Preventive Medicine Reports 2 (2015) 572–576

Contents lists available at ScienceDirect

Preventive Medicine Reports

journal homepage: http://ees.elsevier.com/pmedr

Patterns of folic acid use in pregnant Saudi women and prevalence of neural tube defects — Results from a nested case–control study☆

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ARTICLE INFO

Available online 26 June 2015

Keywords:
Folic acid
Neural tube defects
Periconception and postconception

ABSTRACT

Background. Although the role of folic acid (FA) in preventing neural tube defects (NTDs) is well documented, its optimal intake in pregnant women is still low in many countries. Here, we prospectively studied the prevalence of NTDs in the newborns and the patterns of FA intake in pregnant Saudi mothers.

Methods. This case–control study was nested within a 3-year project (July 2010 to June 2013) to study the patterns of birth defects in the offspring of Saudi women who received their antenatal care and delivered at Prince Sultan Military Medical City, Riyadh—Saudi Arabia. Enrolled mothers were divided into 4 groups: group 1 (FA taken before pregnancy and continued regularly after conception), group 2 (FA taken post-conception), group 3 (no FA intake), and group 4 (did not remember or were unsure of taking FA). Control mothers were randomly selected from those with normal first obstetrical ultrasound scan at 18–22 weeks of gestation.

Results. The cohort included 30,531 mothers giving birth to 28,646 infants. We studied 1179 mothers of babies with birth defects (BDs) and 1262 control mothers. There were 237 (9.7%) mothers in-group 1; 2001 (82%) in-group 2; 154 (6.3%) in-group 3; and 49 (2%) in-group 4. There were 49 babies with NTDs, a prevalence of 1.7/1000 total births. Among the studied mothers 2274 (93%) took FA either full or partial course.

Conclusion. The high prevalence of NTDs and the low optimal FA intake highlight the need for a strict implementation of staple food fortification and health education program for Saudi women.

Introduction

Neural tube defects (NTDs) include anencephaly, encephalocele, cranial meningocele, myelomeningocele, spinal meningocele, lipomeningocele and few other rare cerebral defects. Spina bifida cystica includes spinal meningocele, myelomeningocele, myeloschisis and lipomeningocele, and it's the most common NTDs.

Observational and interventional studies in the 1980s and 1990s have shown that folic acid (FA) supplementation is beneficial in preventing neural tube defects (NTDs; MRC vitamin study group, 1991; Czeizel and Dudãs, 1992; Milunsky et al., 1989; Berry et al., 1999). The most important study is the Medical Research Council (MRC) multicentre, a randomized, double-blind trial involving 33 centers in seven countries, studying the recurrence risk for NTDs. A total of 1817 high-risk mothers were identified because of a previously affected pregnancy and were stratified into four groups — 1] periconceptional use of folic acid, 2] other multivitamins with folic acid, 3] vitamins without folic acid and 4] placebo. The study showed that periconceptional FA supplementation had reduced the rate of NTDs recurrence by up to 72% (MRC vitamin study group, 1991). A study in China including more than 200,000 pregnant women showed a protective effect of periconceptional use of FA also in low-risk populations. (Berry et al., 1999).

Although, the exact mechanism of NTD prevention by FA remains largely unknown, the evidence of its role in NTD prevention has come from several sources. The epidemiological evidence is very strong from the different populations studied using different study designs; investigators have shown that NTD risk was increased after exposure to folate antagonist medications; and the presence of high anti-bodies titre to folate receptors in women with a previously affected child with NTD. Nevertheless, the use of FA supplementation in developed and developing countries continues to be low (Vergel et al., 1990; Brough et al., 2009).

☆ *Disclosure*: This study was supported by a generous grant from King Abdul Aziz City for Science and Technology (KACST) through the National Science, Technology and Innovation Plan (NSTIP). Project No. 09-MED748-21, Riyadh, Saudi Arabia.

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http://dx.doi.org/10.1016/j.pmedr.2015.06.016

The United States Preventive Services Task Force (USPSTF) recommends that all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg of FA (Calonge et al., 2009) starting at least one month prior to conception and continued throughout the first trimester (CDC-MMWR, 1992).

In a Canadian population, De Wals et al. (2007) demonstrated a 46% decrease in the prevalence of NTDs after full food fortification with FA. The decrease was greatest in geographic areas in which the baseline NTD rate was the highest. These authors also reported a higher reduction in the rate of spina bifida (53%) compared with the rate of reductions in anencephaly (38%) and encephalocele (31%). A multi-state FA grain fortification program throughout the United States (Canfield et al., 2005) has led to an expected decrease in the prevalence of NTDs as well as modest but statistically significant decreases in the birth prevalence of some non-neural tube defects like: transposition of great arteries (12%), cleft palate only (12%), omphalocele (21%), upper limb reduction defects (11%), and pyloric stenosis (5%).

Hospital based or community-based studies have not identified the true prevalence of NTDs in Saudi Arabia. All the studies including the most recent ones were retrospective analyses of only live birth cases (Seidahmed et al, 2014). A prevalence ranging between 0.44 and 1.83/1000 live births has been reported (Hakami and Majeed-Saidan, 2011. Dawodu et al., 1988) where excluding stillbirths, and elective terminations of pregnancy for fetal anomalies, thus, these prevalence's represent an underestimate of true prevalence of the disease. In the year 2000, the Grain Silos & Flour Mills Organization in Saudi Arabia began mandatory wheat flour fortification with folic acid following a directive from the Nutritional Administration Department of Ministry of Health (Ministry of Health, 2000). Despite this directive, the prevalence of NTDs remained high at 0.76/1000 live births (Safdar et al., 2007). However, flour produced by other Saudi companies and some of the imported flours packages are not marked as FA fortified. All other grain products such as rice are not fortified with FA. This inconsistent policy about flour and other grain product fortification with FA has led to uncertainty about the amount of FA that Saudi women receive through FA fortification alone.

The prevalence of NTDs in Saudi Arabia has never been studied prospectively, and recent publications about NTD prevalence are contradictory (Safdar et al., 2007; Hakami and Majeed-Saidan, 2011).

Accordingly, our objectives were to study the patterns of FA use in pregnant Saudi women who participated in the case–control study and to prospectively determine the prevalence of NTDs. This case–control study was nested within a 3-year research project in which we studied the patterns of fetal and neonatal malformations in babies born at Prince Sultan Military Medical City (PSMMC), in Riyadh—Saudi Arabia.

Methods

Our study cohort included all babies born at Prince Sultan Military Medical City (PSMMC) in Riyadh—Saudi Arabia over a 3-year period (July 1, 2010 through June 30, 2013) that were studied to determine patterns of fetal and neonatal major birth defects (BDs). A case–control study was nested within this cohort to assess the contribution of various confounding risk factors for BDs, including FA intake by participating pregnant mothers.

Included mothers had their first obstetrical ultrasound screening examination between 18 and 22 weeks of gestation to date their pregnancy, detect multiple gestations, locate the placenta, assess the amount of amniotic fluid, and detect any fetal BDs. Mothers in the control group were randomly selected from those with normal first (at intake) obstetrical ultrasound scan using a computer program for their randomization (www.random.org). All scan results were stored in the Viewpoint computer program (GE Healthcare Viewpoint software version 5.6, Wauwatosa, WI U.S.A) to be reviewed again when needed. Once a major birth defect was antenatally or postnatally detected, or once the mother was selected as a control, they were interviewed by one of the authors (MSR, AMK) or a trained registrar in the department of obstetrics and gynecology. Parental demographic data, including parental age, occupation, mother's weight and height, body mass index (BMI), combined family income, and the level of maternal education was collected for all mothers' current pregnancies. We divided pregnant mothers into four groups based on their FA use. Group 1 (Full FA intake group) included mothers who took FA, or one of the commercial preparations that contained FA before they were pregnant and continued to take FA (0.4 mg per day) regularly after that. Group 2 (Partial FA Intake group) included mothers who took FA irregularly or started taking FA postconceptionally. Group 3 (No FA intake group) included mothers who did not take any form of FA, and group 4 (Not sure group) included mothers who were not sure they received FA or did not remember taking FA.

At PSMMC a trained neonatal physician examined all babies within the first 24 h of life. For mothers of babies with BDs, whether detected antenatally and/or postnatally, and for mothers selected as controls, we completed a study form that included the type of BDs and family demographic data. Pregnancies were terminated because of NTDs and those babies who were stillborn with NTDs were included in the NTD prevalence calculations. However, babies with NTDs as part of a specific recognizable syndrome were not included in the calculation of NTD prevalence.

The collected data from these forms were reviewed by one of the investigators (MAMS) and entered into a modified version of the EUROCAT Data Management Program (EDMP) (www.EUROCAT.com, 2005). The BDs were coded according to the WHO International Classification of Diseases and Related Health Problems, 10th revision (ICD-10) with the British Paediatric Association extension (WHO, 2010).

We excluded (1) babies with major BDs that were referred to PSMMC for further evaluation and management; (2) babies born preterm with malformations related to their prematurity or a complication such as patent ductus arteriosus (PDA) or hydrocephalus secondary to intraventricular hemorrhage; and (3) babies who were born with only isolated minor anomalies such as birth marks, rudimentary digits, those without any major BDs. We also excluded mothers who had their antenatal care outside of PSMMC and been referred for further diagnostic investigation or delivery (i.e., those mothers who were not part of our original cohort).

Statistical analysis

Data measured on the continuous scale were reported as mean ± standard deviation (SD). Categorical data were reported as proportions. Means comparisons were calculated using the independent samples and paired samples t-tests. The association between the outcome and potential risk factors were calculated using the chi-squared test. We set the Type-I error rate at 5%, and used Bonferroni correction to account for the multiplicity of testing used in our analysis (Schlesselman, 1982).

The study was approved by the Research and Ethical Committee of the PSMMC, (project number 366, series of 2009) and funded by King Abdul Aziz City for Science and Technology (KACST) through the National Science, Technology and Innovation Plan (NSTIP).

Results

Cohorts and birth defects prevalence

During the study period (July 1, 2010 through June 30, 2013) there were 28,646 births, including 28,376 live births (98.9%), 252 stillbirths (0.9%), and 18 elective terminations of pregnancy for fetal anomalies (0.1%). There were 2107 fetuses aborted before 20 weeks of gestation. Of these 28,646 babies born during this 3-year period, 1262 were classified as controls before birth and 1179 had major birth defects, a prevalence of 41.1/1000 total births.

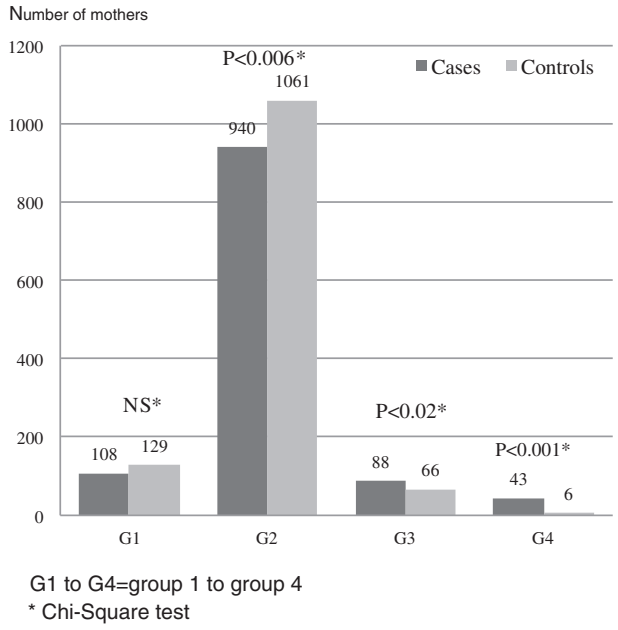

Fig. 1. Distribution of mothers in the case–control cohort according to their folic acid intake.

Folic acid groups

Of the 2441 mothers (case–control cohort), 237 (9.7%) were in the full FA intake group (9.2% among cases vs. 10.2% among controls), 2001 (82.0%) in partial FA intake group (79.7% vs. 84%), 154 (6.3%) in the no FA intake group (7.5% vs. 5.2%), and 49 (2.0%) in the not sure about FA intake group (3.6% vs. 0.5%). Fig. 1 shows the distribution of all mothers according to their FA intake. For mothers in the full FA intake (group 1), there were no significant differences between the numbers of mothers of babies born with BDs compared with controls mothers. However, the number of control mothers were significantly higher in the partial FA intake (group 2) ($p < 0.006$), while in the no FA intake (group 3) and the not sure mothers (group 4), there were more mothers of babies with BDs than mothers of control babies ($p < 0.02$ in group 3 and $p < 0.001$ in group 4).

Parental socioeconomic characteristics

Tables 1 and 2 show the physical and social characteristics of parents. The ANOVA test indicated a statistically significant deference between the group means in general ($p < 0.001$). Post hoc analysis showed that there were more mothers in groups 2 and 3 who were young, illiterate, unemployed housewives, and whose families were within the lowest family income category compared with groups 1 and 4.

The level of education (all grades) was significantly higher among mothers in group 1 (79.3%) compared with 69.4% of mothers in group 2 ($p < 0.01$). There were more employed and/or college student mothers in group 1 (29.5%) compared with mothers in group 2 (20.3%). There were 723 (29.7%) illiterate mothers; 859 (35.2%) primary school graduates; 672 (27.5%) secondary school graduates; and 187 (7.6%) university graduates among our case–control cohort.

Outcome of affected fetuses/babies and NTD prevalence

Table 3 shows infant and maternal characteristics for the babies with neural tube defects (NTDs). Group 4 (not sure of FA intake) mothers did not give birth to any babies with NTDs and were therefore not included in the table. The overall prevalence of isolated NTDs during the study period was 1.7/1000 total births. Of the 49 babies with NTDs, 18 (36.7%) were males with a male:female ratio of 1/1.7. Anencephaly was diagnosed in 25 fetuses or babies (0.9/1000 total birth) and 24 babies had spina bifida (0.8/1000 total birth). Among cases with anencephaly, there were 7 (28%) live births, 11 (44%) terminations, and 7 (28%) fetal deaths. Among spina bifida cases, 21 (87.5%) were live births, 2 (8.3%) were terminated and 1 (4.2%) was a fetal death. All the 5 babies born to mothers who took full course of FA were females.

Discussion

Our study in a population of pregnant Saudi women showed that 9.7% used FA supplementation beginning before and continuing after conception (recommended periconceptional intake); this incidence is low but comparable to the 6.8% incidence previously reported from

Table 1
Maternal characteristics for the case–control cohort according to their FA intake.

Characteristics	Full course FA (Group 1)[a]	Partial course FA (Group 2)[a]	No FA intake (Group 3)[a]	Not sure about FA (Group 4)[a]	Total
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
	237 (9.7)	2001 (82)	154 (6.3)	49 (2)	2441 (100)
Mother age (years)					
Mean ± SD	30.3 ± 5.9	29.7 ± 6.3	31.7 ± 5.3	31.0 ± 5.3	29.9 ± 6.3
95% CI	29.6–31.1	29.4–30.0	30.5–32.9	30.5–32.6	29.7–30.2
Range	17–43	14–47	15–47	22–47	14–47
p value	<0.001				
Parity					
Mean ± SD	2.8 ± 2.5	2.8 ± 2.6	4.1 ± 3.2	3.2 ± 2.4	2.9 ± 2.6
95% CI	2.5–3.1	2.7–2.9	3.6–4.6	2.5–3.9	2.8–3.0
Range	0–12	0–16	0–13	0–10	0–16
p value	<0.0001				
Maternal body mass index (kg/m^2)[b]					
Number (%)	236 (9.6)	1990 (81.5)	153 (6.3)	46 (1.9)	2425 (99.3)[b]
Mean ± SD	29.3 ± 5.7	28.2 ± 6.0	29.3 ± 6.1	31.5 ± 7.5[c]	28.5 ± 6.0
95% CI	28.5–30.0	28.0–28.5	28.3–30.3	29.3–33.7	28.2–28.7
Range	17.6–49.5	14.0–54.5	18.1–50.1	15.4–56.6	14.0–56.6
p value	<0.0001				

[a] Each group includes the total number of mothers of case and control babies.
[b] In 16 mothers either the weight or the height were missing.
[c] The p-value is the summary of the test of significance of the difference among the groups using the omnibus ANOVA methodology. It shows that the groups differ significantly with respect to mother's age, parity and BMI.

Table 2
Maternal social characteristics.

	Full course FA (Group 1)	Partial course FA (Group 2)	No FA intake (Group 3)	Not sure about FA (Group 4)	p value[a]
	Number (%)	Number (%)	Number (%)	Number (%)	
Maternal education					
Illiterate (no formal education)	49 (20.7)	594 (29.7)	60 (39.0)	20 (41.0)	<0.0001
Elementary school graduate	90 (38.0)	718 (36.0)	42 (27.3)	9 (18.4)	
Secondary school graduate	86 (36.3)	552 (27.6)	24 (15.6)	10 (20.4)	
Tertiary (university graduate)	12 (5.1)	137 (6.8)	28 (18.2)	10 (20.4)	
Total	237 (9.7)	2001 (82)	154 (6.3)	49 (2.0)	
Maternal occupation					
Housewife	167 (70.5)	1596 (79.8)	122 (79.2)	39 (79.6)	<0.01
Teacher	38 (16.0)	198 (9.9)	20 (13.0)	5 (10.2)	
Student	13 (5.5)	119 (5.9)	10 (6.5)	2 (4.1)	
Other occupations	19 (8.0)	88 (4.4)	2 (1.3)	3 (6.1)	
Total	237 (9.7)	2001 (82.0)	154 (6.3)	49 (2.0)	
Monthly combined family income in Saudi riyals ($US)					
<3000 (<800)	1 (0.4)	25 (1.2)	5 (3.2)	0	<0.0001
3000–6999 (800–1866)	48 (20.2)	438 (21.9)	31 (20.1)	6 (12.2)	
7000–9999 (1867–2666)	74 (31.2)	729 (36.4)	53 (34.4)	8 (16.3)	
10,000–14,999 (2667–3999)	55 (23.2)	417 (20.8)	36 (23.4)	5 (10.2)	
≥15,000 (≥4000)	53 (22.4)	249 (12.4)	16 (10.4)	5 (10.2)	
Unreported	6 (2.5)	143 (7.1)	13 (8.4)	25 (51.0)	
Group mean income (mean ± SD)	11,098 ± 6594	9433 ± 4958	9767 ± 6645	9997 ± 4926	
Total number of mothers in each group	237	2001	154	49	

[a] The chi-square test of independence of the groups from the variables of interest (education, occupation, income).

Saudi Arabia (Al-Akhfash et al., 2013), and from other countries in the region: Lebanon 14.0% (Tamim et al., 2009), Abu-Dhabi in the United Arab Emirates 7.8% (Al-Hassoni et al., 2010), and from Qatar and Oman 13.2% (Hassan and Al-Kharusi, 2008). Nevertheless, it is lower than the 32.0% incidence reported from Denmark (Hochberg and Stone, 2014) and 39.0% reported from the Netherlands (EUROCAT folic acid working group, 2009).

The 9.7% of periconceptional use of FA might reflect the low awareness about the importance of FA intake in the Saudi society. A study by Kari et al. (2008) reported that only 5.9% of female college students in Jeddah (a major city in western Saudi Arabia) were aware of the importance of receiving FA before and during pregnancy.

Mothers in group 2 (partial FA intake) represent 82% of our cohort group; this substandard use of FA could be improved through better education as reported by one author who showed that the higher the education status of the women, the higher is her knowledge about the benefit and importance of FA (Al-Hakeem, 2012). In addition, this could also be improved through planned pregnancies, as concluded by Tekkesin and Taser (2012) from Istanbul, Turkey. These authors reported a 100% periconceptional intake of FA among educated mothers who had previously planned their pregnancies compared with 67% of mothers who took FA periconceptionally following unplanned pregnancies, although they were at the same educated level. Over the last 50 years, Saudi society has undergone huge transformations because of the oil boom resulting in improvements in education and socioeconomic status of its citizens. This has led to the emergence of new merchant families, and a large number of technocrats with smaller family size among the new generations. Thus, a periconceptional intake of FA and family planning of pregnancy are feasible and acceptable options among the young Saudi and should be utilized.

In Saudi Arabia, it's mandatory for all couples to attend premarital counseling clinics. In addition to meeting their primary goals (general counseling, hepatitis B and HIV screening, sickle cell and thalassemia carrier testing), the clinic personnel could also educate women about the importance of periconceptional use of FA in preventing NTDs. Also, closed circuit television programs in the obstetric outpatient clinics can be used to educate illiterate women about the importance of FA supplementation during the periconceptional period.

Although we agree with Al-Akhfash et al. (2013) that mothers with higher levels of education have more knowledge of, and therefore greater use of FA during the periconceptional period, these authors reported that only 44/1000 (4.4%) Saudi mothers studied took FA before pregnancy, which we believe, is an underestimation of the current periconceptional use of FA by pregnant mothers in the kingdom of Saudi Arabia. In addition, 68/1000 (6.8%) of their sampled mothers took FA before pregnancy and during the first trimester of pregnancy. Thus an 11.2% of the mothers took supplemental FA at the proper time (periconceptionally), which is closer to the 9.7% incidence that we report here.

The prevalence of NTDs in our cohort was 1.7/1000 total births (0.17%) and 0.90/1000 live births (0.09%). A 2011 study from our institution had shown a NTD prevalence of 0.44/1000 live births. The study also showed an increase in prevalence over 10 year period (from 2001 to 2010) (Hakami and Majeed-Saidan, 2011). In our study, the prevalence of NTDs is higher than the 0.94/1000 births reported from the EUROCAT registries in Europe during the period 2004–2008

Table 3
Main infant and maternal characteristics for the 49 babies born with NTDs grouped according to the mother's FA intake.

Characteristic	Groups [a]		
	Full course FA N. (5)	Partial course FA N. (38)	No FA intake N. (6)
Baby			
Male births, N (%)	0 (0)	14 (36.6)	4 (66.6)
Baby's birth weight[b] (kg) mean ± SD	2.4 ± 0.4	2.3 ± 0.9	2.4 ± 1.1
Mother			
Mother's age (yrs.), mean ± SD	30.0 ± 4.8	30.7 ± 6.0	35.6 ± 4.2
Illiterate[c], N (%)	0 (0)	14 (36.6)	1 (16.6)
Housewives, N (%)[d]	2 (40)	32 (84.2)	1 (16.6)
First cousin's parents, N (%)	2 (40)	20 (52.6)	3 (50)
Multiparty ≥3, N (%)	2 (40)	21 (55.2)	4 (66.6)
Parity, mean ± SD	1.8 ± 1.6	2.9 ± 2.3	2.0 ± 1.5

N. = Number.
[a] Group 4 was not included because there were no cases of NTDs reported in this group.
[b] Mean baby's birth weight calculated for the live birth and stillbirth only.
[c] Illiterate mothers include mother who cannot read and write.
[d] Housewives mothers include mothers who do not work.

(Khoshnood et al., 2011). The optimal intake of FA before and during pregnancy can reduce the prevalence of NTDs to approximately 0.5/1000 births (Berry et al., 1999; De Wals et al., 2008). Botto et al. (2005) and Stoll et al. (2006) questioned the role of FA food fortification recommendation alone in preventing FA-preventable NTDs and suggested new strategies need to be implemented to prevent NTDs.

Accordingly, mandatory FA fortification of wheat flour and other grains including rice, a main staple food in Saudi Arabia, could reduce the current prevalence of NTDs substantially. Until such policy is in place for a few years, women of childbearing age should take the daily recommended supplementation of FA (0.4 mg per day).

Among the 49 babies born with NTDs in our study, all (100%) from mothers in group 1, and 24 of 38 (63.1%) from mothers in group 2 were females. This may indicate a selective gender protection in male fetuses and needs further study because these numbers are too small for a meaningful statistical analysis.

The Saudi women participating in this study were asked about their FA supplementation use early in their current pregnancies. This selection method differs from most other cross-sectional studies in which women were asked about their FA intake long after their delivery. Although Saudi women (dependent of military personnel) who were involved in this study represent a special sector of the Saudi society, we believe that the findings from this study may represent the actual status of women in the entire country because the Saudi army recruits personnel from various sectors of the Saudi society, although this could represent a limitation to our study.

Conclusion

Our study found a higher prevalence of NTDs in Saudi Arabia than from other industrialized countries, and highlights the need for a national health education program to educate women of childbearing age in high schools and colleges about the importance of receiving FA before they become pregnant; we also highlight the need for a wider implementation of mandatory FA fortification of staple foods in Saudi Arabia.

Conflict of interest letter

None of the authors has any conflict of interest to declare. None of them received any financial support from any drug companies.

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