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Analysis of Birth Growth: Using a Mixture Cure Frailty Model

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Abstract

Background: The birth rate is important in population growth. Concerns are growing over declining birth rates in Iran, as a developing country in the past decade. The present study aimed to examine population growth in Hamadan and the factors influencing the birth rate.

Methods: This retrospective cohort study utilized data from 633 families with their first child in 2012 in Hamadan—information updated in 2022. The Kaplan-Meier plateau indicates a curing pattern; therefore, a mixture cure frailty model was employed to estimate the probability and hazard rate of having different numbers of children. This model comprises 2 components: the first estimates the probability of birth (or nonbirth, indicating cure), while the second component calculates the birth hazard rate for having different number of children.

Results: Mothers with high school diploma (odds ratio [OR], 0.049; $P = 0.004$) and under diploma (OR, 0.449; $P < 0.001$) education levels and fathers with under diploma (OR, 0.802; $P = 0.021$) education levels were linked to a lower risk of birth and a higher chance of a cure. Moreover, high school diploma (hazard ratio [HR] = 0.668; $P < 0.001$) and under diploma (HR = 0.821; $P < 0.001$) education levels in mothers significantly decreased the birth hazard rate. The shape parameter in the hazard function ($\mu = 0.933$; SE = 0.049) indicates that the hazard rate of birth was decreasing during the follow-up time.

Conclusion: The study found that the mixture cure frailty model was effective in analyzing birth rates, with couples showing a decreased inclination to have more than 2 children. One contributing factor to this trend is the mothers' education and employment.

Keywords: Recurrent Event, Mixture Cure Model, Frailty, Birth

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Introduction

Population growth is determined by the rate of births, which is correlated with birth spacing. Birth spacing refers to the gap between birth times (1). Past studies have shown that female education, the mother's age at childbirth, the father's occupation, the age of the woman at marriage, and menstrual status influence birth spacing (2, 3). The Iranian government had previously implemented a prevention policy around 3 decades ago, and as a result, the population has now reached replacement levels (4) and is currently in a declining trend (5). Iran, as a developing nation, has witnessed a decline in fertility rates over the past decade (6). The birth rate in western Iran specifically in Hamadan prov-

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↑*What is "already known" in this topic:*
In recent decades, the population growth rate in Iran has declined. Various studies have been conducted to examine this trend in birth rates. A thorough investigation requires the application of appropriate statistical methods and an analysis of the factors influencing fertility.

→*What this article adds:*
In this study, for the first time, the birth rate and the probability of having any number of children have been examined using the method of survival analysis for recurrent events. Moreover, the factors influencing the decline in population growth and the reluctance of parents to have more children in recent decades have also been explored.

ince, has shown a decline over the last few years (5). Childbirth is a recurrent event that can occur multiple times, and it is important to consider the dependency between these occurrences. In Previous studies, variance-corrected models, such as the Prentice-Williams-Peterson (Gap Time), have been employed (1, 5). However, these methods do not estimate a separate parameter for the measure of dependency between occurrences. Therefore, frailty models have been preferred (7). Frailty models account for individual-specific random effects that may influence the hazard of an event occurring (8). These models have focused on analyzing birth spacing without considering the cure fraction (9). In contrast, our research examines birth as a recurrent event, acknowledging that some mothers may not experience repeated births, indicating a cure among varying birth numbers. We employ a model for survival analysis of recurrent events that simultaneously consider several vital aspects, including within-subject dependency, cure fraction, and frailty.

To achieve the desired birth rates and maintain a younger population for the progress of the countries and the world, detailed studies based on appropriate models must be conducted. In this study, we examined the cure after each childbirth and the effect of parents' education and occupation using the mixture cure frailty model.

Methods

To analyze this retrospective cohort study, all mothers who had their first child born in 2012 in Fatemiyeh Hospital in Hamadan, Iran, were considered. A 10-year follow-up time was selected. Participants' information was updated in 2022 via phone calls. The mentioned hospital had the highest annual number of deliveries and patient referrals in Hamadan, making it suitable for the research. Participants whose children had passed away during or shortly before and after childbirth were excluded from the study. Some were unwilling to respond when we reached out to them for information updates. The information for certain individuals had been incorrectly recorded in the files. Some phone numbers had been reassigned to other individuals or were blocked. These issues led to the exclusion of some individuals from the study. Finally, 633 mothers remained and were examined. In this study, birth has been considered a recurrent event since this event can occur repeatedly for each mother. The time to birth is an outcome measure, while the differences in the time taken for childbirth among varying numbers of children are referred to as gap times. Three gap times are considered for the intervals between the births of the first and second children, the second and third, and the third and fourth. The study examines several covariates—including the age and educational level (under diploma/diploma/ upper diploma) of the parents, the parents' disease status (yes/no), the employment status of both parents (mother as a housewife/employee and father as self-employed/employee), and the socioeconomic status of families (low/middle/high income).

The inclusion of numerous covariates added complexity to the model. Additionally, there was insufficient collaboration among participants, which hindered the completion of all necessary information. Many families often refrain from providing information about their economic status due to conservative tendencies. They inaccurately selected a middle economic status, resulting in a significant amount of missing data and bias for this variable.

Ultimately, the educational levels and occupational status of the parents were chosen for inclusion in the model because of their more favorable distribution compared with other covariates. If a pattern of cure is observed in recurrent events data, appropriate cure models should be utilized (10, 11). A stable plateau on the right side of the Kaplan-Meier curves (12) in this study indicates the existence of a cure in the data. It is necessary to mention that the cure was examined after each recurrence of events, and a mixture cure model was used. We assume that $\mathrm{R_{ij}}$ is the gap time of j-th recurrent on the i-th subject ($\mathrm{i} = 1, \dots, \mathrm{N}$). The death time of the recent failure and censoring time are defined with $\mathrm{D_i}$ and $\mathrm{C_i}$, respectively. The $\mathrm{C_i}$ is independent of $\mathrm{D_i}$ and $\mathrm{R_{ij}}$. The follow-up time is defined as $\mathrm{T_{ij}} = \min(\mathrm{C_i}, \mathrm{D_i}, \mathrm{R_{ij}})$.

A general mixture cure model for analyzing recurrent events with a cure fraction in the data is as follows:

$$S(t) = 1 - \pi(\boldsymbol{x}) + \pi(\boldsymbol{x})S_u(t;\boldsymbol{x}) \qquad (1)$$

This model includes 2 parts. The first is the proportion of uncured participants $\pi_j(\boldsymbol{x})$ or incidence. In the present study, this part estimates the probability of childbirth.

$$\pi_j(\boldsymbol{x}) = \frac{exp(\varphi_{ij})}{1 + exp(\varphi_{ij})} \qquad \varphi_{ij} = \omega_i^T \alpha + \tau_i \qquad \omega_i = (1 \;\; x_i^T)^T \qquad (2)$$

Where φ_{ij} is a linear predictor, α is the fixed effect vector, which measures the effect of covariate $\boldsymbol{x}$ on the probability of each recurrence. Moreover, τ_i is the frailty term affecting the recurrence probability. Suppose that $\tau = (\tau_1, \dots, \tau_N)^T$ is independent and identically distributed from $N(0\sigma_\tau^2 I_N)$. The second part of the mentioned model, $S_u(t;\boldsymbol{x})$ is named the latency, which can be modeled through the hazard function as follows:

$$h(t_{ij}|u_i) = h_0(t_{ij})\,exp(\boldsymbol{\beta X}_{ij} + ln(u_i)) = u_i h_0(t_{ij})\,exp(\boldsymbol{\beta}^T \boldsymbol{X}_{ij}) \qquad (3)$$

where $h_0(t)$ is the baseline hazard function in uncured patients that follows the Weibull distribution with μ shape parameter. The u_i is a frailty term that affects the hazard rate of each childbirth on $i\text{-}th$ mother. We utilized a Variational Bayes (VB) computational method to estimate parameters. This approach is a quick optimization method, offering a computationally efficient option compared with sampling techniques. To assess the goodness-of-fit of the model, the variance of frailties and the related standard errors (SE) have been utilized. A low value indicates the suitable performance of the model in estimating the parameters. The calculations were conducted utilizing the RSTAN package within RStudio Version 26.2.4. A significance level of 0.05 was employed for the analysis.

Results

In this study, based on the data in Table 1, the number of births ranged from 1 to 4. Out of all the participants, the most of mothers (n = 384; 60.7%) had 2 children. Among the 633 families examined, 310 (49%) had a under diploma

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Table 1. Frequency distribution of childbirth based on the birth data in Hamadan

Variables	Strata	Number (percent)
Number of births	1	177 (28%)
	2	384 (60.6%)
	3	67 (10.6%)
	4	5 (0.8%)
Mothers' education	Under diploma	310 (49%)
	High school diploma	216 (34.1%)
	Upper diploma	107 (16.9%)
Fathers' education	Under diploma	354 (55.9%)
	High school diploma	175 (27.7%)
	Upper diploma	104 (16.4%)
Mother's job	Housewife	588 (92.9%)
	Employer	45 (7.1%)
father's job	Self-employer	540 (85.3%)
	Employer	93 (14.7%)

education. Similarly, 354 of the fathers (55.9%) had a under diploma education. Also, 588 mothers (92.9%) were housewives. A total of 540 fathers (85.3%) were self-employed.

The KM curves for each gap time of births, categorized by mothers' education and fathers' education are shown in Figures 1 and 2, respectively. During the initial gap time, the likelihood of nonrecurrence is consistent across all education levels. However, as time passed, the curves plateaued and showed a sustained survival probability for all education categories, indicating the presence of a cure. This cure pattern becomes more evident between the birth of the second, third, and fourth child, suggesting a declining desire for families to have more than 2 children.

In Table 2, the parameters estimations of 2 parts of the mixture cure frailty model are demonstrated. As exhibited, both mothers' education level and under diploma education levels of fathers, noticeably decreased the odds of birth (odds ratio [OR] <1) and thus raised the probability of a cure. This trend became more apparent with increasing education levels. Fathers with high school diploma education level had an increased chance of birth recurrence by 27.1 %. Based on the estimation of the latency part, mothers' education significantly decreased the birth hazard rate. Additionally, fathers with under diploma education levels decreased this rate by 2.7%, which was not statistically meaningful ($P = 0.234$). Employed women demonstrated a lower probability of birth (higher probability at cure) compared with housewives (OR, 0.827). This pattern also held true for fathers in self-employed occupations compared with those who were employers (OR, 0.922). Moreover, employee women demonstrated a lower rate of recurrence of childbirth compared with housewives (HR, 0.825).

In 2 parts of the mixture cure frailty model, we entered frailty terms (Table 3). As indicated by the stable plateau pattern in the KM curves of Figures 1 and 2, it seems that the mixture cure frailty model effectively modeled the cure of birth. This conclusion is further bolstered by the small variance of frailties and their negligible standard errors. Last, the shape parameter in the hazard function (0.933)

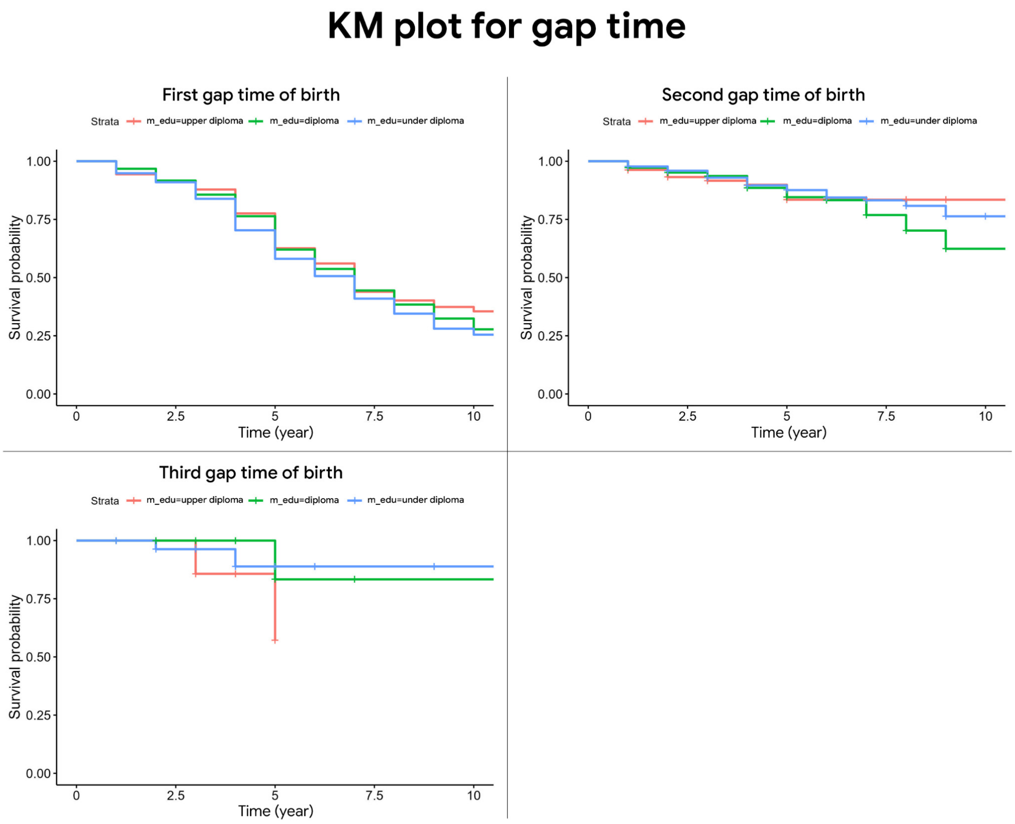

Figure 1. The KM curves for each recurrence of birth, based on mothers' education

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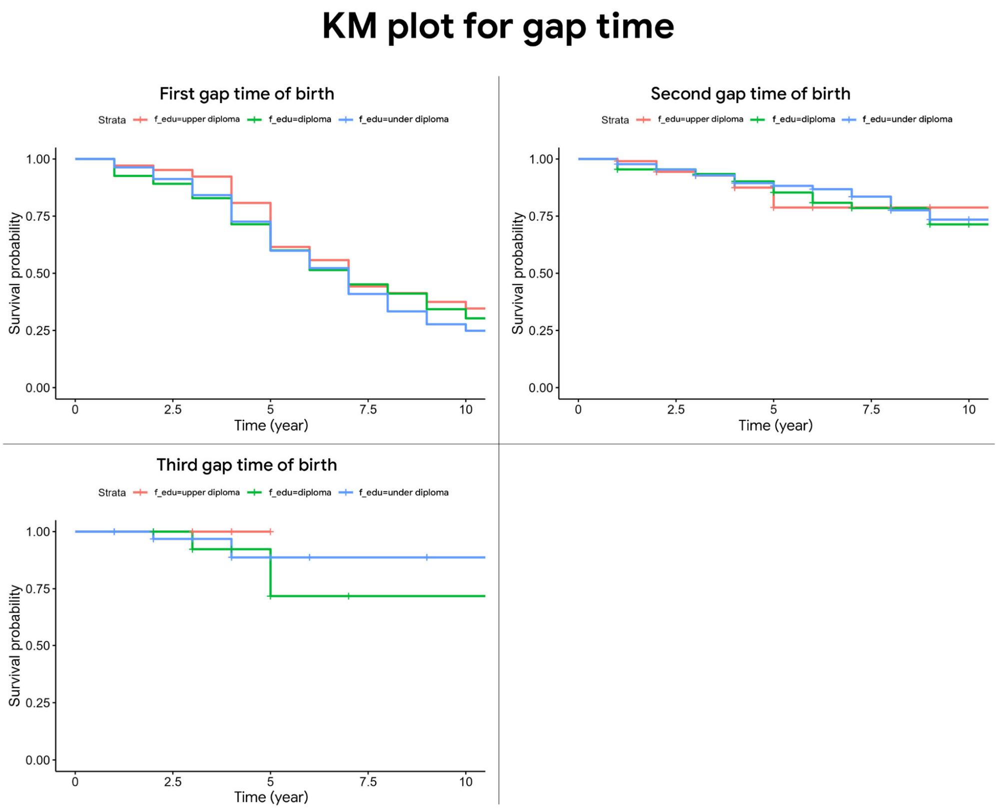

Figure 2. The KM curves for each recurrence of birth, based on fathers' education

Table 2. Estimates of mixture cure frailty model based on the birth data in Hamadan

Part of Model	Parameters	Strata	Estimate	Credible Interval	OR	CI(OR)	*P*-Value
Incidence	Mother's education (ref= Upper diploma)	High school diploma	-3.024*	(-5.554, -0.493)	0.049	(0.004, 0.611)	0.004
		Under diploma	-0.801*	(-1.191, -0.411)	0.449	(0.303, 0.663)	<0.001
	father's education (ref= Upper diploma)	High school diploma	0.240	(-0.332, 0.812)	1.271	(0.717, 2.252)	0.810
		Under diploma	-0.348*	(-0.685, -0.011)	0.802	(0.706, 0.989)	0.021
	Mother's job (ref= Housewife)	Employee	-0.190*	(-0.213,-0.151)	0.827	(0.808,0.860)	<0.001
	father's job (ref= Employer)	Self-employee	-0.081*	(-0.144,0.025)	0.922	(0.866,1.025)	<0.001
Part of Model	Parameters	Strata	Estimate	Credible Interval	HR	CI(HR)	P-Value
Latency	Mother's education (ref= Upper diploma)	High school diploma	-0.402*	(-0.471, -0.334)	0.668	(0.624,0.716)	<0.001
		Under diploma	-0.197*	(-0.234, -0.159)	0.821	(0.791,0.853)	<0.001
	father's education (ref= Upper diploma)	High school diploma	0.039	(-0.071, 0.149)	1.039	(0.931,1.161)	0.787
		Under diploma	-0.027	(-0.107, 0.053)	0.973	(0.899,1.054)	0.234
	Mother's job (ref= Housewife)	Employee	-0.192*	(-0.201,-0.193)	0.825	(0.817,0.824)	<0.001
	father's job (ref= Employer)	Self-employee	-0.203*	(0.192,0.221)	0.816	(1.211,1.247)	<0.001

* Significant at 0.05, ref=reference group, CI=Confidence Interval, OR= Odds Ratio, HR= Hazard Ratio

suggested a decrease in the hazard rate of birth at the follow-up.

Discussion

In this study, the recurrent event of childbirth was examined. KM curves were plotted for each gap time of different

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Table 3. Estimates of variance of frailties based on the birth data in Hamadan

Part of Model	Parameter	Estimate	SE
Incidence	σ_{τ}^{2}	0.412	0.031
Latency	θ^{2}	0.219	0.003
	μ	0.933	0.049

SE= Standard Error

childbirths, and because a cure pattern was observed after each recurrence event, a mixture cure model was applied. A frailty model, which is an extension of the Cox model and can capture within-subject dependency, was used to estimate the latency part of the model. Bagheri et al stated in their study that using traditional statistical methods is not appropriate for accurately analyzing birth spacing because it relies on the assumption of event dependency. Instead, researchers in the fields of medicine and population should consider using frailty models. These models take into account the correlation between intervals and are more effective for analyzing birth spacing (1).

In the study conducted by Amorim et al, it is emphasized that the use of an appropriate model is crucial when analyzing data that include a cure. Failure to do so could lead to inaccurate estimations of parameters and their standard errors (13). In the present study, as well as in the study conducted by Tawiah et al, the use of the cure model has been appropriate, given the small amount of variation in frailties and their corresponding standard errors (10).

The study conducted by Karamoozian et al utilized a cure frailty model to examine the survival rate in gastric cancer patients. They evaluated the studies on the Bayesian mixture cure rate frailty model (14). Souza D et al also applied the cure rate frailty models in survival analysis. A flexible probability distribution induced by discrete frailty is proposed in that study, followed by the presentation of some special discrete probability distributions. As opposed to the Cox frailty model, great potential in modeling unobserved dependence and heterogeneity with a cure fraction was demonstrated by the mentioned methods (15). Similarly, our study implemented the mixture cure frailty model after each childbirth event.

The age at which women marry has increased along with their level of education and social engagement, but their desire to have children has dropped. Women now have greater control over their fertility thanks to easier access to contraception knowledge and resources.

Additionally, improved job opportunities have empowered women to feel financially, socially, and emotionally independent. Educated women prioritize the quality of their children over the quantity, leading to a decrease in fertility rates (16). The findings of our study showed that fewer children were born when mothers' educational attainment and workers' jobs increased. This is consistent with a study by Sabermahani et al that acknowledged that mothers' educational attainment had a detrimental effect on the fertility rate (17).

An important limitation of our study was the difficulty in obtaining accurate information from participants, particularly regarding their incomes and economic status. Additionally, due to incomplete records from previous years, we selected only a 10-year study period.

In practice, the frailty model is often valued for its simplicity. However, given the wide variability in unknown factors influencing birth spacing, it is important to exercise caution when applying frailty models. Future research should consider alternative distributions for frailty terms.

Another limitation is that frailty models typically assume that the effect of covariates remains constant across recurrent events, with any variations attributed to unobserved factors that influence the variance of frailties. Therefore, we suggest that models that can analyze the different effects of variables throughout each gap period of event recurrence be used in future research.

Conclusion

In our study, the mixture cure frailty model performed appropriately when analyzing the birth rate because of the postnatal cure. According to the statistics, couples have not shown much of an interest in having more than 2 children over the last 10 years. An important contributing aspect to this trend is the increase in mothers' employment and educational attainment.

Authors' Contributions

All authors significantly contributed to various aspects of this study. M.H., M.Y., A.N., A.R., K.A., A.M, and M.G. were involved in the conceptualization and methodology development. M.Y., A.N., and H.N. took charge of software implementation and visualization tasks. The validation process included M.H., M.Y., A.N., A.R., K.A., and H.N. Formal analysis was conducted by M.Y. and A.N. All authors participated in the investigation. A.N. and H.S. provided essential resources and led data curation efforts. The original draft was prepared by A.N. Subsequent review and editing were carried out by all authors. Supervision and project administration were managed by M.H. and M.Y.

Ethical Considerations

The study was approved by the TUMS research ethics committee, Tehran University of Medical Sciences (Ethics ID: IR.TUMS.SPH.REC.1401.011).

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Conflict of Interests

The authors declare that they have no competing interests.

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