

The relationship between folate intake and neural-tube defects: an international ecological study

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Abstract

Background & Aims: Inadequate intake of folate is associated with an increased incidence of neural tube defects (NTDs). NTDs could be prevented if women consume sufficient amounts of folate before conception and during early pregnancy. This ecological study aimed to clarify the relationship between the incidence of NTDs and folate intake among several countries in women of two age groups: underage or overage.

Methods: The available data on the amount of folate intake and the rate of neural tube disorder in 9 countries in 2011 were obtained. Considering the strategies for folic acid intake differs by the recommended age, we divided the women into two categories by age: less than 20 years old and over 20 years old. We analyzed the relationship between folate intake and incidence of neural tube disorder using the linear regression and quadratic curve regression methods.

Results: After weight adjustment for population size, the linear regression ($R^2 = 0.622$, $p = 0.012$ for under 20 years, $R^2 = 0.707$, $p = 0.0045$ for 20 years and over) and the quadratic curve regression ($R^2 = 0.949$, $p = 0.0001$ for under 20 years, $R^2 = 0.928$, $p = 0.0004$ for 20 years and over) represented a significant correlation. Our results revealed the nadir for NTD occurrence correlated with a folate intake of 300 to 400 $\mu\text{g}/\text{day}$ in both groups.

Conclusions: In general women, 300 to 400 $\mu\text{g}/\text{day}$ of folate intake is recommended to prevent the onset of NTD. Further investigation is required to reveal the upper safe limit.

Keywords: daily folate intake, neural tube defect, ecological study

Abbreviations

NTD, neural tube defect; ICBDSR, The International

Clearing House for birth defects surveillance and Research;
WHO, World Health Organization

1. Introduction

According to reports from the Ministry of Health, Labor and Welfare in Japan, the incidence of neural-tube defects (NTDs) has been increasing in Japan each year, while based on the incidence of spina bifida, this rate is decreasing in other countries¹.

Since the closure of the neural tube occurs at several sites in humans, the clinical types of neural defects differ depending on the site at which closure fails². NTD includes anencephaly and spina bifida³. All infants with anencephaly are stillborn or die shortly after birth, whereas many infants with spina bifida survive nowadays, thanks to extensive medical and surgical care².

It is well-known that NTDs could be prevented if women consume sufficient amounts of folate before conception and during early pregnancy^{2,4}. In Japan, according to the results from the National Health and Nutrition Survey, the recent intake of folate has decreased among women in all age groups. The reported intake of folic acid in 2006 was 230 $\mu\text{g}/\text{day}$ in the less than 20 years old age group, and 315 $\mu\text{g}/\text{day}$ in the 20 years and over years old age group. In 2015, the amount has decreased to 211 $\mu\text{g}/\text{day}$ and 299 $\mu\text{g}/\text{day}$ in each age group, respectively^{5,6}.

The Ministry of Health, Labor and Welfare in Japan recommends pregnant women to take 400 $\mu\text{g}/\text{day}$ of folate. In the United States, folic acid fortification of cereals is mandatory to increase the intake of the entire population, regardless of age. On the other hand, in some countries like Canada, folate supplementation is recommended only in women who are planning to become pregnant. With such variance in

approaches and targets to increase folate intake, it is fruitful to compare the incidence of NTDs and folate intake internationally based on women's age, to verify the position of Japan compared to other countries. Such a result can be of benefit in designing new awareness strategies to improve the reduced folate intake status among Japanese women, despite the recommendations in place. This ecological study aims at clarifying the relationship between the incidence of NTDs and folate intake among several countries, in two age groups of women: women under 20 years old and women 20 years and over. The results might provide some proof regarding the suggested recommended folate intake and the intervention target group based on age (underage or overage) to prevent NTDs.

2. Materials and Methods

2.1. Country selection

The daily intake of folate and the incidence of NTDs were obtained from publicized nutrition research data and "the International Clearing House for birth defects surveillance and Research"⁷⁾, respectively. We could access the data of daily intake of folate and incidence of neural tube defect in 2011 from 9 countries: America, Japan, Canada, United Kingdom, India, Australia, Italy, Germany and the Netherlands. We divided the research data into two age groups (less than 20 years old and 20 years and over), as there was a possibility that preventive approaches should differ based on the age of the target population.

2.2. Daily Folate intake data

The daily folate intake data was obtained from the following publications: National Health and Nutrition Examination Survey for America, 2011; National Health and Nutrition Survey for Japan, 2011; Canadian Health Measures Survey for Canada, 2012 - 2013; National diet and Nutrition Survey for United Kingdom, 2011; National Nutrition Monitoring Bureau for India, 2011; Australian Health Survey for Australia, 2011-2012; and European Nutrition and Health Report for Germany, the Netherlands and Italy, 2009. Published data from Germany, Italy, the and Netherlands had divided the population of women under 20 years of age into three group: 7-9, 10-14 and 15-18 years of age, and in India the three groups were: 10-12, 13-15 and 16- 17 years of age. For the data from these counties, we calculated the total daily intake of folate by multiplying the total population in each category with the daily intake of folate in each category,

divided by the total population of people under 20 years of age.

2.3. The Incidence rate of NTD

The incidence rate of NTD was obtained from the data provided by "The International Clearing House for birth defects surveillance and Research" (ICBDSR Annual report, 2013)⁷⁾. ICBDSR summarizes prenatal data from all over the world for the purpose of preventing congenital diseases. Hence, the incidence of congenital malformations such as spina bifida and anencephaly is available through their database. Since NTD is mainly considered as anencephaly and spina bifida, we calculated the incidence of NTD by adding the number of anencephaly and spina bifida cases in 2011.

2.4. Statistical analysis

Both linear regression analysis and quadratic curve regression were carried out in both age groups using JMP Pro 12.2.0 (SAS Institute, Cary, NC). A level of significance was set at a value of $p < 0.05$. We also employed weighted adjustment for population size for regression analysis, to account for the differences in the population in each country. The population of each country was obtained from World Health Statistics 2011.

3. Results

We analyzed the relation between daily folate intake and the incidence rate of NTD in the two age groups. The results of the linear regression analysis are shown in Fig 1a and b. Although there was no significant correlation in either linear regression or quadratic curve regression analyses for the group 20 years and over age (linear: $R^2 = 0.192$, $p = 0.238$; quadratic curve: $R^2 = 0.617$, $p = 0.056$), we observed a significant downward convex correlation in the younger than 20 years of age group in the quadratic curve regression analysis ($R^2 = 0.697$, $p = 0.028$), but not in the linear regression analysis for this age group ($R^2 = 0.073$, $p = 0.482$). The nadir of NTD incidence was revealed at 300-400 $\mu\text{g}/\text{day}$ of daily folate intake in both groups.

The relationship between folate daily intake and the population weighted incidence of NTDs is shown in Fig1c and d. We found significant correlation between the two in both linear regression and quadratic curve regression in both younger than 20 years of age (linear: $R^2 = 0.622$, $p = 0.012$; quadratic curve: $R^2 = 0.949$, $p = 0.0001$) and 20 year and over (linear: $R^2 = 0.707$, $p = 0.0045$; quadratic curve:

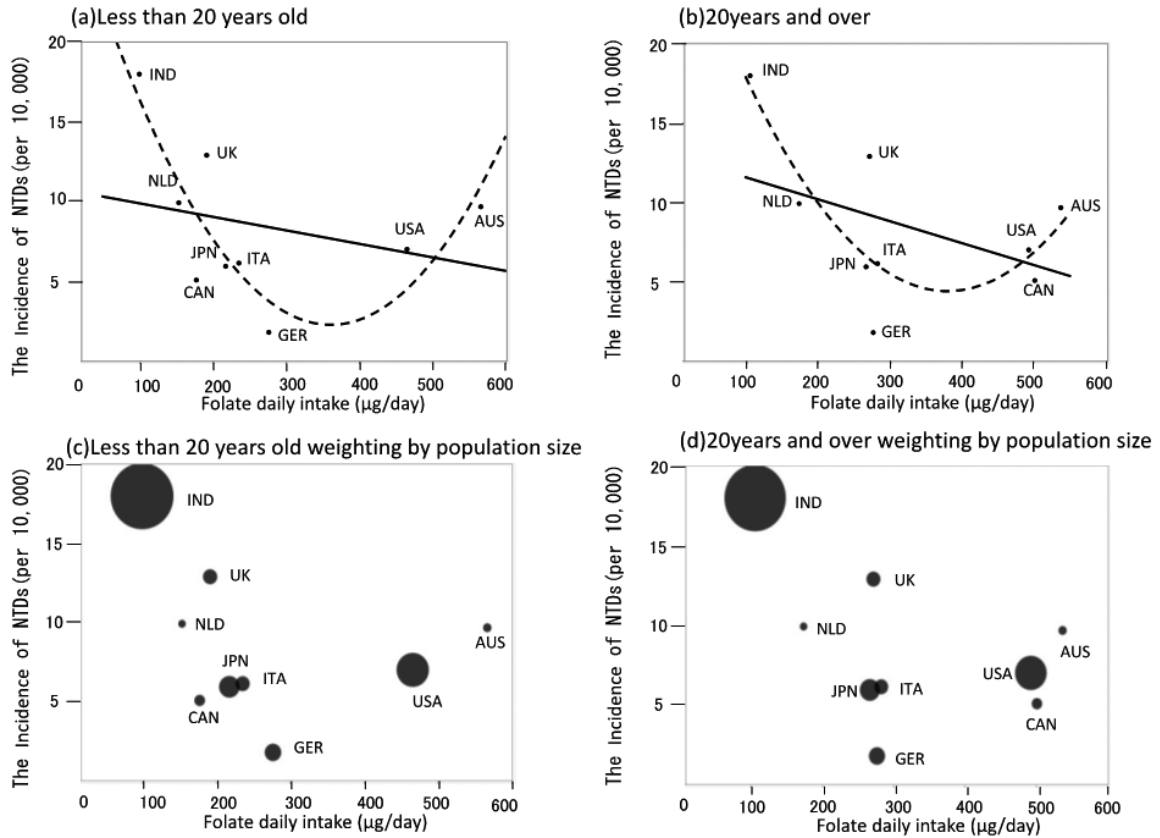


Fig. 1 Relationship between folate daily intake and incidence of neural tube defects.

Fig. 1. Relationship between daily folate intake and incidence of neural tube defects among in women less than 20 (a) and 20 years old and over (b) without population adjustment, and with population adjusting in women less than 20 (c) and 20 years old and over (d). The size of circles resembles the size of population for each country in (c) and (d). NTD: neural tube defect; JPN: Japan; USA: United States of America; CAN: Canada; UK: United Kingdom; GER: Germany; ITA: Italy; AUS: Australia; NLD: the Netherlands; IND: India.

$R^2 = 0.928, p = 0.0004$), with a convex downward quadratic curve regression in the latter.

4. Discussion

Our international ecological study has verified that a folate intake of 300-400 $\mu\text{g}/\text{day}$ is the dose with the least incidence of NTD. Higher amounts do not have any additional effect in decreasing the occurrence of NTD.

The recommended levels of folate is > 0.5 mg/day in the Netherlands, > 0.4 mg/day in Canada, United Kingdom, America and Japan, and > 550 $\mu\text{g}/\text{day}$ in Germany. Though our results revealed the best recommended dose for folate to reduce the incidence of NTD, and the intake of folate in the above-mentioned countries seems to be adequate, studies have revealed that the intake of folate from meals is insufficient⁸⁾. America is the only country where folate intake is recommended in all women, while in other

countries the recommendation is only for women planning to get pregnant. Our results revealed that the lowest incidence of NTD is when the intake of folate is 300 to 400 $\mu\text{g}/\text{day}$ among general women. The intake of folate in Japan is on a downward trend and should increase to the recommended levels.

High intake of folate may pose risks. Although De-Regil et al. reported daily folic acid supplements of 360-4000 $\mu\text{g}/\text{day}$ decrease the incidence of NTD⁹⁾, there are reports that folic acid supplements > 400 $\mu\text{g}/\text{day}$ had reduced NK cytotoxicity among postmenopausal women¹⁰⁾. Our results suggest that receiving more than 400 $\mu\text{g}/\text{day}$ of folate could increase the incidence of NTD, based on the data available from America and Canada. Further study is necessary to understand the effects of excess folate ingestion on the incidence of NTD.

There are some limitations to this study. First, these data cannot be applied to any one individual, because the

analyses were performed using national data. Second, we could not obtain the data on pregnancy status. Future studies should consider the intake of folate in pregnant women as opposed to women in general.

In conclusion, irrespective of age, the recommended dose of folate to prevent the onset of NTD is 300 to 400 $\mu\text{g}/\text{day}$; however, further investigation is required to determine the upper safe limit.

Statement of authorship

The original project design is NY and MO. NY analyzed data, and wrote the manuscript under the advice from MO.

Conflict of interest statement

None declared.

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