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# Oral Contraceptives Induce Lamotrigine Metabolism: Evidence from a Double-blind, Placebo-controlled Trial

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**Summary:** *Purpose:* This study evaluates the effect of oral contraceptives on lamotrigine (LTG) plasma concentrations and urine excretion of LTG metabolites in a double-blind, placebo-controlled, crossover study in patients with epilepsy.

*Methods:* Women with epilepsy, treated with LTG in monotherapy and taking combination-type oral contraceptives, were randomized to treatment with placebo or a standard combination-type contraceptive pill. The dose-corrected trough plasma concentration of LTG and the ratio of *N*-2-glucuronide/unchanged LTG on urine after 21 days of concomitant placebo treatment was analyzed versus those after 21 days of concomitant treatment with the oral contraceptive pill.

*Results:* The mean dose-corrected LTG concentration after placebo treatment was 84% [95% confidence interval (CI), 45–134%] higher than after oral contraceptives, signifying an almost doubling of the concentration after cessation of oral contraceptives. Most of this increase took place within the first week after oral contraceptives were stopped. The *N*-2-glucuronide/LTG ratio in the urine was decreased by 31% (95% CI, −20–61%) when shifting from oral contraceptives to placebo.

*Conclusions:* Cessation of oral contraceptives leads to an 84% increase in the concentration of LTG. In parallel, the excretion of the *N*-2-glucuronide was decreased, indicating that the changes are caused by altered LTG glucuronidation. The change in LTG concentrations was observed within 1 week of the shift of treatment, suggesting that induction and deinduction of LTG glucuronidation is faster than that seen for other metabolic pathways (e.g., cytochrome P450). **Key Words:** Lamotrigine—Oral contraceptives—Interactions—UGT.

Lamotrigine is widely used as an antiepileptic drug (AED) in the treatment of new-onset as well as refractory epilepsy (French et al., 2004a; 2004b). Unlike most other AEDs, the major route (76%) of elimination of LTG is by conjugation with glucuronic acid (glucuronidation) (Dickins and Chen, 2002). This conjugation reaction is catalyzed by the uridine 5′-diphosphate (UDP)-glucuronosyltransferases (UGTs); of which the isoform UGT1A4 probably is the major route of metabolism in humans (Dickins and Chen, 2002). The pathway is inhibited by valproate (VPA) and induced by other anticonvulsants (Dickins and Chen, 2002), which explains the effect of these drugs on LTG metabolism (Patsalos and Perucca, 2003a). Estrogenic substrates are also metabolized by glucuronidation (Ebner et al., 1993; Tephly and Green, 2000; Shipkova and Wieland, 2005) and may potentially interact with the metabolism of LTG.

In the development of LTG for use in epilepsy patients, the effect on the oral contraceptive pill was studied. In contrast to other commonly used AEDs [e.g., carbamazepine (CBZ) and phenytoin (PHT)] (Patsalos and Perucca, 2003b), LTG did not significantly influence the constituents of the oral contraceptive pill (Holdish et al., 1991; Crawford, 2002; Doose et al., 2003). In addition, it was initially assumed from population pharmacokinetic studies that oral contraceptives did not influence the metabolism of LTG (Hussein and Posner, 1997). However, recent studies in patients and healthy subjects indicate that oral contraceptives may increase the metabolism of LTG, resulting in a significant decrease in the plasma concentration of LTG (Sabers et al., 2001; 2003; Browning et al., 2006; Sidhu et al., 2006). Additional studies indicate

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that this effect is probably related to the ethinylestradiol content of the combined contraceptive pill and not to progesterone (Reimers et al., 2005).

To confirm and further to extend these findings, the present study evaluated the effect of oral contraceptives on LTG plasma concentrations and the *N*-2-glucuronide metabolite on urine in a double-blind, placebo-controlled, crossover study in patients with epilepsy.

## METHODS

The study was conducted among outpatients with epilepsy at the Departments of Adult Neurology in Aarhus and Glostrup, Denmark. Women between 18 and 40 years of age with epilepsy, treated with LTG in monotherapy and taking combination-type oral contraceptives, were candidates for inclusion in the study. Patients agreed to use contraception of barrier type throughout the study (see later). They were not admitted to the study if any of the following criteria were present: (a) pregnancy, (b) breast-feeding, (c) abnormal liver function, (d) abnormal renal function, and (e) daily intake of drugs with known or suspected influence on the metabolism of LTG (acetaminophen and sertraline). Blood sampling at visits 1, 3, 4, 6, and 7 (Fig. 1) were used to monitor renal function (sodium, potassium, creatinine) and hepatic function (alkaline phosphatase, alanine aminotransferase, and bilirubin).

The study design is shown in Fig. 1. Patients were allocated to four periods of treatment with contraceptive pill or placebo, each consisting of 21 days of treatment followed by a 7-day pause. In the first period, all patients were given the same oral contraceptive (35 $\mu$g ethinylestradiol/250 $\mu$g norgestimat (Cilest). In the next period (period 2), patients were allocated to receive placebo or contraceptive pill. After a period during which all patients were given oral contraceptives, patients were allocated to receive the opposite treatment as given in period 2. The contraceptive pill was supplied in a gelatin capsule. Placebo was an identical gelatin capsule containing a size-matched glucose pill.

The daily LTG dose was divided into two equal doses taken at 08:00 and 20:00 h to minimize fluctuations in LTG concentrations. The intention was to keep the LTG dose unaltered during the trial. However, if a patient experienced adverse events thought to be dose related, or an increase in seizure frequency, the dose of LTG could be reduced or increased as desired. Blood samples were collected as trough values (i.e., before the next dose) at steady state (i.e., after 5 days of unaltered treatment). Urine was collected in the 12 h between the dose of LTG taken in the evening and immediately before the dose the following morning (i.e., between 20.00 and 08.00 h).

All LTG plasma samples were analyzed at the Department of Clinical Biochemistry, Aarhus University Hospital. LTG concentrations were determined in plasma by using reverse-phase high-pressure liquid chromatography. In brief, drugs were extracted on an RP-8, 40-$\mu$m cartridge and separated on an RP-18 end-capped (5 $\mu$m) 250-4 Lichrospher 100 column. Samples were analyzed as total concentrations. The detection limit in plasma was 1 $\mu M$, and the coefficient of variation was 5%.

LTG and *N*-2-glucuronide was determined on urine at the Division of Clinical Pharmacology, Karolinska Hospital, by using a modification of a liquid chromatographic–mass spectrometric method developed for analysis in plasma. The measuring range of LTG and *N*-2-glucuronide in urine was 3–500 $\mu M$. The coefficient of variation on urine was <5% for LTG and <16% for *N*-2-glucuronide (Beck et al., 2006).

Patients were given a diary and instructed to record adverse events, seizures, and drug intake. At each visit, these elements were evaluated. In addition, specific questions

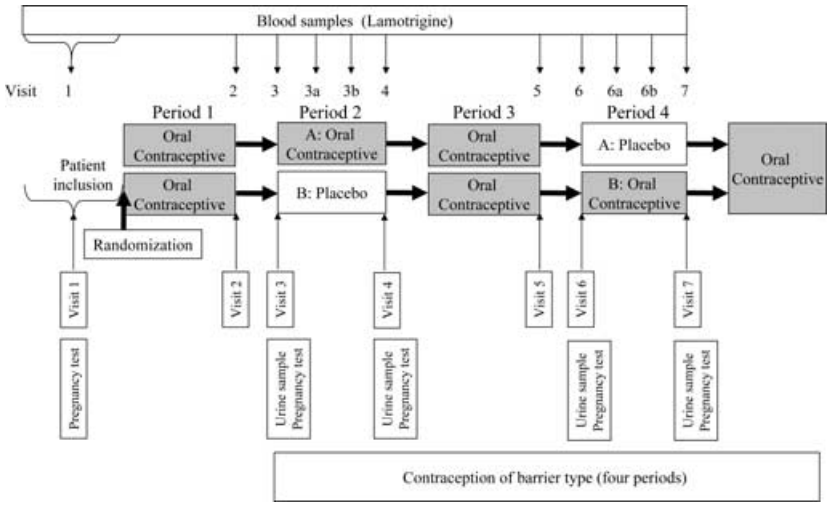


**FIG. 1.** Study design.

with regard to adverse events were asked for the following commonly reported adverse events associated with LTG therapy: (a) vertigo, (b) double vision, (c) headache, (d) fatigue, and (e) sleep problems. Each of these items was graded into low, medium, or high, if present.

In the present study, we tested the hypothesis that discontinuation of the contraceptive pill would lead to an increase in the plasma concentration of LTG. The primary end point was the mean dose-corrected trough plasma concentration of LTG after 21 days of placebo treatment compared with the mean dose-corrected plasma concentration of LTG after 21 days of treatment with the oral contraceptive (see Fig. 1). Secondary end points included the mean trough plasma concentration of LTG after the scheduled 7 days of pause with the oral contraceptive after the 21 days of treatment with oral contraceptives and the mean ratio of *N*-2-glucuronide to LTG on urine samples (placebo vs. oral contraceptives).

Power calculation was based on the assumption that the dose-corrected mean trough concentration of LTG in plasma would increase 80% after placebo versus oral contraceptives. Given a coefficient of variation of 25% on this efficacy parameter and a significance level of 5% ($\alpha = 0.05$), the allocation of five patients to each treatment arm would ensure a power >90%. Patients were randomized by using computer-assisted randomization to the order of treatment (A or B) in two blocks (Aarhus and Glostrup Hospitals). Treatment sequence A: oral contraceptives followed by placebo [Arhus (n = 3) and Glostrup (n = 2)]; and treatment sequence B: placebo followed by oral contraceptives [Arhus (n = 2) and Glostrup (n = 3)].

The order of treatment was unknown to all investigators and was contained in a set of sealed envelopes, each bearing only the trial name and patient number. All study personnel and participants were blinded to treatment assignment for the duration of the study. The Pharmacy at Aarhus University Hospital had a copy of the randomization code, but none of the staff had any contact with study participants. Plasma concentrations of LTG were not blinded (for safety reasons), and patient blinding was not evaluated. All patients who had corresponding blood samples taken at visit 4 and 7 were included into the statistical analysis. LTG data analysis was carried out according to a preestablished analysis plan. Log-transformed, dose-corrected LTG plasma concentrations and the ratio of *N*-2-glucuronide to LTG on urine at visits 4 and 7 were compared by using a special *t* test for the analysis of crossover studies (Armitage and Berry, 1996). The data were analyzed by Intercooled Stata 9.0 for Windows (StataCorp LP, College Station, TX, U.S.A.).

The investigation was conducted in accordance with Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95). Monitoring of the study was performed by the GCP-Units at Aarhus University Hospital (Jorgensen et al., 2000) and Glostrup Hospital. The regional scientific ethical committees, the Danish Medicines Agency, and the Danish Data Protection Agency approved the study.

## RESULTS

In total, 13 patients were enrolled, but only seven completed both visits 4 and 7. After $1\frac{1}{2}$ years of trial duration, it was not considered realistic to find more eligible patients to enroll, and, as a consequence, the trial was terminated. Of the six patients that dropped out of the study, four did so before receiving allocated treatment (i.e., before period 2). Of these patients, one patient reported side effects (tunnel vision and jerks) after the division of the LTG into two daily dosages; one patient started taking acetaminophen on a regular basis and discontinued LTG therapy because of adverse events (vertigo, double vision, headache, fatigue, and sleep problems), one patient did not follow the scheduled visit plan, and one patient decided that she would not participate in the study, without any specific reason declared. The two patients who dropped out after receiving allocated treatment gave no specific reason for failing to comply with scheduled visits. One dropped out in period 3, and the other in period 4 (allocated to taking oral contraceptives). Patient 4 was started on clobazam (Frisium; 5 mg/day) because of seizures in period 4 but was not excluded from the trial.

Baseline characteristics of the seven patients who were included in the primary analysis are shown in Table 1. All patients were white except for patient 1, who was of Sri-Lankan descent.

The LTG concentration in plasma and the ratio between *N*-2-glucuronide and LTG on urine at visits 4 and 7 is presented for individual patients in Table 1. The mean concentration of LTG in plasma increased by 84% (95% CI, 45–134%) after placebo treatment for 21 days versus oral contraceptive treatment for 21 days (Fig. 2A). The log-transformed plasma concentrations were analyzed for treatment, carryover, and period effect (Armitage and Berry, 1996). The treatment effect was significant ($p = 0.001$), and no sequence ($p = 0.94$) or period effect was observed ($p = 0.20$). The ratio between *N*-2-glucuronide and LTG on urine decreased by 31% (95% CI, −20–61%) after shift from oral contraceptives to placebo (Fig. 2B). The treatment effect was not significant ($p = 0.14$), and no sequence ($p = 0.18$) or period effect was found ($p = 0.65$). Figure 3 shows the relative change in the individual dose-corrected LTG plasma concentration for periods with oral contraception (Fig. 3A) and placebo (Fig. 3B). We analyzed the log-transformed plasma concentration of LTG in the treatment pause between visits 2 and 3, and 5 and 6, respectively. A mean increase in LTG plasma concentration of 73% (95% CI, 47–104%) occurred between visits 2 and 3, and 68% (95% CI, 25–125%) between visit 5 and 6 (patient 4 did not provide data, because plasma samples were missing from visits 3 and 6). The plasma

**TABLE 1.** *Baseline characteristics, daily dose, and plasma concentration of lamotrigine and urine concentration of N-2-glucuronide and lamotrigine*

| Patient no. | Treatment sequence | Age (yr) | Duration of epilepsy (yr) | Weight (kg) | Lamotrigine dose (mg) | | Plasma lamotrigine concentration ($\mu M$) | | Urine concentration of *N*-2-glucuronide ($\mu M$) | | Urine concentration of lamotrigine ($\mu M$) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | Visit 4 | Visit 7 | Visit 4 | Visit 7 | Visit 4 | Visit 7 | Visit 4 | Visit 7 |
| 1 | A | 25.1 | 1.5 | 50 | 400 | 400 | 27 | 36 | 3,410 | 3,507 | 76 | 143 |
| 2 | B | 19.5 | 14.7 | 63 | 400 | 400 | 26 | 11 | 6,007 | 4,734 | 144 | 93 |
| 3 | B | 24.2 | 14.1 | 54 | 400 | 400 | 25 | 14 | 3,871 | 2,824 | 81 | 58 |
| 4 | A | 27.3 | 13.4 | 65 | 600 | 700[a] | 32 | 50 | 3,273 | 3,811 | 140 | 188 |
| 5 | A | 31.6 | 17.7 | 61 | 600 | 600 | 17 | 42 | 3,794 | 1,056 | 80 | 91 |
| 6 | A | 25.1 | 15.8 | 60 | 600 | 700[a] | 18 | 32 | 3,102 | 5,706 | 75 | 111 |
| 7 | B | 21.0 | 6.0 | 52 | 150 | 150 | 18 | 8 | 1,620 | 1,089 | 65 | 24 |
| Mean (SD) | — | 24.8 (4.0) | 11.9 (5.8) | 57.9 (5.8) | 450 (166) | 478 (200) | 23.3 (5.7) | 27.5 (16.6) | 3,582 (1,304) | 3,246 (1,746) | 94 (33) | 101 (54) |

Treatment sequence A, oral contraceptives followed by placebo; treatment sequence B, placebo followed by oral contraceptives.
[a]Dose increased because of increased seizure frequency.

concentration of LTG decreased to the baseline value after 1 week of reinstitution of oral contraceptives (Fig. 3A), whereas for patients allocated to placebo, the LTG plasma concentration remained elevated but appeared to increase slightly further throughout the remaining period (Fig. 3B).

Three patients reported seizures during intake of oral contraceptives, whereas none reported seizures when taking placebo. Adverse effects thought to be associated with LTG treatment were assessed in detail, but their appearance did not seem to be specifically associated with concomitant placebo use (data not shown). No serious adverse events were reported. Patient 4 experienced seizures and had a low LTG concentration at an unscheduled visit during period 3 (i.e., during treatment with oral contraceptives). The LTG dose was increased, and clobazam (Frisium) was added. Patient 6 had a tonic–clonic seizure in period 3, prompting an increase of the LTG dose (Table 1).

## DISCUSSION

In this prospective controlled trial in patients with epilepsy, we showed that oral contraceptives significantly decrease the concentration of LTG and thereby confirmed findings from our previous retrospective studies (Sabers et al., 2003) and a study in healthy volunteers (Sidhu et al., 2006). The effect is probably by induction of the glucuronidation pathways involved in the metabolism of both ethinyl estradiol and LTG (Ebner el al., 1993; Tephly and Green, 2000; Dickins and Chen, 2002; Reimers et al., 2005; Shipkova and Wieland, 2005). This is supported by our finding of a (nonsignificant) mean decrease in the *N*-2-glucuronide/LTG ratio in urine of 31% when contraceptives were replaced by placebo, indicating that UGT metabolism of LTG is affected by oral contraceptives. The decrease in the *N*-2-glucuronide/LTG ratio in urine was not observed for two patients (patients 3 and 6) and indicates that, in these patients, other factors may explain the changes in plasma concentration. However, collection of urine is cumbersome, and the results most likely reflect inaccuracy in sampling of the urine. In addition, a relatively large variation exists in the accuracy of the analysis of the LTG and the *N*-2-glucuronide metabolite in urine, which may explain the deviations.

An important finding of this study is that the effect of ethinyl estradiol on the metabolism of LTG occurs rapidly. An increase and a subsequent decrease in LTG plasma concentrations was observed within 1 week, indicating that induction and deinduction of UGT pathways may be faster than that seen for other metabolic pathways (e.g., CYP450). This finding is similar to that of another study of the interaction between oral contraceptives and LTG, showing a 116% increase in LTG plasma concentration 7 days after a treatment period of 21 days with oral contraceptives (Sidhu et al., 2006). This is in contrast to the influence of physiologic hormonal fluctuations during an ovulatory cycle that were not associated with clinically

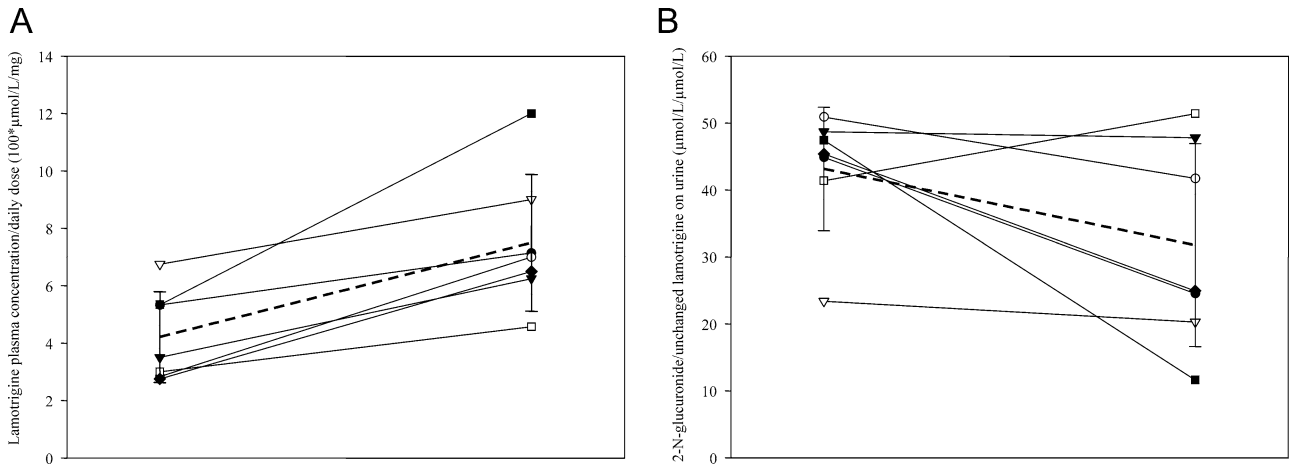


**FIG. 2. A:** Dose-corrected lamotrigine concentration in plasma after 21 days of treatment with placebo versus 21 days of treatment with oral contraceptives. **B:** Ratio of *N*-2-glucuronide to unchanged lamotrigine on urine after 21 days of treatment with placebo versus 21 days of treatment with oral contraceptives. ● Patient 1; ○ Patient 2; ▼ Patient 3; ▽ Patient 4; ■ Patient 5; □ Patient 6; ◆ Patient 7; – – Mean (SD).

relevant changes in LTG serum concentrations (Reimers et al., 2006). The increase in LTG plasma concentration after cessation of oral contraceptives may be sufficient to induce adverse effects in some patients (Sabers, 2001). The increase was observed shortly after cessation of oral contraceptives, and adverse events may thus potentially be observed even in the 7-day period between the 21-day treatment cycles. Information on specific adverse events was collected and quantified in this study, but no unequivocal pattern could be identified (i.e., more adverse events associated with concomitant placebo therapy). However, this study was not designed to show differences in adverse events and thus does not exclude the possibility that higher LTG plasma concentrations may induce adverse events in some patients. Seizures appeared to be more frequent in patients taking oral contraceptives compared with placebo. This may be due to the low LTG plasma concentration induced by oral contraceptives. However, several precautions should be taken when interpreting these findings: (a) the study was not designed to assess

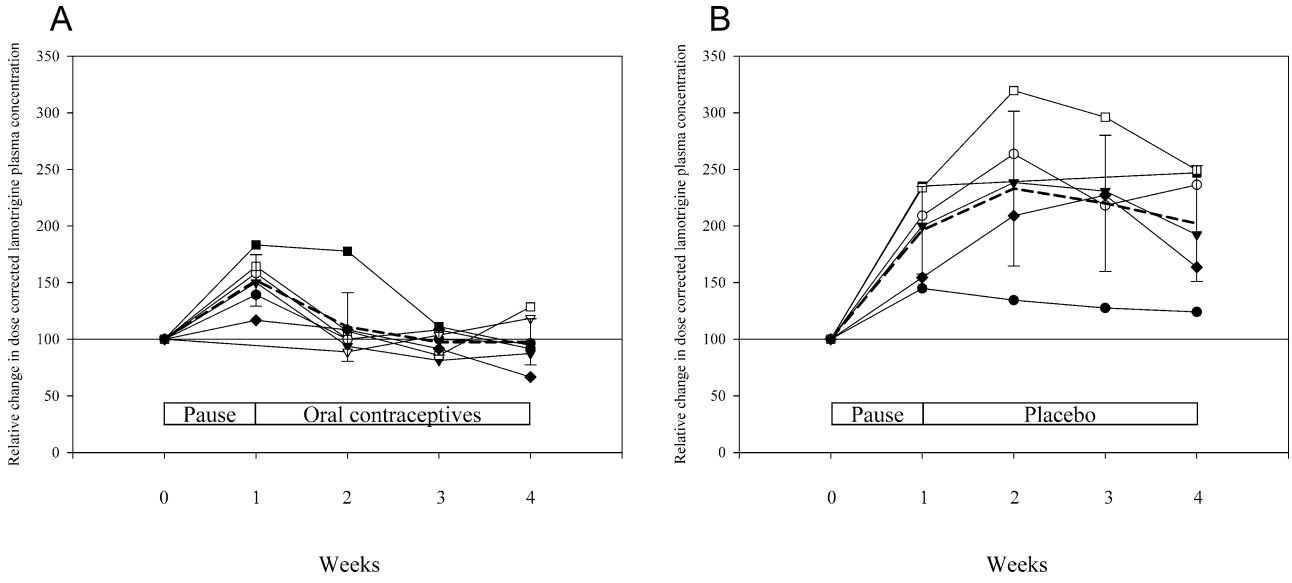


**FIG. 3.** Relative change in dose-corrected lamotrigine plasma concentration during treatment with oral contraceptives **(A)** and placebo **(B)**. ● Patient 1; ○ Patient 2; ▼ Patient 3; ▽ Patient 4; ■ Patient 5; □ Patient 6; ◆ Patient 7; – – Mean (SD).

seizure frequency and did not have sufficient power; (b) oral contraceptives per se, and not the low plasma concentration of LTG might contribute; (c) the plasma concentration of LTG was not blinded, and because the effect of oral contraceptives on LTG plasma concentrations was rather obvious, the treatment allocation was not effectively blinded; (d) two patients experiencing seizures had their LTG doses increased, and one patient had an additional drug (clobazam) added, all factors that might have influenced seizure frequency in the remaining part of the trial.

Thus in conclusion, use of oral contraceptives decreases the plasma concentration of LTG substantially within few days, probably because of increased UGT metabolism. Because of the magnitude of the decrease, a clinical significance is likely. The latter possibility should be addressed in further appropriately designed studies.

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