. *Documents de travail*, 273. [Article in French]
<https://doi.org/10.48756/ined-dt-273.0923>
- Boardman, F. (2014). Experiential knowledge of disability, impairment and illness: the reproductive decisions of families genetically at risk. *Health*, 18(5):476-492.
<https://doi.org/10.1177/1363459313507588>
- Boardman, F., & Clark, C. (2022). 'We're kind of like genetic nomads': Parents' experiences of biographical disruption and uncertainty following in/conclusive results from newborn cystic fibrosis screening. *Social Science and Medicine*, 301.

- <https://doi.org/10.1016/j.socscimed.2022.114972>
- Boettcher, J., Boettcher, M., Wiegand-Grefe, S., & Zapf, H. (2021). Being the pillar for children with rare diseases-A systematic review on parental quality of life. *International Journal of Environmental Research and Public Health*, 18(9).
<https://doi.org/10.3390/ijerph18094993>
- Burgel, P. R., Sermet-Gaudelus, I., Girodon, E., Durieu, I., Houdouin, V., Audousset, C., et al. (2024). The expanded French compassionate programme for elxacaftor-tezacaftor-ivacaftor use in people with cystic fibrosis without a F508del CFTR variant: a real-world study. *Lancet Respiratory Medicine*, 12(11):888-900.
[https://doi.org/10.1016/s2213-2600\(24\)00208-x](https://doi.org/10.1016/s2213-2600(24)00208-x)
- Burke, K., Jones, M. C., & Noufaily, A. (2020). A flexible parametric modelling framework for survival analysis. *Journal of the Royal Statistical Society, Series C*, 69(2):429-457.
<https://doi.org/10.1111/rssc.12398>
- Cheema, Z. M., Gomez, L. C., Johnson, N., Laflamme, O. D., Rabin, H. R., Steele, K., Wallenburg, J., Leong, J., Cheng, S. Y., Quon, B. S., Stephenson, A. L., Dominika Wranik, W., Sadatsafavi, M., & Stanojevic, S. (2024). Measuring the burden of cystic fibrosis: a scoping review. *Journal of Cystic Fibrosis*, 23(5):823-830.
<https://doi.org/10.1016/j.jcf.2023.11.014>
- Chudleigh, J., Holder, P., Clark, C., Moody, L., Cowlard, J., Allen, L., Walter, C., Bonham, J. R., & Boardman, F. (2024). Parents' and children's views of wider genomic testing when used as part of newborn screening to identify cystic fibrosis. *SSM - Qualitative Research in Health*, 6:100455.
<https://doi.org/10.1016/j.ssmqr.2024.100455>
- Continisio, G. I., Serra, N., Guillari, A., Civitella, M. T., Sepe, A., Simeone, S., Gargiulo, G., Toscano, S., Esposito, M. R., Raia, V., & Rea, T. (2020). An investigation on parenting stress of children with cystic fibrosis. *Italian Journal of Pediatrics*, 46:33.
<https://doi.org/10.1186/s13052-020-0795-7>
- Cox, D. R. (1972). Regression models and life-tables. *Journal of the Royal Statistical Society, Series B*, 34(2):187-202.
<https://doi.org/10.1111/j.2517-6161.1972.tb00899.x>
- Cukrowska-Torzewska, E., & Grabowska, M. (2023). The sex preference for children in Europe: children's sex and the probability and timing of births. *Demographic Research*, 48(8):203-232.
<https://doi.org/10.4054/DemRes.2023.48.8>
- Daly, C., Ruane, P., O'Reilly, K., Longworth, L., & Vega-Hernandez, G. (2022). Caregiver burden in cystic fibrosis: a systematic literature review. *Therapeutic Advances in Respiratory Disease*, 16.
<https://doi.org/10.1177/17534666221086416>

- Davies, J. C., Alton, E. W., & Bush, A. (2007). Cystic fibrosis. *British Medical Journal*, 335(7632):1255-1259.
<https://doi.org/10.1136/bmj.39391.713229.AD>
- Dawood, S. N., Rabihi, A. M., Niaj, A., Raman, A., Uprety, M., Calero, M. J., Villanueva, M. R. B., Joshaghani, N., Villa, N., Badla, O., Goit, R., Saddik, S. E., & Mohammed, L. (2022). Newly discovered cutting-edge triple combination cystic fibrosis therapy: a systematic review. *Cureus*, 14(9).
<https://doi.org/10.7759/cureus.29359>
- Dudding, T., Wilcken, B., Burgess, B., Hambly, J., & Turner, G. (2000). Reproductive decisions after neonatal screening identifies cystic fibrosis. *Archives of Disease in Childhood. Fetal and Neonatal Edition*, 82(2):F124-F127.
<https://doi.org/10.1136/fn.82.2.f124>
- Farrell, P. M., Kosorok, M. R., Rock, M. J., Laxova, A., Zeng, L., Lai, H. C., Hoffman, G., Laessig, R. H., Splaingard, M. L., & the Wisconsin Cystic Fibrosis Neonatal Screening Study Group (2001). Early diagnosis of cystic fibrosis through neonatal screening prevents severe malnutrition and improves long-term growth. *Pediatrics*, 107(1):1-13.
<https://doi.org/10.1542/peds.107.1.1>
- Foil, K., Christon, L., Kerrigan, C., Flume, P. A., Drinkwater, J., & Szentpetery, S. (2023). Experiences of cystic fibrosis newborn screening and genetic counseling. *Journal of Community Genetics*, 14(6):621-626.
<https://doi.org/10.1007/s12687-023-00666-8>
- Gee, M., Piercy, H., & Machaczek, K. (2017). Family planning decisions for parents of children with a rare genetic condition: a scoping review. *Sexual and Reproductive Healthcare*, 14:1-6.
<https://doi.org/10.1016/j.srhc.2017.08.001>
- Grosse, S., Do, T., Vu, M., Feng, L., Berry, J., & Sawicki, G. (2018). Healthcare expenditures for privately insured US patients with cystic fibrosis, 2010-2016. *Pediatric Pulmonology*, 53(12):1611-1618.
<https://doi.org/10.1002/ppul.24178>
- Harris, S., Harris, P. R., Lenton, J., Warde, C., Gold, E., Gane, T., & Seddon, P. (2021). "Nurturing Parents"-Mindfulness-Based parent well-being group in pediatric cystic fibrosis. *Clinical Practice in Pediatric Psychology*, 9(2):123-134.
<https://doi.org/10.1037/cpp0000394>
- Henneman, L., Bramsen, I., Van Os, T. A., Reuling, I. E., Heyerman, H. G., van der Laag, J., van der Ploeg, H. M., & ten Kate, L. P. (2001). Attitudes towards reproductive issues and carrier testing among adult patients and parents of children with cystic fibrosis (CF). *Prenatal Diagnosis*, 21(1):1-9.
[https://doi.org/10.1002/1097-0223\(200101\)21:1%3C1::AID-PD967%3E3.0.CO;2-%23](https://doi.org/10.1002/1097-0223(200101)21:1%3C1::AID-PD967%3E3.0.CO;2-%23)
- Hosmer Jr, D. W., Lemeshow, S., & May, S. (2008). *Applied survival analysis: regression modeling of time-to-event data*, Second ed., John Wiley & Sons, Hoboken.
- Jones, R. K., Tapales, A., Lindberg, L. D., & Frost, J. (2015). Using longitudinal data to understand changes in consistent contraceptive use. *Perspectives on Sexual and Reproductive Health*, 47(3):131-139.
<https://doi.org/10.1363/47e4615>
- Kerem, B. S., Rommens, J. M., Buchanan, J. A., Markiewicz, D., Cox, T. K., Chakravarti, A., Buchwald, M., & Tsui, L. C. (1989). Identification of the cystic fibrosis gene: genetic analysis. *Science*, 245(4922):1073-1080.
<https://doi.org/10.1126/science.2570460>
- Klein, J. P., Van Houwelingen, H. C., Ibrahim, J. G., & Scheike, T. H. (2014). *Handbook of survival analysis*, Chapman and Hall/CRC, New York.
- Laborde, C., Lelièvre, E., & Vivier, G. (2007). Trajectoires et événements marquants, comment dire sa vie? Une analyse des faits et des perceptions biographiques [Life paths and defining moments: How do we tell our life story? An analysis of biographical facts and perceptions]. *Population*, 3(62):567-585. [Article in French]
<https://doi.org/10.3917/popu.703.0567>
- Leridon, H. (1973). *Aspects biométriques de la fécondité humaine [Biometric aspects of human fertility]*, Institut national d'études démographiques, Paris.
- Li, S., Douglas, T., & Fitzgerald, D. A. (2023). Psychosocial needs and interventions for young children with cystic fibrosis and their families. *Paediatric Respiratory Reviews*, 46:30-36.
<https://doi.org/10.1016/j.prrv.2023.04.002>
- Milo, F., Ranocchiari, S., Lucidi, V., & Tabarini, P. (2021). Coping with cystic fibrosis: an analysis from the sibling's point of view. *Child: Care, Health and Development*, 47(6):825-833.
<https://doi.org/10.1111/cch.12890>
- Mlcoch, T., Decker, B., Tuzil, J., Turkova, B., Doleckova, K., Koznarova, B., Zabranska, S., Blazkova, T., Dolezal, H., Pilnackova, B., & Dolezal, T. (2025). Life with cystic fibrosis: the socioeconomic impact on patients and their caregivers. *Value in Health Regional Issues*, 47:101085.
<https://doi.org/10.1016/j.vhri.2025.101085>
- Myring, J., Beckett, W., Jassi, R., Roberts, T., Sayers, R., Scotcher, D., & McAllister, M. (2011). Shock, adjust, decide: reproductive decision making in cystic fibrosis (CF) carrier couples: a qualitative study. *Journal of Genetic Counseling*, 20(4):404-417.
<https://doi.org/10.1007/s10897-011-9363-z>
- Riordan, J. R., Rommens, J. M., Kerem, B. S., Alon, N., Rozmahel, R., Grzelczak, Z., Zielenski, J., Lok, S., Plavsky, N., Chou, J. L., Drumm, M. L., Iannuzzi, M., Collins, F. S., & Tsui, L. C. (1989). Identification of the cystic fibrosis gene: cloning

- and characterization of complementary DNA. *Science*, 245(4922):1066-1073.
<https://doi.org/10.1126/science.2475911>
- Rommens, J. M., Iannuzzi, M. C., Kerem, B. S., Drumm, M. L., Melmer, G., Dean, M., Rozmahel, R., Cole, J. L., Kennedy, D., Hidaka, N., Zsiga, M., Buchwald, M., Tsui, L. C., Riordan, J. R., & Collins, F. S. (1989). Identification of the cystic fibrosis gene: chromosome walking and jumping. *Science*, 245(4922):1059-1065.
<https://doi.org/10.1126/science.2772657>
- Royston, P. (2001). Flexible parametric alternatives to the Cox model, and more. *The Stata Journal*, 1(1):1-28.
<https://doi.org/10.1177/1536867X0100100101>
- Royston, P., & Parmar, M. K. B. (2002). Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. *Statistics in Medicine*, 21(15):2175-2197.
<https://doi.org/10.1002/sim.1203>
- Sawyer, S. M., Cerritelli, B., Carter, L. S., Cooke, M., Glazner, J. A., & Massie, J. (2006). Changing their minds with time: a comparison of hypothetical and actual reproductive behaviors in parents of children with cystic fibrosis. *Pediatrics*, 118(3):e649-e656.
<https://doi.org/10.1542/peds.2005-2551>
- Schultz, C. L., Tchume-Johnson, T., Jackson, T., Enninful-Eghan, H., Schapira, M., & Smith-Whitley, K. (2014). Reproductive decisions in families affected by sickle cell disease. *Blood*, 124(21):2175.
<https://doi.org/10.1182/blood.V124.21.2175.2175>
- Seyoum, S., Regenstein, M., Benoit, M., Dieni, O., Willis, A., Reno, K., & Clemm, C. (2023). Cost burden among the CF population in the United States: A focus on debt, food insecurity, housing and health services. *Journal of Cystic Fibrosis*, 22(3):471-477.
<https://doi.org/10.1016/j.jcf.2023.01.002>
- Yeatman, S., & Sennott, C. (2015). The sensitivity of measures of unwanted and unintended pregnancy using retrospective and prospective reporting: evidence from Malawi. *Maternal and Child Health Journal*, 19(7):1593-1600.
<https://doi.org/10.1007/s10995-015-1669-2>

Appendix

A1. Cystic fibrosis

Cystic fibrosis (CF) is a genetically inherited disease that causes the human body to produce a thick, viscous mucus instead of what many organs of the body need, which is a thin, slippery mucus. Healthy mucus acts as a lubricant and protector for organs. In contrast, maladaptive mucus that is caused by CF obstructs the proper function of organs such as the lungs and pancreas, leading to acute breathing problems, frequent infections, and severe indigestion. Though life expectancy has greatly improved through medical interventions and therapies, persons with CF still have compromised lives and higher mortality and morbidity rates than the general population.

As stated, persons are born with CF. The disease cannot be contracted, nor does it have a cure. If a person has CF, that means the person's *CFTR* gene, located on chromosome seven, has mutated. The mutation causes the cystic fibrosis transmembrane conductance regulator (CFTR) protein to be absent from the cell linings of sweat glands, the lungs, and the pancreas, among other organs.

From birth until death, persons with CF may face many medical and psychological challenges. For instance, chronic pulmonary obstructions can lead to lung transplants or death. Due to the daily care required, starting at birth, and the burden of life-long medical interventions and treatments, the disease has numerous repercussions: reduced quality of life, disrupted schooling, and interrupted careers and employment for adults.

Not only does CF change the lives of persons who inherit it, but it also affects the parents of the child with CF. Whether or not the parents knew beforehand or after the birth that they were both carriers of the mutated gene, the research overwhelmingly suggests that they had to revise their future family-planning decisions. Those revised decisions included whether to have more children and, if so, when, that is, the timing of a subsequent birth (couples have a 25% risk with each pregnancy of passing the disease on to the child).

Geneticists have studied the future family-planning decisions of carrier couples following the birth of a child with an autosomal recessive disorder, such as CF or sickle cell anemia. To study the future family-planning decisions for these diseases, they have used qualitative methods to determine how knowledge of the risk of recurrence might influence parents' decisions to have another child. To our knowledge, none of the studies used relatively large samples, nor advanced quantitative methods. For example, survey data utilizing regression methods that took into account the effect of the birth order of the child with CF on the parental decision to have another child, while accounting for existing family size, duration of the parental couple's relationship, and the mother's age at the time of each birth during her fertile years.

A2. Sample selection procedures

At the time of the Cystic Fibrosis, Family and Society Survey, the French Cystic Fibrosis Registry had 3,617 adults aged 18 years or older. The sample size to be drawn from this medical Registry for the survey was calculated based on the already known prevalence of adults in the Registry. The theoretically predicted sample size for the survey was calculated to be 588 adults, with a survey precision of $\pm 3\%$ and a margin of error (α) of 5%. Although we hoped to achieve this theoretical sample size, we knew from the survey methods literature that there would be non-responses to the survey among those eligible to participate in the survey. As expected, due to survey non-response, the number of persons in the Registry who agreed to participate in the survey was 454, of whom 428 were adults. Importantly, these 428 adults represented 94.3% of the adults in the Cystic Fibrosis, Family, and Society Survey sample. Further analysis based on the survey design found that this group was statistically representative of all the adults with CF in the Registry. Among the 428 adults, there was some attrition and some logical exclusions due to responses to survey questions on families: 267 of the adults completed the entire "Family" module of the questionnaire in full.

To ensure that regressions estimated with less bias the effect of birth order of the individuals with CF on the next birth, we excluded certain people, even though they gave full family histories. First, transmitting the CF gene to offspring requires both partners to maintain their union. If one parent re-partners, then presumably different parental decision-making about having another child and when it occurs, and the individual with CF gains a younger half-sibling (they may also gain a younger or older step-sibling). This same dynamic is possible if one of the parents with the CF gene dies after the birth of the individual with CF. Again, if the surviving parent re-partners, then presumably different parental decision-making about having another child and when it occurs, and the individual with CF would gain a younger half-sibling. By excluding individuals with CF with such family histories, we argue that our regression estimates on the timing of the next births are

less likely to be biased by these types of parental “decoupling” in the family. Finally, if an individual with CF indicated that a sibling also had the disease, but we could not identify them as older or younger due to missing data, they too were excluded. Omitting them was prudent since we cannot make assumptions about parental decisions about the timing of births, whether it be the timing of the birth of the individual with CF or the timing of the next birth. For example, if the individual with CF was the second born and their older first-born sibling also had CF, then the parents’ decision about having a third child and when may be profoundly affected. Alternatively, in this example, the sibling could have been the younger third-born. Either scenario is possible, but unknown. These meticulous steps meant that the sequencing of births was accurate, including circumstances such as precisely identifying the third child having CF while their older siblings, that is, the first- and second-born siblings, did not have CF.