

# The Use of Electronic Medical Record Data to Analyze the Association Between Atrial Fibrillation and Birth Month

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## Abstract

**Objectives:** Cardiovascular disease is a condition of enormous public health concern. Recently, a population study newly revealed associations between cardiovascular diseases and birth month. Here, we investigated the association between atrial fibrillation in cardiovascular disease and birth month.

**Methods:** We retrospectively extracted birth date data from 6,016 patients with atrial fibrillation (3,876 males; 2,140 females) from our electronic medical records. The number of live births in Japan fluctuates seasonally. Therefore, we corrected the number of patients for each birth month based on a Japanese population survey report. Then, a test of the significance of the association between atrial fibrillation and birth month was performed using a chi-square test. In addition, we compared the results of an analysis of patient data with that of simulated data that showed no association with birth month.

**Results:** The deviations of birth month were not significant (overall:  $p = 0.631$ , males:  $p = 0.842$ , females:  $p = 0.333$ ). The number of female patients born in the first quarter of the year was slightly higher than those born in the other quarters of the year ( $p = 0.030$ ). However, by comparing the magnitudes of dispersion in the simulated data, it seems that this finding was mere coincidence.

**Conclusion:** An association between atrial fibrillation and birth month could not be confirmed in our Japanese study. However, this might be due to differences in ethnicity. Further epidemiologic studies on this topic may result in reduction of disease risk in the general population and contribute to public health.

**Key words:** birth month; season of birth; cardiovascular disease; atrial fibrillation; melatonin

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## Introduction

Birth month may be associated with several medical conditions [1]. This tends to be a very popular topic among the general public, and thus news media often erroneously report such ideas as scientific fact. However, with few exceptions, these associations have remained tentative. Although such associations appear simple, on closer examination they are complex; therefore, additional rigorous research is necessary.

Associations between birth month and medical conditions can be divided into three types. The first type is observed only in early life. In these associations, the effects of seasonal exposure during fetal life or infancy do not persist because of repeated exposure throughout life, and the association disappears in adulthood. Neonatal anthropometric measurements are an example of associations included in this type [2,3]. The second type describes an association between birth month and a special trait. Such traits are affected by seasonal exposure only during fetal life or infancy. Because there is little change in the trait from subsequent repeated exposure, the influence in early life persists as a vestige throughout life. Studies on this type of association include those on hyperopia and corneal curvature, since the theoretical grounds for associations with these conditions have been demonstrated [4-6]. Finally, the third type of association concerns the development of a disease in the future being dependent on past seasonal exposure despite the fact that the disease did not develop at the time of the original exposure. This type of association is difficult to explain. Well-known diseases in this type are schizophrenia and multiple sclerosis [7,8].

We propose a hypothesis to explain the origin of many of the diseases in this third type of association. Although an association between the pineal gland and birth month has not been previously reported, the pineal gland exhibits special traits of the second type of association described above. In the pineal gland, cell differentiation and organ growth are completed during infancy, and the secretory capacity for melatonin is also determined during this time [9-11]. Based on this, if light seasonally influences the development of the pineal gland during infancy, then melatonin secretion should exhibit variations dependent on birth month. In addition, melatonin might contribute to the pathogenesis of schizophrenia and multiple sclerosis [12,13]. These findings suggest that the mechanisms underlying the risk of developing diseases of the third type of association could be related to melatonin secretion.

A population study systematically explored the relationship between birth month and lifetime disease risk for 1,688 conditions and newly revealed associations between cardiovascular diseases and birth month [1]. Moreover, numerous studies have suggested that melatonin plays an important role in various cardiovascular diseases [14]. Therefore, according to our hypothesis, it is entirely possible that cardiovascular diseases are linked to birth month. Cardiovascular diseases are common diseases compared to schizophrenia or multiple sclerosis, and are responsible for considerable mortality in the population. Associations with birth month carry profound meaning and might present new valuable information for public health. Here, we attempted a confirmatory study on the association between one cardiovascular disease and birth month.

## Methods

Our study was based on a retrospective analysis of the electronic medical records of patients at the Osaka City University Hospital (Osaka, Japan, northern latitude of 34.7 degrees). We focused on

atrial fibrillation [15] because of its rigorous diagnostic criteria among the reported cardiovascular conditions, such as essential hypertension, congestive cardiac failure, angina, cardiac complications of care, mitral valve disorder, pre-infarction syndrome, cardiomyopathy, and chronic myocardial ischemia [1]. The electronic medical record data for other cardiovascular conditions include complications and outcomes that might be dependent upon ambiguous diagnostic criteria. Our dataset included 6,016 patients (3,876 males, 2,140 females) ranging in age from 12 to 101 years (average =  $68.1 \pm 12.0$  years) who were diagnosed with atrial fibrillation from May 1986 to August 2016.

The number of live births in Japan fluctuates seasonally. Therefore, to cancel this variation, we corrected the number of patients for each birth month based on a Japanese population survey report separated by sex [16]. The formula used to correct the variation was as follows: weighing coefficient =  $N_{\text{year}} / (12 \times N_{\text{month}})$ , where “ $N_{\text{year}}$ ” is the number of national births during the year a patient was born, and “ $N_{\text{month}}$ ” is the number of national births in the month during the year the patient was born. The chi-square test was performed to determine the significance of the association with birth month.

Knowledge of the inevitable dispersion of birth months is a prerequisite to avoid overestimating the results of analysis. We therefore compared the current results of patient data with simulated data showing no association between atrial fibrillation and birth month. This simulated data was generated using the Excel<sup>®</sup> function ‘=INT(RAND()\*12)+1’. Briefly, we threw a dice with 12 pips 6,016 times. We referred to the first 3,876 times as male and the following 2,140 times as female. To show the association pattern of atrial fibrillation with birth month graphically, it is necessary to decrease the potential random disturbances in the time-series data. Consequently, we calculated three-point moving averages that also included values for the preceding and following month. For example, the number for January was the average of the data for the three months of December, January, and February.

Our study received approval from the Ethics Committee of the Osaka City University Hospital.

## Results

Table 1 shows the observed numbers and the corrected numbers of patients with atrial fibrillation for each birth month. The peak birth month was March, regardless of sex. The trough birth month was June for all patients, August for male patients, and September for female patients. However, chi-square analysis showed that the deviations of birth month were not statistically significant (overall:  $p = 0.631$ , males:  $p = 0.842$ , females:  $p = 0.333$ ).

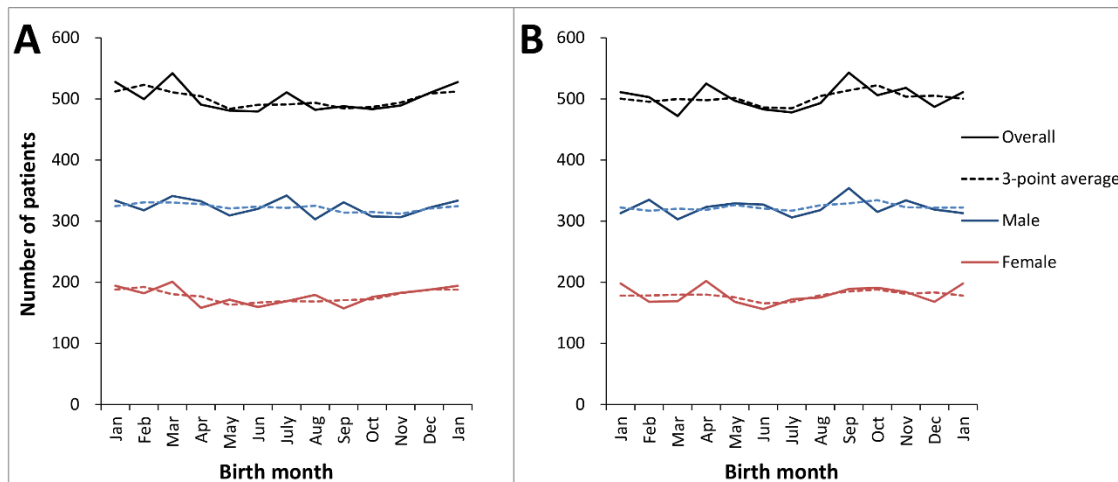
**Table 1. Number of patients with atrial fibrillation by birth month**

| Birth month | Overall (n = 6,016) |               | Male (n = 3,876) |               | Female (n = 2,140) |               |
|-------------|---------------------|---------------|------------------|---------------|--------------------|---------------|
|             | n                   | Corrected (%) | n                | Corrected (%) | n                  | Corrected (%) |
| January     | 750                 | 527.6 (8.82)  | 467              | 333.5 (8.63)  | 283                | 194.1 (9.17)  |
| February    | 573                 | 499.7 (8.35)  | 362              | 317.7 (8.22)  | 211                | 182.0 (8.60)  |

|                 |       |               |       |               |       |               |
|-----------------|-------|---------------|-------|---------------|-------|---------------|
| March           | 693   | △542.0 (9.06) | 427   | △341.2 (8.83) | 266   | △200.8 (9.48) |
| April           | 442   | 490.6 (8.20)  | 300   | 332.6 (8.60)  | 142   | 158.0 (7.46)  |
| May             | 406   | 480.9 (8.04)  | 264   | 309.4 (8.00)  | 142   | 171.5 (8.10)  |
| June            | 375   | ▼479.5 (8.01) | 252   | 320.1 (8.28)  | 123   | 159.4 (7.53)  |
| July            | 451   | 510.8 (8.54)  | 305   | 341.9 (8.84)  | 146   | 168.9 (7.98)  |
| August          | 453   | 482.3 (8.06)  | 288   | ▼303.0 (7.84) | 165   | 179.3 (8.47)  |
| September       | 473   | 488.0 (8.16)  | 321   | 330.8 (8.56)  | 152   | ▼157.2 (7.42) |
| October         | 475   | 483.3 (8.08)  | 303   | 307.5 (7.95)  | 172   | 175.8 (8.30)  |
| November        | 488   | 489.2 (8.18)  | 310   | 306.5 (7.93)  | 178   | 182.7 (8.63)  |
| December        | 437   | 509.6 (8.52)  | 277   | 322.0 (8.33)  | 160   | 187.6 (8.86)  |
| Average         | 501.3 | 498.6 (8.33)  | 323.0 | 322.2 (8.33)  | 178.3 | 176.4 (8.33)  |
| <i>p</i> -value |       | 0.631         |       | 0.842         |       | 0.333         |

*p*-values were computed using the chi-square test, degrees of freedom = 11.

△ represents a peak, ▼ represents a trough among all, male, and female patients, respectively.



**Figure 1. Association pattern between atrial fibrillation and birth month**

A: results using corrected numbers of patients in this study

B: simulated data with no association between atrial fibrillation and birth month

Figure 1 shows the pattern of the association between atrial fibrillation and birth month. In Figure 1A, the number of patients born in the first quarter of the year among all patients was slightly higher than those born in the other quarters of the year. However chi-square analysis showed that the deviation between quarters was statistically significant only for females (overall:  $p = 0.156$ ,

males:  $p = 0.623$ , females:  $p = 0.030$ , see Table 2). In Figure 1B, a simulation result with no association between atrial fibrillation and birth month showed a casual peak in September. By comparing the magnitudes of dispersion in the simulation (see Figure 1B), the findings in patients seemed mere coincidence (see Figure 1A).

**Table 2. Corrected number of patients with atrial fibrillation by birth quarter**

| Birth quarter   | Overall | Male  | Female |
|-----------------|---------|-------|--------|
| First quarter   | 1569.3  | 992.4 | 576.9  |
| Second quarter  | 1451.0  | 962.1 | 488.9  |
| Third quarter   | 1481.1  | 975.7 | 505.4  |
| Fourth quarter  | 1482.1  | 936.0 | 546.1  |
| Average         | 1495.9  | 966.6 | 529.3  |
| <i>p</i> -value | 0.156   | 0.623 | 0.030  |

*p*-values were computed using the chi-square test, degrees of freedom=3.

## Discussion

The number of female patients with atrial fibrillation born in the first quarter of the year was slightly higher than those born in the other quarters. However, there were no statistically significant deviations in birth month and birth quarter for the remaining patients. Additionally, an analysis of the simulation results also showed that this finding might be mere coincidence. The birth month with the highest number of patients was March, similar to previous reports [1,17]. It is unclear whether this consistency in peak birth month is due to chance or is a non-negligible finding. The association between atrial fibrillation and birth month could not conclusively be confirmed in the present study of Japanese patients. However, differences in ethnicity may account for the lack of significance. North American and European studies demonstrate a relationship between schizophrenia and birth month. However, Asian studies, particularly Japanese and Korean studies, have difficulty finding such associations [18]. In general, any condition that is associated with birth month largely varies with geographical condition, ethnicity, sex, and generation [2,7,18,19]. Further studies are required to confirm any association between birth month and cardiovascular diseases. The most well-known association between a disease and birth month is that reported for schizophrenia. Recent work has progressed beyond the stage of merely confirming the existence of this association, which was established 40 years ago [20]. Currently, the aim of research in this area is to investigate the causes of the association, although designing suitable experiments is challenging because large numbers of participants are needed due to the low prevalence of schizophrenia. In contrast to schizophrenia, the prevalence of cardiovascular diseases is high. Moreover, these can be assessed quantitatively by measuring blood pressure and other values [17]. Therefore, the details of the association between cardiovascular diseases and

birth month can be analyzed much more easily than that of schizophrenia. Recently, medical records have been computerized in many facilities, allowing large data sets to be investigated.

Generally, studies on associations between diseases and birth month, including this study, have the same limitation. Specifically, even if a significant association is observed, it is impossible to derive practical information from the study that should be applied to public health practice. The reason for this limitation is that the origin of an observed association is unknown. To overcome this limitation, various association patterns that have been strictly confirmed should be compared among various kinds of diseases. We suspect that associations are not caused by a different origin for each disease. Associations can be roughly divided into a group of diseases that are often seen in individuals born in the spring and a group of diseases that are often seen in individuals born in the autumn [1]. The associations observed in these groups may have a common origin. If diseases in the former group are affected by melatonin insufficiency, all infants must be exposed to a light environment that allows for sufficient pineal gland development. Accordingly, further investigation into this topic will overcome the limitation and provide practical information for disease prevention.

This study has two further limitations. One is that we used diagnostic data only from electronic medical records. Using record details introduces the problem of the diagnostic data not always being correct. When considering heart failure or hypertension, the ambiguity of diagnostic data may affect the study results. However, it was impossible to confirm the diagnostic data by checking the details of each medical record in this study. Therefore, taking this into consideration, we limited our examination to atrial fibrillation, which has clear diagnostic criteria.

The other limitation is that our study method required a correction for the number of patients for each birth month. If we had studied blood pressure, the average values of participants born in January and June could have been compared directly. However, when comparing the number of patients, it is necessary to consider the bias in birth month within the population. In Japanese population statistics, the magnitude of that bias differs by birth year [16]. Therefore, we corrected the number of patients even by considering the birth year to eliminate the seasonal fluctuation within the population.

Our hypothesis was that the risk of developing a medical condition in the future is related to birth month via melatonin secretion. It is possible that development of the pineal gland is influenced seasonally by the light environment during the infantile period. If we can show proof of differences in melatonin secretion associated with birth month, our hypothesis would be supported. Unfortunately, no evidence of this was found in the present study. However, if our hypothesis is true, an association between cardiovascular diseases and birth month should exist, and improvement of the light environment during the infantile period might lead to prevention of cardiovascular diseases. Moreover, an association between birth month and age-related maculopathy, which involves developmental differences in melatonin secretion [21-23], should be also found in the future. Age-related maculopathy is the leading cause of blindness in older people in the United States, United Kingdom and many other industrialized countries [24]. Though associations between birth month and medical conditions have been limited to a few rare diseases thus far, this issue is worthy of study from a public health point of view.

## Conclusions

An association between atrial fibrillation and birth month could not be confirmed in our study of Japanese patients. However, the lack of statistical significance could be due to differences in ethnicity. Previously, even if a significant association were observed, it was impossible to derive practical information that should be applied to public health practice. However, further studies on this topic will carry a profound meaning and present new valuable information on the environment in infancy that can reduce the risk of cardiovascular disease in the general population. Consequently, though associations between birth month and medical conditions have been limited to a few rare diseases so far, this issue is worthy of study from a public health point of view.

## Conflict of interests:

None declared.

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