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Smoker Intake from Cigarettes in the 1-mg Federal Trade Commission Tar Class

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Cigarette yields measured by the standard analytical procedures of the U. S. Federal Trade Commission (FTC) may not be sufficiently informative to smokers of low-yield brands because actual intake is likely to depend mainly on the aggressiveness of personal behavior. This study determined intake in smokers of 1-mg FTC tar class cigarettes, as they switched brands. Plasma cotinine levels, used as a marker of intake, spanned over a similar range of values from non-detectable to about 800 ng/ml in all brands tested. Pharmacokinetic considerations suggest that smokers of these brands—as a group—intake nicotine in excess of posted FTC values. However, mean values across smokers for each brand, as well as the brand differences in individual smokers, were closely proportional to the analytical differences of FTC nicotine yields for each brand smoked. Thus, standard analytical values may not predict absolute intake of smoke, but they appear to inform about the relative intake smokers can expect from different brands in the 1-mg FTC tar class.

INTRODUCTION

Numerous studies of cigarette smoking indicate that the intensity of effects depends on the amounts inhaled (Surgeon General, 1981). On this basis, cigarettes of low smoke yield have been advocated as being less hazardous (Gori and Bock, 1980).

In the United States, cigarette yields are officially ranked using an analytical procedure adopted by the Federal Trade Commission (FTC) with wide concurrence (Pillsbury *et al.*, 1969). Similar methods are used in other countries. Lately, concerns over the differences of individual smoking behavior have questioned whether such standard methodology is relevant in providing the consumer with a realistic measure of expected intake (Kozlowski *et al.*, 1982; Russell *et al.*, 1982). The particular implication has been that variance may be more pronounced for smokers of low-yield cigarettes.

The present study set forth to measure the range of intake in individual smokers of three popular U. S. cigarette brands, advertised as nominally yielding 1-mg FTC tar. It also addressed the question of how smokers responded to small differences in FTC smoke yields as they switched among these brands.

At the present state of the art, smoke intake in man can be measured directly through suitable physiologic markers. The use of carbon monoxide (CO) for field

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studies is questionable, because smokers are exposed to CO from environmental sources and also from endogenous physiologic processes (Ashton *et al.*, 1981; Sjostrand, 1951).

Nicotine is a specific marker of tobacco smoke, although it is present in insignificant amounts in tomatoes, peppers, and eggplant. Its terminal half life is over 100 min in the bloodstream (Armitage *et al.*, 1975; Benowitz *et al.*, 1982; Cohen and Roe, 1981; Gritz *et al.*, 1981; Rosenberg *et al.*, 1980), and likely to make its determination sensitive to short-term sampling variables and dependent on the last two or three cigarettes smoked. This is of concern because individuals smoke with different intensity at different times. Ideally, a marker should give an average indication of the cumulative results of discrete intake episodes over a suitable period of time, and not simply a momentary experience.

Cotinine is a principal and direct metabolite of nicotine, from which it arises at predictable and rates (Cohen and Roe, 1981; Gritz *et al.*, 1981; Langone *et al.*, 1973; Matsukura *et al.*, 1979; Rosenberg *et al.*, 1980). This correspondence is confirmed by a high linear correlation of nicotine and continine plasma levels, as reported later in this study and by others (Gritz *et al.*, 1981). A terminal half-life of about 20 hr (Cohen and Roe, 1981; Langone *et al.*, 1973; Matsukura *et al.*, 1979) only requires that subjects be sampled during late afternoon and at fixed days during the week, to synchronize weekly and circadian steady-state patterns (Gritz *et al.*, 1981). On this account, cotinine is a better indicator of overall cumulative smoke intake.

Significantly, nicotine is delivered in close physical association with tar particles (George and Keith, 1967). Only a negligible amount is delivered in the vapor phase, and at the average pH of cigarette smoke most of it is not absorbed in the upper respiratory tract but rather in the lung, where it is rapidly transferred to the bloodstream (Armitage, 1973). Because of this, nicotine and cotinine are also valid indicators of tar intake, once the ratio of tar to nicotine of a cigarette's smoke is known.

The experiment was designed so that it could be analyzed as a sequential one, in a self-matching design where individual smokers provide their own control.

MATERIALS AND METHODS

Cigarettes. The study utilized three commercial brands in the 1-mg FTC tar class, purchased from commercial distributors. Each brand came from the same production batch, to minimize input variance. Specific analytical data are summarized in Table 1. Analysis of cigarette yields was performed according to FTC procedures (Pillsbury *et al.*, 1969), utilizing 400 cigarettes per brand.

Subjects. Subjects were selected who customarily smoked either brand A or brand B yielding 1 mg nominal FTC tar. The subjects (117 men and 171 women) were approached randomly in shopping malls and through notices in community newspapers in each of five cities. Qualified respondents were at least 21 years of age, had been smoking at least 20 cigarettes daily for at least 3 months, and engaged in no other smoking-related practices (cigars, pipes, snuff, chewing tobacco, nontobacco smoking products). Only individuals in good health, nonpregnant, and under no medication were recruited. Subjects were dropped from the study if disease or medical treatment intervened. Individuals with alcoholic problems were also excluded. Each subject was informed at the outset that participation in the study would require

TABLE 1

ANALYTICAL DATA OF CIGARETTES TESTED[a]

Brand	Batch code	Mean and SD[b]	
		Tar	Nicotine
A	1XL	0.9 ± 0.2	0.18 ± 0.02
B	00025	0.5 ± 0.2	0.10 ± 0.02
C	EB	0.6 ± 0.2	0.11 ± 0.02

[a] All cigarettes 85 mm length, filter, soft pack.
[b] In milligrams per cigarette. Four hundred cigarettes per brand were tested.

smoking specific 1-mg tar brands provided free of charge; they also were asked not to consciously change any of their customary smoking practices.

Schedule. On their first visit, the subjects completed a brief questionnaire on their smoking history and related factors, and provided a 10-ml sample of blood. Subjects were always sampled in the late afternoon on Wednesdays or Thursdays.

Each respondent was given a week's supply of his/her own customary brand of cigarettes to smoke for the following week, and a cigarette tally sheet to record the exact time for each cigarette smoked since the day preceding sampling. They were also provided with special containers to collect all cigarette butts during the tallying period as objective evidence of consumption. Respondents reported on the following week and again provided blood samples, obtained additional cigarettes, and turned in the tally sheets and collected butts.

At this point, smokers of brand A were given brand B and vice versa. Respondents stayed on the alternate brand for 3 weeks, reporting to the test center weekly to provide blood samples, etc. Starting with the fifth visit to one of the test centers, all respondents were given brand C cigarettes to smoke for 2 weeks, once again reporting to the center each week for blood samples, etc. All subjects received a nominal monetary compensation at each sampling.

Nicotine–cotinine correlation. A separate group of 45 male and 41 female smokers of 1-mg tar cigarettes was recruited for validating plasma cotinine as a marker of plasma nicotine and smoke intake. These subjects had the same general characteristics as the main group above, but special precautions were taken to ensure that daily steady-state levels of nicotine and cotinine were synchronized, as required by pharmacokinetic considerations and previous experiences (Gritz *et al.*, 1981). Subjects in this group habitually smoked at regular intervals during the day, and especially during the 3 hr preceding the sampling, which occurred on a Thursday between 5:00 and 7:00 PM. A control group of 23 male and 26 female nonsmokers was also recruited and sampled once for plasma nicotine and cotinine.

Blood samples. Blood samples were drawn by a certified technician; plasma was obtained by centrifugation and frozen without preservatives within 15 min of being drawn. Samples were blind coded and stored frozen at −20°C or below until assayed.

Cotinine and nicotine analysis. Cotinine and nicotine were determined using published methods (Jacob *et al.*, 1980). Standard curves were constructed and repeated every 40 determinations, by using the internal standards *N*-ethylnornicotine for nicotine, and *N*-(2-methoxyethyl) norcotinine for cotinine. The peak height correlation

was linear over the range 25 to 600 ng/ml for cotinine, and 0-100 ng/ml for nicotine. Throughout the procedure, precautions were taken to avoid exogenous contamination (Feyerabend and Russell, 1980). As a quality control check, 178 plasma samples were selected randomly for reanalysis of cotinine values. The average of the original values was 245 ng/ml, with a standard error of the mean (SEM) of 11.4 ng/ml. The duplicate values had an average of 258 ng/ml, with SEM of 11.9 ng/ml. The simple correlation coefficient between the original and duplicate values was 0.93, and the paired t test was not statistically significant ($P > 0.05$). For nicotine, 21 samples were selected at random for reanalysis. The average of the original values was 26.3 with SEM 2.5 ng/ml; the duplicate set had an average of 26.8 with SEM 2.3 ng/ml. The paired t test value was not statistically significant ($P > 0.05$).

To exclude possible interferences from other compounds, a random group of samples was analyzed by high-resolution gas chromatography and mass spectrometry (GS/MS). Ten plasma samples, previously analyzed as above, were processed according to the standard analytical methodology for the determination of cotinine. Prior to GC/MS analysis, the sample extracts were pooled and concentrated to a volume of 20 μl. A 1-μl aliquot was then analyzed by GC/MS. The GC/MS conditions were as follows.

GC/MS: Finnigan 4000
AMU range: 35–450
Scan speed: 1 scan/sec
Mode: Electron Impact, 70 eV, positive ion
Column: Fused silica, 30 m × 0.312 mm
Flow rate: 2 ml/min helium
Liquid phase: DB5, J & W Scientific
Temperature program: 50°C (4 min) to 280°C at 8°C/min
Injector temperature: 260°C
Injection volume: 1 μl, splitless

No interfering molecules were found. The calculated concentration of cotinine was 594 ng/ml by GC/MS, which compared favorably with the 526 ng/ml measured by the GC analysis routinely used.

RESULTS

Subject characteristics. General characteristics of the subjects entering the study are summarized in Table 2. The groups represented predominantly white collar occupations and housewives. Male–female differences were reflected throughout the results, thus calling for separate analysis of the data.

Plasma cotinine. Table 3 summarizes weekly trends of mean values for plasma cotinine measurements separated by groups having homogeneous characteristics, i.e., by the brand of cigarettes customarily smoked and by sex. Baseline values were averaged over the two initial measurements taken. Expected values were based on the FTC nicotine yield ratios for the brands smoked (Table 1). No statistically significant differences were noted between observed and expected values in a self-matching paired t test analysis, except in the two instances given in Table 3. Although significant, these two deviations were small.

TABLE 2

RESPONDENT CHARACTERISTICS AT FIRST ENTRY

Customary brand of cigarette	Number of respondents		Average No. of months smoking customary brand		Average No. of cigarettes smoked/day		Average age	
	M	F	M	F	M	F	M	F
Brand A[a]	67	75	5.2 (0.4)	6.4 (0.4)	30.6 (0.8)	29.8 (0.9)	35.3 (1.1)	38.4 (1.2)
Brand B	50	96	10.8 (0.5)	10.6 (0.4)	30.2 (1.1)	27.7 (0.7)	39.8 (1.7)	39.1 (1.2)

Note. Standard error of the mean in parentheses.

[a] Brand A had been introduced on the market about 10 months prior to the study. Brand B had been on the market for several years.

The results indicate that—after switching brands—habitual smokers of brand A reached the plasma cotinine levels of habitual smokers of brand B and vice versa. They also indicate a consistent stability of individual plasma cotinine levels week after week.

TABLE 3

WEEKLY TRENDS OF PLASMA CONTININE IN SMOKERS OF DIFFERENT BRANDS

	Week	Subjects Customarily smoking			
		Brand A		Brand B	
Sex		M	F	M	F
Initial subjects		67	75	50	96
Customary brand	1	334	312	228	201
Customary brand	2	308	333	176	178
Baseline, overall		317 (13.9)	328 (18.0)	206 (16.8)	189 (10.9)
Alternate brand[a]	3	209	207	305	291
Alternate brand[a]	4	235	210	342	286
Alternate brand[a]	5	228	201	320	273
Alternate brand[a] overall		222 (13.9)	207 (18.5)	322 (24.5)	284[b] (15.4)
Brand C	6	240	212	202	192
Brand C	7	230	197	238	179
Brand C, overall		235 (17.3)	203 (14.0)	223 (20.2)	185[c] (11.6)

Note. Statistical significance was determined on a self-matching basis, paired t tests (two tailed), after adjusting individual values for the number of daily cigarettes consumed. Values expressed as means and SEM in nanograms per milliliter.

[a] Brand A for brand B smokers and vice versa.

[b] Significantly lower than expected, $P < 0.05$.

[c] Significantly lower than expected, $P < 0.01$.

In an overall assessment, Table 4 summarizes the results for all respondents as they smoked the three brands tested. Because the level of cotinine partially depends on the number of cigarettes smoked daily, a normalization was carried out for each data point of each respondent, dividing individual plasma cotinine values by the number of daily cigarettes used prior to that sampling. Averages of these normalized values are given in Table 4. The ratios of these averages agreed well with the ratios of the analytical nicotine yields of the cigarettes tested (Table 1). The correspondence is especially clear for the baseline mean plasma cotinine values for brands A and B, which are presumably undisturbed by experimental stress (Fig. 1). Maximum recorded values of plasma cotinine are also given in Table 4, indicating that each brand tested generated a similar range of values. The sample coefficient of skewness was calculated for each experimental set of values. In all cases the coefficient was positive, suggesting a slight dispersion of values to the right of the mean. No coefficient was significantly greater than zero, nor did any coefficient change significantly for any group.

Number of cigarettes smoked daily. Table 5 summarizes the average number of cigarettes smoked daily, separated by the brand customarily smoked and by sex. In all four groups of respondents, brand A cigarettes were smoked the least. The men smoked the largest numbers of cigarettes while on brand C and the women smoked the largest numbers of cigarettes while on brand B. The average change was always below 10%. Paired t tests for each individual experience revealed no significant differences at the 5% level, suggesting negligible compensation in the number of cigarettes smoked daily.

Nicotine–cotinine correlation and nonsmoking controls. Figure 2 gives data from the group of 86 subjects expressly sampled to explore the correlation of plasma nicotine and cotinine. The linear correlation coefficient $r = 0.84$ was significant at $P < 0.001$. In the control group of nonsmokers, no subject had a detectable level of plasma cotinine (25 ng/ml or greater). Plasma nicotine in the males ranged from 0.5 to 4.8 ng/ml, with a mean of 1.9 and 0.3 ng/ml SEM. For the females, the plasma nicotine ranged from nondetectable to 7.7 ng/ml, with a mean of 1.5 and 0.3 ng/ml SEM. The male and female subjects combined had a mean plasma nicotine level of 1.7 and 0.3 ng/ml SEM.

Observed and expected plasma cotinine values. Available data on the pharmacokinetics of nicotine and cotinine (Armitage *et al.*, 1975; Benowitz, 1982; Benowitz

TABLE 4

SUMMARY OF PLASMA COTININE VALUES IN SMOKERS OF DIFFERENT BRANDS

	Brand A	Brand B	Brand C
Mean plasma cotinine, ng/ml (SEM)	301 (10.1)	204 (8.2)	208 (8.2)
Maximum value recorded, ng/ml	833	859	899
Mean cigarettes smoked daily	29.0	30.5	31.1
Mean normalized plasma cotinine, ng/ml[a]	10.8	6.8	6.7
Ratio to brand C[b]	0.16	0.10	0.10
Nicotine mg/cigarette	0.18	0.11	0.10

[a] For each respondent, plasma cotinine values were divided by his/her average daily cigarette consumption. Averages of overall results are reported.

[b] Ratios of the normalized plasma cotinine values taking the brand C value as 0.10.

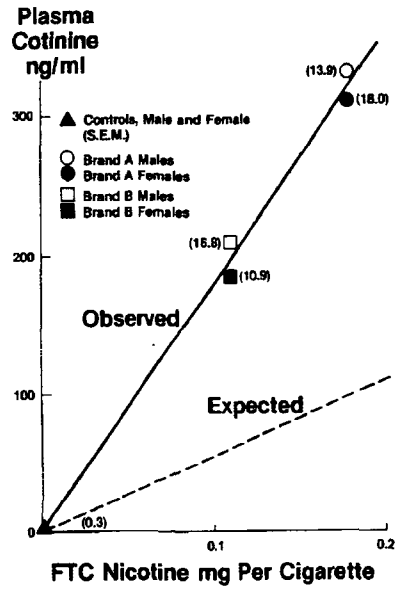

FIG. 1. Observed and expected baseline plasma cotinine values as a function of FTC nicotine delivery of brands A and B.

et al., 1982; Cohen and Roe, 1981; Gritz *et al.*, 1981; Langone *et al.*, 1973; Matsukura *et al.*, 1979; Rosenberg *et al.*, 1980) allow a rough estimate of the expected mean values of maximum plasma cotinine levels reached at virtual daily steady-state conditions ($C_{max.ss}$), if the nicotine intake per cigarette were equivalent to the FTC(N) analytical values. The parameters utilized in the estimate were: cotinine half-life h = 20 hr (Benowitz, 1982; Langone *et al.*, 1973); volume of distribution for cotinine V_d = 1000 ml/kg (Benowitz, 1982); interval between cigarettes dt = 32 min (equivalent to 30 cigarettes/day); conversion rate of nicotine to cotinine $k_{n\to c}$ = 0.7 (Cohen and Roe, 1981); and average weight of subjects W = 70 kg. The equation becomes (Curry, 1980)

$$c_{max.ss} = \frac{FTC(N) \times K_{n\to c}}{W \times V_d} \Big/ (1 - (0.5)^{dt/h}).$$

Figure 1 indicates that—as a group—smokers of the low-yield brands tested tend to intake nicotine in excess of posted FTC values. Plasma cotinine in smokers may not

TABLE 5

DAILY CIGARETTE CONSUMPTION IN SMOKERS OF DIFFERENT BRANDS

Customary brand	Sex	Baseline range	N	Means and (SEM)		
				Brand A	Brand B	Brand C
Brand A	M	20–52	67	31 (0.4)	33 (0.7)	34 (0.7)
Brand B	M	20–51	50	30 (0.8)	31 (0.4)	33 (1.1)
Brand A	F	20–55	75	29 (0.3)	31 (0.6)	30 (0.8)
Brand B	F	20–47	96	27 (0.5)	28 (0.2)	29 (0.6)

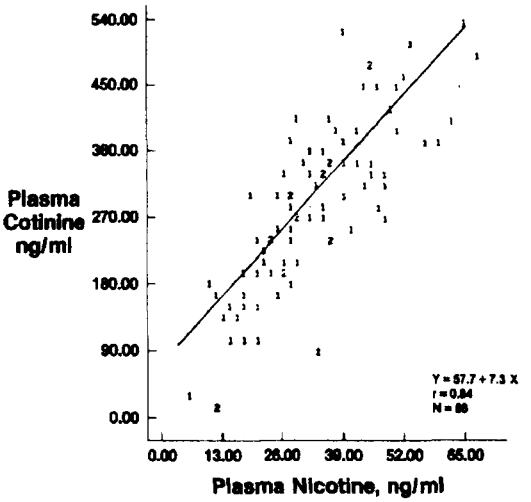

FIG. 2. Plasma cotinine values as a function of plasma nicotine values. Males and females.

reach true steady-state conditions on account of the long half-life; thus, the actual difference between expected and observed values may be wider than estimated. Although informative, it is necessary to emphasize the uncertain quantitative meaning of these conclusions, owing to the diverse sources and natural variance of the parameters utilized in this estimate, and to the approximation of assumptions.

Plasma cotinine as a function of cigarettes smoked daily. Figure 3 relates baseline plasma cotinine of female smokers to available daily nicotine (ADN), defined by the FTC nicotine yield of the cigarette smoked (FTC(N)) and the number (CPD) of cigarettes smoked daily: ADN = FTC (N) × CPD. A positive correlation is discernible, although the variance is large at $r = 0.47$. A similar distribution was noted for males, with $r = 0.55$. Both correlation coefficients were significantly greater than zero

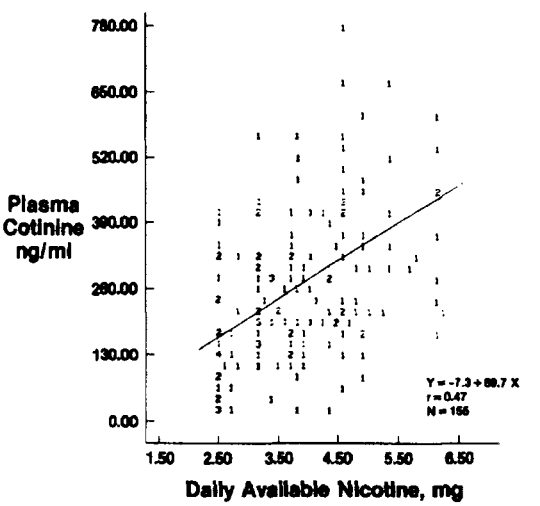

FIG. 3. Baseline plasma cotinine as a function of available daily nicotine, defined by the FTC nicotine mg/cigarette and the cigarettes smoked per day: ADN = FTC (N) × CPD. Males.

($P < 0.01$). The coefficients did not improve after adjusting cotinine values for subject weight, indicating that behavioral and sampling factors are the more likely sources of variance, metabolic factors probably being stable, as suggested by the high correlation between plasma nicotine and cotinine.

DISCUSSION

Plasma nicotine and cotinine correlation. The kinetics of nicotine intake, excretion, and metabolism are known to depend on differences in individual behavior, weight, lean body mass, urinary pH, etc., resulting in measurably different plasma nicotine and cotinine values in various individuals smoking the same cigarettes (Armitage *et al.*, 1975; Benowitz *et al.*, 1982; Cohen and Roe, 1981; Gritz *et al.*, 1981; Langone *et al.*, 1973; Matsukura *et al.*, 1979; Rosenberg *et al.*, 1980; Russell *et al.*; 1982). Moreover, the metabolism of nicotine in the liver, its major site of detoxification, is mediated by *P*-450 microsomal enzymes that can be activated or depressed by a number of dietary components, alcohol, drugs, pathologic, and physiologic conditions (Cohen and Roe 1981).

However, two observations in this study suggest that these potential sources of variance are relatively small in our sample, and at least within the range of plasma concentrations measured. One is the high correlation of plasma levels of nicotine and cotinine (Fig. 2), which confirms previous findings (Gritz *et al.*, 1981). The other is the remarkable stability of individual plasma cotinine values week after week, while smoking the same cigarette (Table 3).

The validity of these results is reinforced by the positive correlation of plasma cotinine levels and the number of cigarettes smoked daily (Fig. 3).

Intake. Any of the brands tested resulted in plasma cotinine levels over a similar range of values. The virtually unchanging number of daily cigarettes smoked by individuals, and the correlation of plasma nicotine and cotinine values, indicate that the same statement is valid for nicotine intake. In turn, the physical association of nicotine and tar in cigarette smoke, and the nearly equal tar to nicotine ratio of the brands tested, suggest that similar conclusions are probably valid for tar intake. However, inferences on tar intake will have to be further verified by direct experimental evidence on the tar to nicotine ratio in individual smokers, which is bound to vary under different conditions of ventilation, puff volume, profile, duration, frequency, etc.

Previous studies found that compensation under experimental switching conditions is usually only partial (Russell *et al.*, 1982). For the nominal 1-mg FTC tar cigarettes tested in this study, small absolute differences in analytical cigarette yields did not change daily cigarette consumption, and resulted in plasma cotinine levels proportional to such differences of FTC nicotine yields for the brands smoked (Fig. 1), suggesting no behavioral compensation upon switching. For individual smokers, this proportionality occurs within a limited segment of the overall range of observed values, high inhalers remaining high, and vice versa. This suggests that individual smokers of 1-mg tar cigarettes may find satiation at different levels of nicotine and smoke intake, probably reflecting the influence of exertion and effort in extracting smoke from low-yield brands. For equal exertion, smokers may attain nicotine intakes roughly proportional to the cigarette yields. Regardless of the proportionality of plasma

cotinine and FTC nicotine for different brands, it is also apparent that most smokers of low-yield cigarettes compensate upward, and extract nicotine—and hence smoke—in excess of what the FTC yields of individual brands imply (Fig. 1).

CONCLUSIONS

This study suggests that FTC values for low-yield cigarette brands understate the actual intake of average smokers. However, they appear to offer a valid representation of the relative intake that individual smokers can expect from the 1-mg FTC tar class cigarettes tested, and probably from similar brands in that class.

Since FTC values should be interpreted as having relative rather than absolute significance, they remain valid in ranking the expected mean relative intake from cigarettes in the 1-mg FTC tar class. The meaning of FTC values in ranking higher-yield cigarettes is being investigated in separate studies.

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