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Sinusoidal Cox Regression—A Rare Cancer Example

Jimmy Thomas Efir^{1,2}

¹Epidemiologist/Chief Statistician and Director of Shared Resources, Center for Health Disparities Research, Brody School of Medicine, East Carolina University, 1800 W. 5th Street (Medical Pavilion), Greenville, NC 27834 USA.

²Associate Professor, Department of Public Health, Brody School of Medicine, East Carolina University, 600 Moye Blvd., Greenville, NC 27834 USA. Corresponding author email: jimmy.efird@stanfordalumni.org

Abstract: Evidence of an association between survival time and date of birth would suggest an etiologic role for a seasonally variable environmental exposure occurring within a narrow perinatal time period. Risk factors that may exhibit seasonal epidemicity include diet, infectious agents, allergens, and antihistamine use. Typically data has been analyzed by simply categorizing births into months or seasons of the year and performing multiple pairwise comparisons. This paper presents a statistically robust alternative, based upon a trigonometric Cox regression model, to analyze the cyclic nature of birth dates related to patient survival. Disease birth-date results are presented using a sinusoidal plot with peak date(s) of relative risk and a single P value that indicates whether an overall statistically significant seasonal association is present. Advantages of this derivative-free method include ease of use, increased power to detect statistically significant associations, and the ability to avoid arbitrary, subjective demarcation of seasons.

Keywords: sinusoidal Cox regression, seasonality of birth

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Introduction

The fetal origin hypothesis purports that early life environmental exposures may influence disease phenotype in adulthood.¹ Accordingly, individuals born during a specific season may experience unique exposures at a time when they are particularly sensitive to such exposures. A key premise of the theory is that certain exposures and experiences around the time of birth lead to adaptive phenotypes that better prepare the individual for events that may occur later in life. However, not all developmental adaptations have an apparent value in modern society, such as the disruptive response to a host of man-made teratogens.

Experts have hypothesized an etiologic link between season of birth and various childhood diseases, in particular cancer.²⁻⁵ This is partly due to the temporal brevity between the perinatal window of susceptibility to environmental carcinogens and disease development. This narrow age-dependent period is characterized by rapid cell growth and division and an undeveloped immune system.^{6,7} Various chemicals and oncogenic viruses have been shown in the laboratory to induce developmental cancers when specifically administered during perinatal life versus maturity.⁸⁻¹⁰ Infectious agents, pesticides, anti-histamines, indoor environmental tobacco smoke, and vitamin D are a few environmental exposures that tend to follow a seasonal pattern and conceivably may play a role in disease risk or protection.¹¹

There also is evidence suggesting that prenatal and early childhood exposures may play a role in adult diseases. For example, exposure to airborne infections during infancy has been associated with increased mortality from similar infections in old age.¹² A birth cohort from 1634 through 1870 in the small village on Minorca Island, Spain was used to demonstrate decreased mortality among summer births, thus suggesting the importance of early seasonal exposures in disease development decades later.¹ Similarly, seasonal birth exposures have been implicated in some adult cancers.¹¹

Evidence of an association between season of birth and childhood disease would suggest that a seasonally variable environmental exposure may underlie the disease. The type, nature, timing, and severity of the exposure ultimately may be important determinants of whether a seasonal factor has long-term negative

or positive consequences for disease development and patient survival.

To the best of our knowledge, no studies have examined day of birth as a seasonal determinant of survival time, when controlling for outcome related covariates. This paper presents a simple method to determine the statistical significance of a seasonal risk factor in a Cox regression model that allows for control of confounding variables.

Methodology

Cox regression, also known as the proportional hazards model, is a continuous time technique in which event rates vary instantaneously as a function of time.¹³⁻¹⁵ A common use of Cox regression is to estimate the relative risk (RR) for a binary event such as death or cancer recurrence, taking into account the variable length of follow-up among participants in a study. That is, some participants may not have experienced the event by the end of the study. A key advantage of the Cox technique over single variable methods (eg, Kaplan-Meier) for analyzing time to event/survival data is the ability to account for confounding and effect modification of other variables in the model. Another important feature is that survival probabilities may be estimated even when some participants fail to complete the trial (ie, censored data). Importantly, ignoring censored data may lead to serious bias and the distortion of study results. A simple modification of the basic Cox model also allows for the inclusion of covariates that change over the course of the study (eg, participant gets married). Cox regression has been widely used in the fields of epidemiology and clinical research for the analysis of nested case-control, case-cohort, and cohort studies including clinical trials.¹⁶

Letting x_1, \dots, x_r denote a study participant's values for (r) predictor variables, the Cox model specifies that $\log(\text{hazard rate}) = \hat{\alpha}(t) + \hat{\beta}_1 x_1 + \dots + \hat{\beta}_r x_r$, where (t) represents time and $\hat{\alpha}, \hat{\beta}_1, \dots, \hat{\beta}_r$ are estimates of the intercept and model coefficients.¹⁷ Unlike traditional regression models where the intercept is constant, the $\hat{\alpha}(t)$ term in the Cox model is defined as the logarithm of an unspecified but positive baseline hazard function that depends on time. Setting all the x_i equal to zero in the Cox model yields the baseline hazard. The hazard rate [$h(t)$] is the instantaneous

incidence for an event and is mathematically defined as $h(t) = \lim_{\Delta t \rightarrow 0^+} \{\Pr[t \leq T < t + \Delta t \mid t \leq T] / \Delta t\}$, where T denotes the event time.¹³ In other words, the hazard rate is the probability of an event occurring in a very short interval, divided by the length of the interval. A desirable property of Cox regression is that the event times are not required to be normally distributed, as is the case for many statistical procedures, because the baseline hazard function is estimated independently of any parametric assumptions.

The exponentiation of $\hat{\beta}$ corresponding to a dichotomous variable in the Cox model gives an estimate for the hazard ratio of the comparison and referent groups, holding all other variables in the model constant. In applied terms, the hazard ratio may be interpreted as the odds that an individual in the group with the higher hazard reaches the endpoint first. Accordingly, the probability of reaching the endpoint first equals $HR / (1 + HR)$.¹⁸ However, the HR does not gauge “how much faster” an event occurs in a particular arm of the study. When x_i is continuously distributed, the HR represents the multiplicative factor for risk corresponding to a unit increase in that variable.¹⁷

A key assumption of Cox regression is that the hazard ratio is constant over time. This implies that the hazard for any study participant is a fixed proportion of the hazard for any other participant. Thus, the individual log hazards plotted over time should be parallel.¹⁹

Given the observed data for (n) individuals, an estimate of the vector of β coefficients, ie, $\hat{\beta} = (\hat{\beta}_1, \dots, \hat{\beta}_r)$, is obtained by maximizing the partial likelihood function $\sum_{i \in R_i} [\beta' x_i - \log \{\sum_{j \in R_i} \exp(\beta' x_j)\}]$, where $x_i = (x_{i1}, \dots, x_{ir})$ is a r -dimensional vector of covariates, $t_1 < \dots < t_k$ denote the k ordered distinct event times, and the censored observations occupy the remaining $n-k$ places in arbitrary order.²⁰ The k risk sets are defined such that j is an element of R_p , representing the participants at risk immediately prior to the i th event, if and only if $t_j \geq t_i$. The unknown parameter estimates are determined iteratively by setting the first partial derivatives in the above equation equal to zero, computing the matrix of second partial derivatives, and applying the Newton-Raphson method. An estimate for the hazard rate is easily found to equal $[(t_i - t_{i-1}) (\sum_{j \in R_i} \exp(\beta' x_j))]^{-1}$. Although the Cox model as specified does not allow for tied values, approximate

partial likelihood functions have been developed to handle non-distinct event times and these approximations have been incorporated into commonly available computer software packages.¹⁹

A seasonal variable in the simplest case may be expressed as a binary term, eg, where birth occurred in summer compared with winter. However, more complex forms may be important to consider when modeling annual seasonality. A temporal variable such as date of birth (DOB, coded as an integer from 1 to 365) may be expressed as a trigonometric function.^{21,22} In this example, let $x_1 = \cos[2 \cdot \arccos(-1) \cdot ((DOB - \xi_{\max}) / 365)]$, where ξ_{\max} is determined iteratively by finding the value from 1 to 365 that maximizes $\hat{\beta}_1$. In the case of a leap year, the 29th day of February is recoded as calendar day 59 so that the respective year consists of 365 days.²³

The maximum 3-month seasonal period of risk for a time-to-event outcome is found by taking the 91.25 day wide interval centered on ξ_{\max} . Analogously, the minimum risk period is found by taking the symmetrically opposite 3-month interval centered on ξ_{\min} (ie, the value from 1 to 365 that minimizes $\hat{\beta}_1$ in the equation for x_1). Dummy coding $x_1 = 1$ if DOB falls within the maximum window of risk and $x_1 = 0$ if DOB falls within the minimum window of risk and exponentiating $\hat{\beta}_1$ gives an estimate of the peak-to-trough HR, assuming 4 distinct seasons. Using standard statistical methods, a corresponding 95% confidence interval (CI) may be computed assuming asymptotic normality of $\log(HR)$.¹⁹

A P value for determining the statistical significance of the sinusoidal term may be determined by taking twice the logarithm of the ratio of the partial likelihood for the model with and without the variable. The resulting value is compared with a χ^2 statistic having 1 degree of freedom. The seasonal association is visualized by plotting harmonic displacement ($\hat{\beta}_1 x_1$) against DOB over the range 1 to 365.

The sinusoidal Cox model also may be used to model multiple cycles within a period of interest. For example, certain biologic phenomenon may occur in synchrony with a lunar cycle and have a peak incidence every 29.53 days. The model for a lunar cycle would be computed by substituting 29.53 for 365 in the denominator of the sinusoidal term. In another example, a scientist wishes to test the hypothesis



that weather-related stress (eg, cold winters and hot summers) at the time of birth triggers epigenetic mechanisms which program immune response later in life. As above, 182.5 would be substituted for 365 in the denominator of x_1 in order to fit a bi-modal sinusoidal model to the data.

Example

Using anonymized DOB data for a rare neurogenic cancer (see Appendix), we conducted analyses using the method described above, and for comparison, the typical, more basic method to examine whether a seasonal pattern of birth significantly predicts time to death following diagnosis (note: this simplified example is presented for illustration purposes only and is not intended to represent a comprehensive epidemiologic analysis of the data). The identification of an underlying sinusoidal trend in births would be consistent with the hypothesis that a seasonally varying exposure around the time of birth influences the risk of dying from this cancer later in life.

Among patients alive at last follow-up, 17% were >60 years of age compared with 32% who died (Table 1). A discernable pattern for period of birth was not observed, although a higher percentage of living patients were born during the 1950s than deaths. Overall, the percentage of deaths was higher among patients born in winter and summer than those born during spring and fall, suggesting a possible seasonal of birth survival difference. However, individual follow-up times differed considerably.

A traditional Cox regression model was used to obtain HR's for month-to-month birth comparisons and to account for differences in patient follow-up times (Table 2). Similar to the above results comparing the percentage of deaths by month, a bimodal pattern was observed in the month-to-month birth HR's. However, all CI's overlapped unity after adjusting for multiplicity.²⁴

Applying an unimodal sinusoidal Cox regression model to the data, peak seasonal risk for death was observed at calendar day 254 (mid-September), however the result was not statistically significant (Fig. 1). Furthermore, the 3-month peak-to-trough HR did not statistically differ from a null result (HR = 1.1, 95% CI = 0.89–1.4) (not shown in Fig. 1). However, when fitting a bimodal model to the data, statistically significant seasonal peaks for birth (likelihood ratio test,

Table 1. Characteristics of patients by survival status (N = 958).

Characteristic	Alive n (%)	Dead n (%)
Age (years)		
≤40	56 (23)	145 (20)
41–50	66 (27)	141 (20)
51–60	78 (32)	202 (28)
>60	42 (17)	228 (32)
Period of birth		
1917–1929	1 (0)	38 (5)
1930–1939	19 (8)	107 (15)
1940–1949	52 (21)	207 (29)
1950–1959	83 (34)	178 (25)
1960–1969	46 (19)	114 (16)
1970–1979	29 (12)	55 (8)
1980–1989	12 (5)	17 (2)
Month of birth		
January	15 (6)	62 (9)
February	14 (6)	50 (7)
March	25 (10)	52 (7)
April	23 (10)	58 (8)
May	24 (10)	48 (7)
June	15 (6)	70 (10)
July	16 (7)	84 (12)
August	24 (10)	60 (8)
September	24 (10)	55 (8)
October	28 (12)	58 (8)
November	21 (9)	54 (8)
December	13 (5)	65 (9)

$P = 5.6E-6$) were observed at day 15 (mid-January) and day 196 (mid-July) (Fig. 2).

Simulation Results

Using the SAS[®] programming language (version 9.2, Cary, NC), a simulation was performed to illustrate the relative efficiency of sinusoidal Cox regression compared with a traditional season-to-season Cox regression model. Sinusoidally varying observations, with the longest average survival times occurring among participants born during spring versus fall (ie, greatest risk of dying for fall births), were simulated as

$$\text{survival_time} = (10 + \text{sqrt}(50000) * \text{abs}(\text{rannor}(501))) * (((0.33196 * \cos(\text{floor}(365 * \text{ranuni}(714) + 1)) - 62) / 365) * 2 * \arccos(-1))) + 0.5);$$

In the above code, rannor and ranuni are SAS[®] functions that generate values from a standard normal and uniform distribution, respectively. The numbers within the parenthesis for the functions denote random number generator seed values. The floor function



Table 2. Month-to-month birth hazard ratios (HR) and 95% confidence intervals (CI) of dying following diagnosis.^s

HR	Jan ^t	Feb ^t	Mar ^t	Apr ^t	May ^t	Jun ^t	Jul ^t	Aug ^t	Sep ^t	Oct ^t	Nov ^t	Dec ^t
95% CI												
Jan ^t	1.0	0.89	0.66	0.66	0.72	0.87	1.3	0.76	0.83	0.75	0.71	0.97
Feb ^t	-	0.61-1.3	0.45-0.96	0.46-0.95	0.49-1.1	0.62-1.2	0.91-1.8	0.53-1.1	0.57-1.2	0.52-1.1	0.49-1.03	0.68-1.4
Mar ^t	1.1	1.0	0.74	0.74	0.81	0.98	1.4	0.86	0.93	0.84	0.80	1.1
Apr ^t	0.77-1.6	-	0.50-1.1	0.51-1.1	0.54-1.2	0.68-1.4	1.01-2.0	0.59-1.3	0.63-1.4	0.57-1.2	0.54-1.2	0.75-1.6
May ^t	1.5	1.4	1.0	1.0	1.1	1.3	1.9	1.2	1.3	1.1	1.1	1.5
Jun ^t	1.04-2.2	0.91-2.0	-	0.69-1.5	0.73-1.6	0.92-1.9	1.4-2.8	0.79-1.7	0.86-1.9	0.77-1.7	0.74-1.6	1.02-2.2
Jul ^t	1.5	1.3	0.99	1.0	1.1	1.3	1.9	1.2	1.3	1.1	1.1	1.5
Aug ^t	1.1-2.2	0.92-2.0	0.68-1.4	-	0.74-1.6	0.93-1.9	1.4-2.7	0.80-1.7	0.87-1.8	0.78-1.6	0.75-1.6	1.03-2.1
Sep ^t	1.4	1.2	0.91	0.92	1.0	1.2	1.8	1.1	1.2	1.0	0.99	1.4
Oct ^t	0.95-2.0	0.83-1.8	0.61-1.4	0.62-1.4	-	0.84-1.8	1.2-2.5	0.72-1.6	0.78-1.7	0.71-1.5	0.67-1.5	0.93-2.0
Nov ^t	1.1	1.0	0.75	0.76	0.82	1.0	1.5	0.87	0.95	0.85	0.82	1.1
Dec ^t	0.81-1.6	0.71-1.5	0.52-1.1	0.53-1.1	0.57-1.2	-	1.1-2.0	0.62-1.2	0.66-1.4	0.60-1.2	0.57-1.2	0.79-1.6
	0.79	0.70	0.52	0.52	0.56	0.69	1.0	0.60	0.65	0.59	0.56	0.76
	0.56-1.1	0.49-0.99	0.36-0.73	0.37-0.73	0.39-0.81	0.50-0.94	-	0.43-0.84	0.46-0.92	0.42-0.82	0.40-0.79	0.55-1.1
	1.3	1.2	0.86	0.87	0.94	1.1	1.7	1.0	1.1	0.98	0.94	1.3
	0.92-1.9	0.80-1.7	0.59-1.3	0.60-1.2	0.64-1.4	0.81-1.6	1.2-2.3	-	0.75-1.6	0.68-1.4	0.65-1.4	0.89-1.8
	1.2	1.1	0.79	0.80	0.87	1.1	1.5	0.92	1.0	0.90	0.86	1.2
	0.84-1.7	0.73-1.6	0.54-1.2	0.55-1.2	0.59-1.3	0.74-1.5	1.1-2.2	0.63-1.3	-	0.62-1.3	0.59-1.3	0.82-1.7
	1.3	1.2	0.88	0.88	0.96	1.2	1.7	1.0	1.1	1.0	0.96	1.3
	0.94-1.9	0.81-1.7	0.60-1.3	0.61-1.3	0.66-1.4	0.83-1.7	1.2-2.4	0.71-1.5	0.77-1.6	-	0.66-1.4	0.91-1.9
	1.4	1.2	0.92	0.93	1.0	1.2	1.8	1.1	1.2	1.0	1.0	1.4
	0.97-2.0	0.84-1.8	0.62-1.4	0.64-1.3	0.68-1.5	0.86-1.7	1.3-2.5	0.74-1.6	0.80-1.7	0.72-1.5	-	0.95-2.0
	1.0	0.91	0.68	0.68	0.74	0.90	1.3	0.79	0.85	0.77	0.74	1.0
	0.73-1.5	0.63-1.3	0.46-0.98	0.47-0.97	0.51-1.1	0.64-1.3	0.94-1.8	0.55-1.1	0.59-1.2	0.54-1.1	0.51-1.1	-

Notes: ^tHazard ratios and 95% CIs adjusted for period of birth and age; ^s95% CIs shown in table were not adjusted for multiplicity. All CIs overlapped unity after multiplicity correction; ^tReferent month; [†]Comparison month.

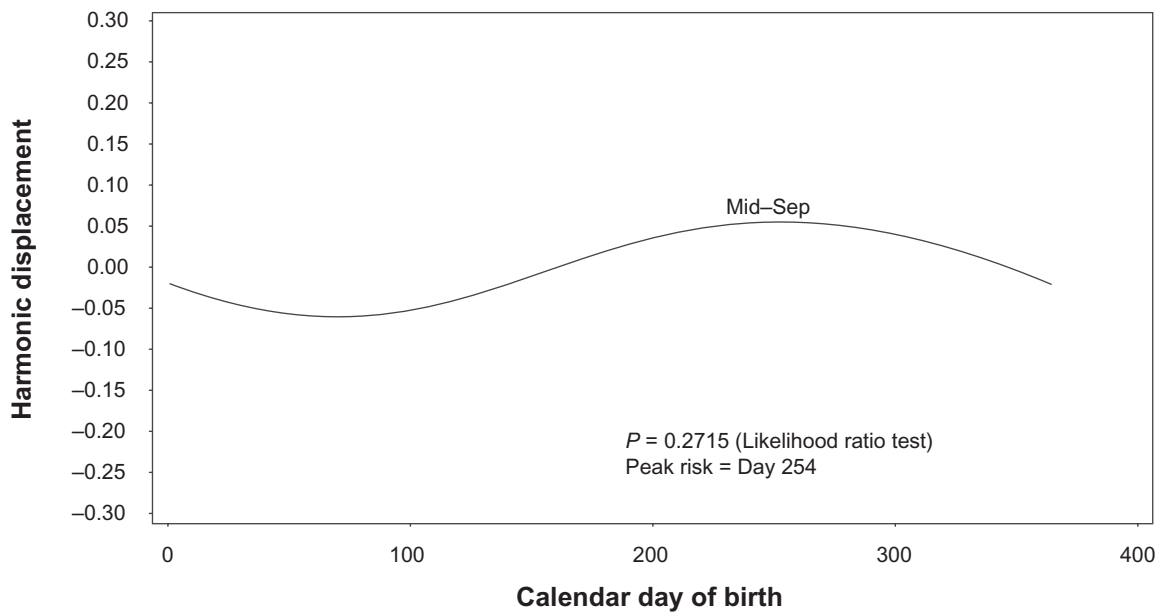


Figure 1. Calendar day of birth for peak risk of dying following diagnosis—unimodal fit (adjusted for period of birth and age).

returns the largest integer that is less than or equal to the argument and gives the day of birth.

A sinusoidal Cox regression model, as presented in this paper, was used to test the seasonality hypothesis that fall births were more likely to die sooner from disease than spring births. A season-to-season analysis involved comparing survival times among fall and spring (referent group) births by dummy coding season of birth (ie, fall = 1, spring = 0) as the independent variable in a Cox regression model.

The sinusoidal Cox regression model was observed to be relatively more efficient than the traditional season-to-season method at detecting a statistically significant season-of-birth effect, and efficiency improved as the number (n) of simulated survival time observations increased (Table 3). For example, for $n = 35$, the sinusoidal Cox model detected a significant season-of-birth effect on disease survival ($P = 0.01491$), whereas the season-to-season analysis failed to achieve a statistically significant

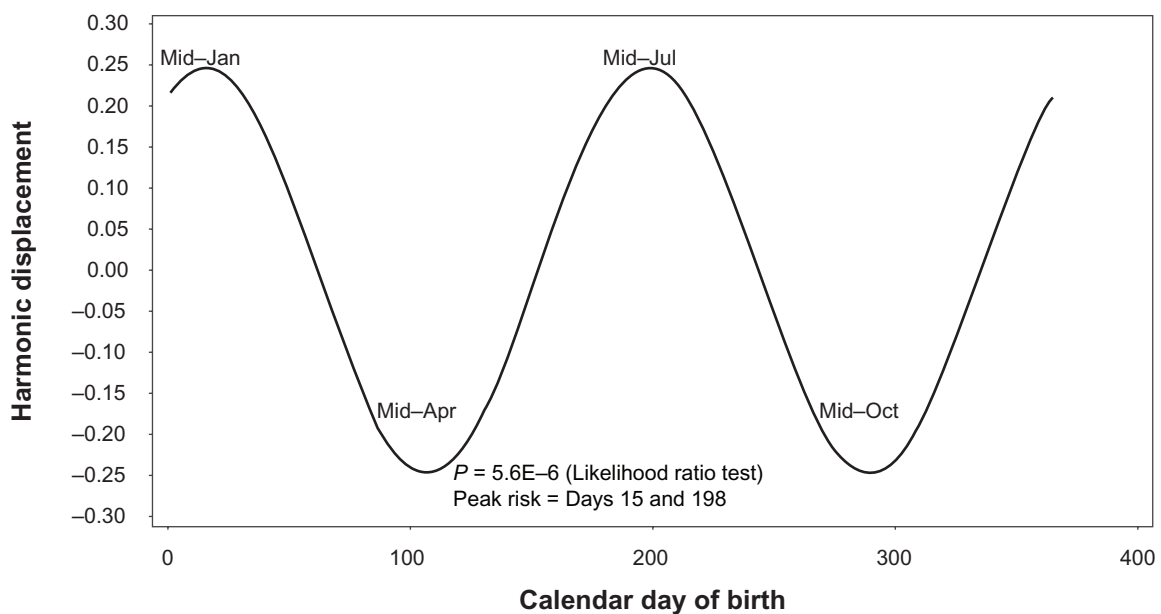


Figure 2. Calendar day for birth and peak risk of dying following diagnosis—bimodal fit (adjusted for period of birth and age).

**Table 3.** Comparison of sinusoidal and season-to-season Cox regression models.

Number of simulated survival time observations	Sinusoidal Cox regression model <i>P</i> value [†]	Season-to-season Cox regression model (fall vs. spring) <i>P</i> value [†]
35	0.01491	0.23593
45	0.00710	0.11987
50	0.00175	0.02745
100	1.05E-5	0.01103
150	5.21E-11	0.00021
200	1.57E-13	7.35E-6

Note: [†]Likelihood ratio test.

result ($P = 0.23593$). A Kaplan-Meier plot ($n = 200$) contrasting survival curves for fall and spring births is shown in Fig. 3.

Discussion

We have presented a simple, iterative Cox regression-based method to analyze censored time-to-event outcome data with seasonal predictor variables. The method is a simple extension of earlier trigonometric models yet is easier to apply and interpret.^{25–30} A parallel sinusoidal logistic regression model has been presented in the literature for analyzing non-censored binary event data.²³

A useful feature of sinusoidal Cox regression is its ability to optimally fit a sinusoidal curve to the underlying data by plotting harmonic displacement against calendar time. Whereas no single method provides

a universal approach to analyze harmonic data, the current method accommodates varying lengths of months, different populations at risk, simultaneous adjustment for multiple confounders, and it is reasonably robust when used for small samples. The accompanying statistical test will have greater family-wise power to detect a sinusoidal pattern than performing multiple pairwise seasonal or monthly comparisons.

Similar to a dose response relationship based upon a best-fitting monotonic model and *a priori* biologic mechanism of action, multiplicity correction is not necessary for the optimal peak sinusoidal Cox regression model. Additionally, the model takes into account consecutively high/low time periods (eg, order of events), and the definition of season does not depend on an arbitrary start and end date but rather is determined by the model algorithm.

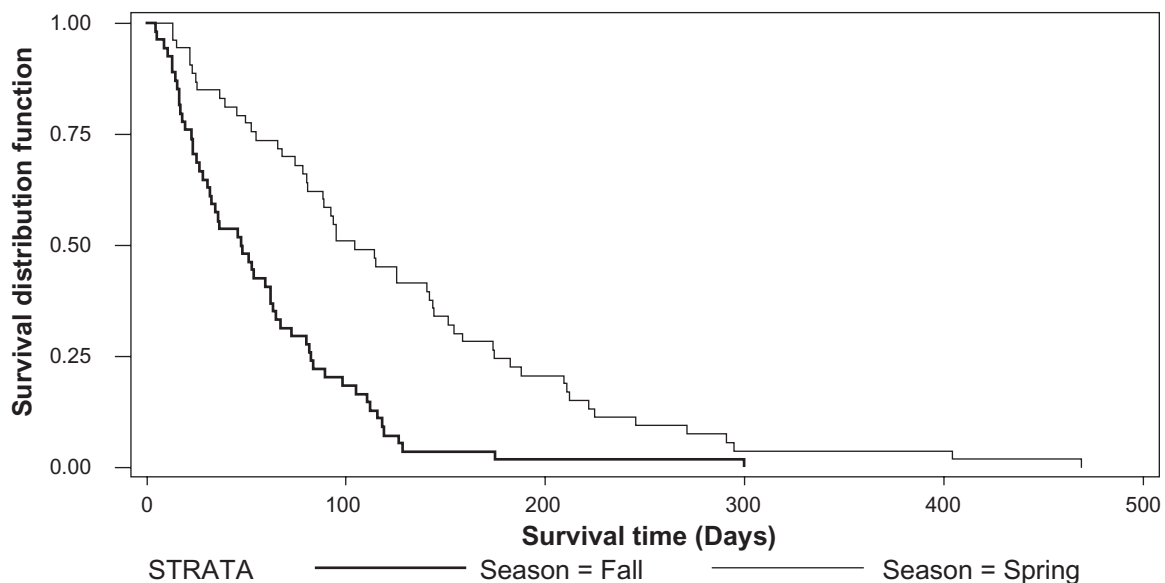


Figure 3. Kaplan-Meier plot comparing survival times for fall and spring births ($n = 200$ simulated observations).



Several potential limitations should be noted when interpreting the results of a sinusoidal Cox regression analysis. A discrepancy between values expected under the model and the actual data may result in biased parameter estimates. Accordingly, the data should be tested for goodness-of-fit using standard statistics methods for Cox regression.¹⁹ Ambiguous results may occur in the case of competing out-of-phase cycles resulting in a cancelling of effects (eg, opposing seasonally effects by hemisphere of birth). When appropriate, stratification or the use of a multimodal model may help mitigate this problem. Additionally, the sinusoidal Cox regression model as specified will not distinguish between major and minor peaks since the magnitude of harmonic displacement will be equal for all peaks.

A statistically insignificant seasonal risk factor in the model does not necessarily rule out an underlying seasonal effect. For example, the factor may have a lopsided shape that may be difficult to statistically detect using a sinusoidal Cox model. Conversely, the seasonal association of a specific risk factor with disease does not necessarily imply causality. As with any statistical model, the results of sinusoidal Cox regression should be carefully interpreted in light of underlying limitations and biologic plausibility. Furthermore, the lack of a well defined hypothesis in advance of analysis and selection bias may lead to spurious results. Selection bias generally is difficult to correct after the data have been collected. A type of selection bias based on differential survival of certain individuals in the population at risk is a particular concern in season-of-birth studies. For example, susceptible individuals with a weak immune system may die soon after birth and distort the population base of adult survival studies.

The example presented in this paper is limited in scope. Future studies would be needed to determine whether a bimodal peak of seasonal risk is unique to this data set. New studies also would benefit by adjusting for potential confounders such as tumor grade, gender, diet, and body weight, and stratifying analyses by hemisphere or latitude of birth. The sinusoidal Cox regression model will provide a flexible tool for conducting such analyses.

In summary, seasonal environmental exposures occurring within a brief “critical window” during prenatal development or early infancy have been

hypothesized to influence susceptibility to disease and survival later in life.^{31,32} Studies of season of birth and survival time have been difficult to interpret due to limitations of the statistical methods used to analyze the data. In this paper, we have presented a sinusoidal Cox regression method that is derivative-free, easy to use, and it does not require the arbitrary demarcation of seasons characterizing other techniques. Furthermore, the sinusoidal Cox regression model yields a single *P* value, unlike traditional methods for analyzing seasonal data which require multiple pairwise comparisons. The sinusoidal model also is statistically more powerful in detecting season-of-birth trends in the data.

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Appendix

Data File

CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C
226	7	1	1	60	160	6	1	1	245	48	6	1	0	215	23	5	1	1
77	7	1	1	92	269	6	1	1	237	300	6	1	0	357	240	5	1	1
94	7	1	0	271	192	6	1	1	206	307	5	1	1	220	90	6	1	0
142	7	1	1	26	69	6	1	1	168	309	6	1	0	320	236	5	1	1
148	7	1	1	94	59	7	1	0	52	249	6	1	1	57	52	6	1	1
95	7	1	1	86	265	6	1	1	293	280	6	1	1	94	180	5	1	0
317	7	1	1	90	317	5	1	0	874	200	6	1	0	180	225	5	1	1
257	7	1	0	282	292	6	1	0	202	22	5	1	1	490	331	5	1	1
98	7	1	1	112	271	6	1	1	56	18	6	1	0	190	365	5	1	1
84	7	1	1	194	106	6	1	1	172	219	6	1	0	76	206	5	1	1
66	7	1	1	154	46	6	1	1	107	242	6	1	0	196	275	5	1	1
325	6	1	1	601	340	7	1	1	6	14	6	1	1	66	354	5	1	1
230	7	1	1	62	55	6	1	0	185	96	6	1	1	150	107	6	1	0
117	7	1	0	2	31	6	1	0	74	10	5	1	1	348	259	5	1	0
283	6	1	1	240	105	5	1	1	592	314	6	1	1	126	332	5	1	1
307	6	1	1	404	256	6	1	1	179	282	6	1	0	112	105	4	1	1
156	7	1	1	270	1	6	1	1	223	318	6	1	1	73	169	5	1	1
192	7	1	0	176	359	6	1	1	101	356	5	1	1	238	356	5	1	1
70	7	1	1	95	14	6	1	0	156	169	6	1	1	88	31	5	1	1
135	6	1	1	245	22	6	1	1	390	163	5	1	1	443	336	5	1	1
150	7	1	0	132	75	6	1	1	153	319	5	1	1	239	183	5	1	1
345	6	1	1	263	23	5	1	1	330	104	6	1	1	181	118	5	1	0
30	7	1	1	162	159	6	1	1	36	339	6	1	1	238	129	5	1	1
280	6	1	1	94	145	6	1	0	93	169	6	1	1	84	288	5	1	1
155	7	1	1	221	277	6	1	1	259	277	6	1	0	39	303	5	1	0
287	7	1	0	119	16	6	1	1	124	122	6	1	0	1	340	5	1	1
205	7	1	1	275	89	5	1	1	237	161	6	1	1	230	271	5	1	1
247	6	1	1	449	122	6	1	1	1	241	6	1	0	69	308	5	1	0
213	6	1	0	387	197	6	1	1	172	150	6	1	1	41	37	5	1	1
333	7	1	0	42	1	6	1	1	266	202	6	1	1	150	17	5	1	1
7	6	1	1	344	354	6	1	1	191	162	5	1	1	381	128	5	1	1
351	6	1	1	136	177	6	1	1	93	14	5	1	1	339	140	5	1	1
284	6	1	1	97	120	6	1	0	52	294	5	1	0	305	246	5	1	1
200	6	1	1	350	282	5	1	1	377	38	5	1	0	357	169	5	1	1
294	7	1	0	71	60	6	1	0	89	137	6	1	0	75	148	5	1	1
325	5	1	1	641	266	6	1	0	413	29	5	1	1	570	48	5	1	1
218	7	1	0	71	25	6	1	1	93	361	5	1	1	127	299	5	1	1
163	6	1	1	65	266	6	1	1	342	246	6	1	1	135	365	5	1	1
91	6	1	1	359	86	6	1	0	211	257	5	1	0	358	102	4	1	1
297	6	1	1	127	282	5	1	0	728	222	5	1	1	267	308	5	1	1
355	6	1	1	113	104	5	1	1	783	64	5	1	1	205	117	5	1	0
238	6	1	0	209	308	6	1	1	153	330	6	1	0	69	267	5	1	1
36	7	1	0	42	162	6	1	1	81	177	6	1	0	55	300	5	1	1
193	7	1	1	120	15	6	1	0	328	138	5	1	1	168	157	4	1	1
247	7	1	0	54	262	6	1	0	256	16	5	1	1	231	22	5	1	1
233	4	2	1	86	345	4	2	0	212	121	4	3	1	47	119	4	3	0
176	4	2	1	94	285	3	2	0	417	324	3	3	1	573	326	4	3	0
327	4	2	1	74	285	3	2	1	425	192	4	3	1	74	138	4	3	1
20	4	2	1	77	69	4	3	1	213	244	4	3	1	68	97	3	3	1
80	4	2	1	57	241	4	3	1	11	104	4	3	0	60	186	4	3	1
324	4	2	1	60	29	4	3	1	4	292	4	3	1	36	81	3	3	1



STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM
87	365	5	1	1	65	135	4	2	0	68	175	5	2	1	92	26	5	2	0	68
73	336	4	1	1	645	24	5	2	1	34	120	4	2	1	131	255	4	2	1	72
150	300	5	1	0	77	261	5	2	1	87	112	4	2	1	145	138	4	2	1	171
236	67	5	1	1	105	61	5	2	1	15	362	4	2	1	28	364	4	2	0	114
75	289	5	1	1	143	50	5	2	1	117	276	4	2	0	46	67	4	2	1	235
380	197	5	1	1	144	345	4	2	0	522	88	5	2	1	32	36	5	2	0	71
93	253	5	1	1	79	56	5	2	1	192	348	4	2	0	63	194	4	2	1	87
145	179	5	1	1	161	232	5	2	1	77	73	4	2	1	66	181	4	2	1	51
230	183	5	1	0	66	264	4	2	1	27	334	5	2	1	264	99	5	2	0	48
451	202	5	1	1	59	95	5	2	0	235	250	4	2	1	51	336	4	2	1	195
62	189	5	1	1	86	207	4	2	1	43	334	5	2	1	266	119	5	2	1	3
2	38	5	1	1	160	36	5	2	1	36	276	5	2	1	38	23	5	2	1	47
145	201	5	1	1	48	244	5	2	0	9	73	4	2	1	89	236	4	2	1	55
176	125	5	1	1	96	97	5	2	0	68	60	3	2	0	69	108	3	2	1	380
162	312	5	1	0	165	3	5	2	1	53	276	4	2	1	43	174	4	2	1	44
809	332	5	1	1	101	75	5	2	1	15	255	4	2	0	117	141	4	2	0	125
383	196	5	1	1	39	90	5	2	0	51	124	4	2	1	114	134	4	2	1	100
42	55	5	1	1	100	96	5	2	0	204	94	5	2	1	264	322	5	2	0	76
38	159	5	1	1	42	93	5	2	1	66	360	4	2	0	130	207	4	2	1	18
339	199	5	1	0	1	329	4	2	0	62	68	4	2	0	71	118	4	2	1	39
434	300	5	1	1	305	4	5	2	1	41	201	4	2	0	57	2	4	2	1	64
160	187	5	2	0	160	225	5	2	1	106	18	4	2	1	181	3	4	2	0	215
56	13	5	2	1	37	234	5	2	0	280	267	4	2	1	47	156	4	2	1	91
95	159	5	2	1	121	55	4	2	1	338	71	4	2	1	57	239	4	2	1	32
542	260	5	2	1	151	192	5	2	1	14	290	4	2	0	214	158	4	2	1	15
114	229	5	2	0	65	47	5	2	0	90	131	4	2	1	46	5	4	2	1	47
208	192	5	2	1	102	232	4	2	1	97	26	4	2	1	122	299	4	2	1	65
96	40	5	2	1	81	243	5	2	0	113	89	4	2	1	409	46	4	2	1	69
87	252	5	2	1	88	240	5	2	1	90	144	4	2	1	56	171	4	2	0	198
300	65	5	2	0	34	346	4	2	1	29	363	4	2	1	6	94	4	2	0	100
117	231	5	2	1	70	218	5	2	1	114	206	3	2	1	53	343	3	2	0	747
60	244	5	2	0	63	254	4	2	0	419	310	4	2	0	183	38	4	2	1	102
132	54	5	2	1	156	143	5	2	1	99	94	4	2	1	7	209	4	2	1	47
294	103	5	2	1	183	308	5	2	0	211	8	5	2	1	12	304	5	2	0	14
90	139	5	2	1	56	211	4	2	1	51	211	5	2	1	65	265	5	2	0	35
36	208	5	2	1	29	20	5	2	1	32	301	4	2	0	363	318	4	2	1	55
142	228	5	2	1	145	274	4	2	0	61	172	4	2	0	52	128	4	2	1	78
147	85	5	2	0	269	114	4	2	1	206	273	4	2	0	106	303	4	2	1	92
394	76	5	2	0	27	160	5	2	0	253	237	4	2	0	78	163	4	2	1	131
86	164	5	2	1	71	4	4	2	0	75	211	3	2	1	35	169	3	2	1	690
470	59	5	2	1	2	172	5	2	1	50	162	4	2	1	52	310	4	2	1	139
65	189	5	2	1	124	355	5	2	1	71	84	4	2	0	67	263	4	2	0	292
55	84	5	2	1	58	234	4	2	1	33	75	4	2	1	52	133	4	2	1	87
596	249	5	2	1	66	276	4	2	1	23	232	4	2	1	38	352	4	2	1	65
51	96	5	2	1	67	164	5	2	0	94	193	4	2	1	59	285	4	2	1	269
135	50	3	3	1	75	341	4	3	0	92	286	3	3	0	51	134	3	3	1	39
35	115	4	3	0	237	91	3	3	1	9	36	3	3	0	114	354	3	3	1	61
83	257	3	3	1	125	326	3	3	1	101	290	3	3	1	105	182	3	3	1	48
86	36	4	3	0	13	328	4	3	0	90	209	3	3	1	46	234	3	3	0	67
123	330	3	3	0	214	165	3	3	1	14	106	3	3	1	46	234	3	3	1	95
55	215	4	3	0	51	209	3	3	1	16	151	3	3	0	42	143	3	3	0	161

(Continued)



Appendix. (Continued)

CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C
204	4	2	0	96	344	4	3	1	69	45	4	3	1	63	285	3	3	1
178	4	2	1	173	37	4	3	1	144	283	4	3	1	208	147	4	3	0
238	4	2	0	92	185	4	3	1	68	14	4	3	1	62	156	2	3	1
285	4	2	0	41	351	3	3	1	223	1	4	3	0	38	200	4	3	1
151	4	2	0	333	234	4	3	1	81	337	4	3	1	44	50	4	3	1
194	4	2	1	44	78	4	3	1	205	204	4	3	1	52	175	4	3	1
32	4	2	1	109	287	4	3	1	26	223	4	3	0	127	141	3	3	1
325	4	2	1	89	173	4	3	1	94	297	4	3	1	164	319	3	3	1
44	4	2	0	109	20	4	3	1	68	124	4	3	0	161	242	4	3	0
261	4	2	1	243	153	4	3	0	258	163	4	3	1	27	55	4	3	0
118	4	2	0	49	213	4	3	1	65	229	4	3	1	81	213	3	3	1
77	4	2	0	281	315	4	3	0	117	281	4	3	0	49	175	4	3	1
2	4	2	1	87	157	4	3	1	38	172	3	3	1	36	259	3	3	1
284	4	2	1	37	195	4	3	1	95	352	3	3	1	85	258	3	3	1
95	4	2	1	63	60	4	3	1	98	205	4	3	1	94	274	4	3	0
85	4	2	1	21	280	4	3	1	166	357	4	3	1	113	117	4	3	1
46	4	2	1	37	127	4	3	0	248	242	4	3	0	57	147	3	3	1
9	4	2	1	39	265	4	3	1	15	284	4	3	1	109	320	4	3	0
248	4	2	0	166	145	4	3	0	89	126	4	3	1	96	258	4	3	0
89	4	2	0	149	266	4	3	1	5	110	4	3	1	103	105	4	3	1
352	4	2	1	66	112	4	3	0	66	303	4	3	1	53	159	3	3	1
282	4	2	0	346	98	4	3	1	142	197	4	3	1	58	344	3	3	1
145	4	2	1	90	313	4	3	0	121	348	4	3	1	180	308	3	3	1
147	4	2	0	48	99	4	3	1	12	82	4	3	1	28	354	4	3	1
293	3	2	1	313	328	4	3	1	120	216	4	3	0	33	94	4	3	1
28	3	2	0	705	152	4	3	0	84	294	4	3	0	64	315	3	3	1
262	4	2	1	88	57	4	3	1	56	79	4	3	0	88	167	3	3	1
272	4	2	1	127	169	4	3	1	57	199	4	3	0	80	196	3	3	1
160	4	2	1	19	197	4	3	1	34	203	4	3	1	56	110	3	3	1
202	4	2	1	106	68	4	3	0	176	278	3	3	1	91	66	4	3	0
342	4	2	0	165	285	4	3	1	67	355	3	3	1	81	271	4	3	0
313	4	2	1	16	359	4	3	1	49	289	3	3	1	282	202	3	3	1
49	4	2	1	36	235	4	3	1	90	57	4	3	1	128	260	4	3	0
255	4	2	1	118	258	4	3	0	39	187	4	3	1	48	94	4	3	0
205	4	2	1	64	35	4	3	1	47	262	4	3	0	63	320	3	3	1
212	4	2	1	71	276	4	3	1	66	320	4	3	0	71	359	3	3	1
72	4	2	1	50	353	3	3	1	187	129	4	3	0	74	293	3	3	1
215	4	2	1	20	158	4	3	1	162	9	4	3	1	48	266	3	3	1
118	3	4	1	8	149	3	4	1	43	51	3	4	1	10	170	2	4	1
303	3	4	1	38	105	3	4	1	91	349	3	4	1	35	166	3	4	1
81	3	4	1	29	199	3	4	0	234	1	3	4	1	19	291	2	4	1
51	3	4	1	11	191	2	4	1	118	144	2	4	1	101	280	3	4	0
283	3	4	1	55	174	3	4	0	141	189	3	4	1	66	236	2	4	1
113	3	4	1	80	143	2	4	1	161	352	3	4	1	26	9	3	4	1
169	3	4	1	42	237	3	4	1	70	35	2	4	1	107	221	2	4	1
72	3	4	0	31	77	3	4	1	52	178	3	4	1	23	364	2	4	1
210	3	4	1	48	365	3	4	1	46	316	2	4	1	84	281	2	4	1
101	3	4	1	34	361	3	4	1	63	339	3	4	0	185	207	3	4	0
45	3	4	1	168	284	3	4	1	39	194	3	4	1	45	115	2	4	1
299	3	4	1	90	103	3	4	1	103	140	2	4	1	62	228	3	4	1
207	3	4	1	10	301	3	4	0	64	87	2	4	1	121	127	3	4	0
286	3	4	1	6	133	3	4	1	195	162	2	4	1	124	211	2	4	1
58	2	4	1	164	172	3	4	1	71	79	3	4	0	10	87	2	4	1
257	3	4	0	128	341	3	4	1	85	215	3	4	1	23	210	2	4	0



STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM
40	292	4	3	1	33	131	3	3	1	118	131	3	3	1	18	353	3	3	1	67
50	144	4	3	1	85	299	3	3	1	73	341	3	3	1	99	163	3	3	1	22
730	321	3	3	1	9	1	3	3	1	52	182	3	3	1	25	201	3	3	0	3
7	208	3	3	1	90	198	3	3	1	54	248	3	3	1	115	179	3	3	1	53
58	56	3	3	1	348	326	4	3	1	30	221	3	3	0	162	124	3	3	1	59
38	315	3	3	1	36	205	3	3	1	3	345	3	3	1	69	245	3	3	1	62
261	200	4	3	1	71	313	4	3	0	23	3	3	3	1	79	223	3	4	1	215
68	275	3	3	1	49	254	3	3	1	189	119	3	3	1	1	213	3	4	1	74
200	331	3	3	1	240	48	4	3	1	61	81	3	3	0	211	70	3	4	0	44
123	31	4	3	1	130	75	4	3	0	116	160	3	3	1	47	322	3	4	1	48
55	321	3	3	1	17	119	3	3	1	46	137	3	3	1	29	262	3	4	0	90
51	8	4	3	0	100	150	4	3	1	56	91	3	3	1	27	1	3	4	1	4
79	183	3	3	1	122	17	3	3	0	374	230	3	3	1	99	35	3	4	1	95
60	232	3	3	1	86	265	4	3	0	39	252	3	3	1	235	225	3	4	1	62
48	23	4	3	1	63	347	3	3	1	72	104	3	3	1	143	183	3	4	1	14
199	123	3	3	0	391	358	4	3	0	51	113	3	3	0	48	228	3	4	1	30
217	194	4	3	1	48	321	3	3	1	38	169	3	3	1	223	29	3	4	1	50
37	208	3	3	1	92	265	3	3	1	46	179	3	3	1	10	229	3	4	1	99
77	280	4	3	0	52	241	3	3	1	53	32	3	3	1	40	86	3	4	1	74
33	32	4	3	1	14	100	3	3	1	118	106	3	3	0	130	29	3	4	1	73
90	339	4	3	1	84	158	3	3	1	75	354	3	3	1	73	226	3	4	1	99
18	306	4	3	1	125	265	3	3	1	98	289	2	3	0	737	153	3	4	0	21
56	177	3	3	1	77	176	3	3	1	89	61	3	3	0	24	64	3	4	1	78
53	242	4	3	0	62	358	3	3	1	92	317	3	3	0	82	172	3	4	1	119
51	331	3	3	1	114	150	3	3	0	253	353	3	3	1	20	221	3	4	1	7
57	216	4	3	1	44	218	3	3	1	78	31	3	3	0	169	129	3	4	1	69
162	198	4	3	0	58	262	3	3	1	134	40	3	3	1	57	187	3	4	1	237
12	5	3	3	1	60	238	3	3	0	94	288	3	3	1	78	98	3	4	0	24
63	182	4	3	0	54	135	3	3	0	114	304	3	3	1	73	100	3	4	1	64
88	284	3	3	1	168	277	3	3	0	99	238	3	3	0	164	303	3	4	1	42
107	250	3	3	1	103	266	4	3	0	45	107	3	3	1	219	271	3	4	1	68
63	107	3	3	1	45	71	3	3	1	86	15	3	3	1	66	209	3	4	0	70
40	135	4	3	0	91	179	3	3	0	220	31	3	3	1	72	356	3	4	0	110
23	160	3	3	1	74	31	3	3	1	20	234	3	3	1	22	49	3	4	1	27
149	4	4	3	0	101	54	3	3	1	50	149	3	3	0	158	54	3	4	1	8
64	227	4	3	1	72	143	3	3	1	147	162	3	3	1	28	55	3	4	1	64
4	197	3	3	1	115	258	3	3	1	24	40	3	3	0	374	82	3	4	0	128
38	125	3	3	1	79	113	3	3	1	41	348	3	3	1	52	157	3	4	1	38
21	340	2	4	1	9	115	1	4	1	353	93	2	4	1	6	360	1	4	1	5
38	112	2	4	1	71	120	2	4	1	40	315	2	4	1	86	168	2	4	0	2
148	62	2	4	1	18	227	2	4	1	59	73	1	4	1	100	205	1	4	1	45
42	83	2	4	1	57	245	2	4	1	43	34	2	4	1	20	200	1	4	1	20
12	109	2	4	0	27	3	2	4	1	38	272	2	4	1	42	69	2	4	0	40
85	144	2	4	1	74	37	2	4	1	6	361	2	4	1	39	193	2	4	0	29
76	74	2	4	1	59	172	2	4	1	60	200	1	4	1	6	69	1	4	1	41
22	266	2	4	1	75	62	2	4	1	219	21	2	4	1	11	73	1	4	1	17
85	320	2	4	1	84	205	2	4	1	31	345	1	4	1	60	183	1	4	1	29
43	220	2	4	1	47	242	2	4	1	8	211	2	4	1	76	116	1	4	1	64
135	192	2	4	1	47	360	2	4	0	47	206	2	4	1	53	170	1	4	1	43
17	285	2	4	1	16	14	2	4	1	23	141	2	4	0	61	212	1	4	1	38
45	68	2	4	1	34	147	2	4	1	74	330	1	4	1	137	336	1	4	1	16
38	50	2	4	1	19	281	2	4	1	4	224	2	4	1	14	100	1	4	1	10
89	109	2	4	1	69	231	2	4	0	5	239	2	4	1	15	346	1	4	1	14
185	102	2	4	1	23	150	2	4	1	17	333	1	4	1	12	270	1	4	1	15

(Continued)


Appendix. (Continued)

CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C
282	3	4	1	96	362	2	4	0	121	97	2	4	1	86	223	2	4	1
149	3	4	1	59	250	2	4	1	50	54	2	4	1	80	353	2	4	1
317	3	4	1	45	297	3	4	1	54	66	2	4	1	86	56	3	4	0
216	3	4	1	99	187	3	4	1	13	235	2	4	1	70	9	3	4	0
242	3	4	1	63	331	2	4	1	99	248	2	4	1	9	41	2	4	1
311	3	4	1	48	213	3	4	1	252	108	3	4	1	58	287	2	4	1
24	2	4	1	279	18	2	4	1	7	85	2	4	1	2	225	2	4	1
158	3	4	1	25	351	3	4	1	150	167	3	4	0	38	242	2	4	1
33	3	4	1	130	359	3	4	1	60	230	3	4	0	59	12	2	4	1
89	3	4	0	77	59	3	4	1	86	152	3	4	0	159	80	1	4	1
260	3	4	1	50	24	2	4	1	31	17	3	4	1	4	333	2	4	1
355	3	4	1	40	87	3	4	1	48	205	2	4	1	1	39	2	4	1
346	3	4	1	102	24	3	4	1	88	262	3	4	1	29	298	2	4	0
15	3	4	1	7	98	3	4	0	55	238	3	4	1	108	63	2	4	1
72	4	3	1	37	174	4	3	1	115	188	3	3	1	78	211	3	3	1



STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM	CDB	P	A	C	STM
48	185	2	4	1	5	270	2	4	1	24	27	1	4	1	26	327	1	4	1	44
52	254	2	4	1	19	167	2	4	1	42	328	2	4	1	65	123	1	4	1	18
36	172	2	4	1	55	320	2	4	1	44	328	2	4	1	27	329	1	4	1	16
43	196	2	4	1	17	168	1	4	1	50	179	2	4	1	18	144	1	4	1	10
49	240	2	4	1	30	207	2	4	1	18	149	2	4	0	187	246	1	4	0	17
61	302	2	4	1	23	198	2	4	1	6	301	1	4	1	31	63	1	4	1	51
152	127	2	4	0	13	356	2	4	1	13	310	2	4	1	13	173	1	4	1	101
81	316	2	4	1	109	50	2	4	1	47	337	1	4	1	1	66	1	4	1	22
42	316	2	4	0	165	194	2	4	1	39	90	2	4	1	51	195	1	4	1	22
508	56	2	4	0	0	196	2	4	1	14	266	1	4	1	122	130	1	4	1	13
66	94	2	4	0	184	12	2	4	1	16	34	2	4	1	1	290	1	4	1	6
135	258	2	4	1	14	66	2	4	0	1	29	2	4	1	38	324	1	4	1	35
6	232	2	4	1	48	86	2	4	1	9	318	2	4	0	20	21	4	2	0	198
45	100	2	4	1	101	265	1	4	1	63	250	1	4	1	10	193	4	3	1	18
49	167	3	3	0	19	231	2	3	0	1008										

Abbreviations: CDB, calendar day of the year birth date; P, period of birth (1 = 1917–29, 2 = 1930–39, 3 = 1940–49, 4 = 1950–59, 5 = 1960–69, 6 = 1970–79, 7 = 1980–89) A, age category (1 = ≤40 yrs., 2 = 41–50 yrs., 3 = 51–60 yrs., 4 = >60 yrs.); C, Censor variable (1 = Dead, 0 = Alive); STM, survival time in weeks.

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