Meta-analysis of the effect of an essential oil–containing mouthrinse on gingivitis and plaque

Marcelo W.B. Araujo, DDS, MS, PhD; Christine A. Charles, RDH, BS; Rachel B. Weinstein, PhD; James A. McGuire, MS; Amisha M. Parikh-Das, PhD, MPH; Qiong Du, MMS; Jane Zhang, PhD; Jesse A. Berlin, ScD; John C. Gunsolley, MS, DDS

ABSTRACT

Background. Standard recommendations for oral hygiene practices have focused on mechanical methods (toothbrushing and interdental cleaning). Published evidence indicates antimicrobial mouthrinses provide oral health benefits beyond mechanical methods alone. The purpose of this meta-analysis was to evaluate the combined effectiveness of mechanical methods with essential oil–containing mouthrinses (MMEO) versus mechanical methods (MM) alone in achieving site-specific, healthy gingival tissue and reducing plaque and gingivitis.

Types of Studies Reviewed. All industry-sponsored clinical trials investigating the antigingivitis and antiplaque effects of essential oil (EO)–containing mouthrinses conducted from 1980 to 2012 were reviewed; 29 of 32 studies met the inclusion criteria of 6 months or longer duration, randomized, observer-masked, placebo-controlled, and with individual-level site-specific data. By-study treatment effects were estimated through generalized linear models for binary data and analysis of covariance for continuous data, and then combined using standard meta-analysis techniques; heterogeneity was also assessed.

Results. Summary odds ratios for a healthy gingival site and for a plaque-free site were, respectively, 5.0 (95% confidence interval [CI], 3.3-7.5) and 7.8 (95% CI, 5.4-11.2) for MMEO participants versus MM participants at 6 months. The summary percentage reductions in whole-mouth mean gingivitis and plaque at 6 months were 16.0 (95% CI, 11.3-20.7) and 27.7 (95% CI, 22.4-32.9), respectively. Responder analyses using aggregate individual-level data showed 44.8% of MMEO participants and 14.4% of MM participants achieved at least 50% healthy sites in their mouths at 6 months. Similarly, 36.9% of MMEO participants and 5.5% of MM participants achieved at least 50% plaque-free sites in their mouths at 6 months.

Conclusions and Practical Implications. This is the first meta-analysis to demonstrate the clinically significant, site-specific benefit of adjunctive EO treatment in people within a 6-month period (that is, between dental visits).

Key Words. Meta-analysis; antiplaque; antigingivitis; oral hygiene; mouthrinse; essential oils.

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Oral health is integral to the general health and well-being of patients.[1-5] Although largely preventable, oral disease is recognized to significantly burden the economic, psychological, and social development of communities across the globe.[6] Gingivitis and other periodontal diseases continue to exist as serious challenges on a global scale. The Third National Health and Nutrition Examination Survey (NHANES) publication (NHANES III) reports gingivitis prevalence to be 86% of the adult US population,[1] whereas studies in Latin America report it to be as high as 100%[7] and affecting over 95% of adults in Southeast Asia.[8] In the United Kingdom, the Adult Dental Health Survey (2009) found that 54% of dentate adults had bleeding in the mouth, which is a sign of gingival inflammation.[9]

Treatment and prevention of gingivitis are important because, if left untreated, it can progress to more advanced periodontal disease.[5] Recommendations on oral hygiene practices from dental practitioners have largely focused on the mechanical methods of daily oral hygiene, including toothbrushing and interdental cleaning as standards to achieving and maintaining good oral health.[10] However, systematic reviews and meta-analyses have reported that mouthrinses can provide a benefit beyond mechanical oral hygiene alone in preventing plaque accumulation and gingivitis.[3,10-12]

Published and unpublished evidence was collected by the sponsor (Johnson & Johnson Consumer Companies) from 32 long-term randomized clinical trials that totaled more than 5,000 healthy participants with gingivitis for whom an essential oil (EO)–containing

antimicrobial mouthrinse (Listerine, Johnson & Johnson) was used.[13-41] These studies were conducted for various reasons, including demonstrating efficacy of flavor variants, investigating modifications in formula excipients or process, examining efficacy and safety comparisons with marketed products, or evaluating oral hygiene regimens in comparison with mechanical methods.

All studies were designed to meet the commonly accepted professional and regulatory standards set by the American Dental Association (ADA) and the US Food and Drug Administration (FDA).[42,43] The unpublished studies were not previously made available to the general public as peer review articles because some of them were implemented either to support regulatory submissions, applications for a seal of acceptance, or for internal knowledge. However, in the context of the recent movement of biomedical science toward increased data sharing, it is important that results from these long-term studies are disclosed to the scientific community, thereby contributing to evidence-based research in dentistry.

The purpose of this meta-analysis was to compare the degree of response to therapy (mechanical only versus mechanical with essential oil mouthrinse use) toward achieving gingival health. The primary objective was to compare the efficacy of combined mechanical oral hygiene and use of essential oils containing mouthrinses with that of mechanical oral hygiene (negative control) based on the percentage of healthy gingival sites identified at 6 months. A second objective was to examine treatment effects using other summary measures based on the plaque index (PI). Lastly, we evaluated and reported potential sources of heterogeneity of the treatment effect as related to differences among studies and study results.

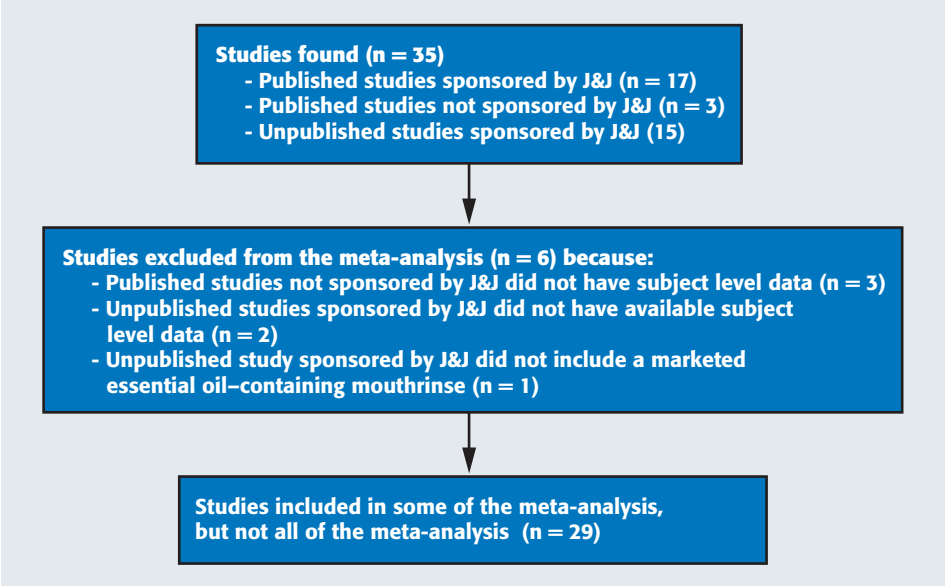

Figure 1. Study inclusion and exclusion criteria. J&J: Johnson & Johnson.

METHODS

Individual study protocols were reviewed by each institutional review board committee at the time the individual study was conducted. This meta-analysis protocol was registered on PROSPERO (www.crd.york.ac.uk/PROSPERO, registration number: CRD42013006356), an international prospective register of systematic reviews and meta-analyses.

Types of studies included. Thirty-two clinical studies, 6 months or longer duration, observer-masked, parallel, randomized, placebo-controlled, sponsored by Johnson & Johnson Consumer Companies and its predecessors that assessed the effect of marketed mouthrinses containing the fixed combination of 4 essential oils on gingivitis and plaque were considered for this meta-analysis. Twenty-nine studies met the inclusion criteria for this meta-analysis as individual-level data were required for both the site-specific measures in the meta-analysis and in the responder analysis. Twenty-nine studies were included in the gingivitis analyses, 27 of those studies were included in the analysis of the primary outcome variable, and 28 studies were included in the plaque analyses. It is not clear if other researchers of EO-containing mouthrinses have conducted 6-month clinical trials according to the ADA guidelines. Therefore, other trials of the intervention were not included, as not all published 6-month trials adhered to the ADA guidelines, utilized the modified gingival index (MGI), included a placebo control, and most importantly, had

ABBREVIATION KEY. **ADA:** American Dental Association. **B/F:** Brushing and flossing. **DOF:** Data on file. **EO:** Essential oil. **FDA:** Food and Drug Administration. **GI:** Gingival index. **H:** 5% Hydroalcohol control. **J&J:** Johnson & Johnson. **MGI:** Modified gingival index. **MM:** Mechanical methods alone. **MMEO:** Mechanical methods with essential oil–containing mouthrinses. **N:** No. **NHANES:** National Health and Nutrition Examination Survey. **PI:** Plaque index. **SW:** Sterile colored water control. **Y:** Yes.

TABLE 1

Summary of study characteristics.

STUDY	YEAR STUDY INITIATED	COUNTRY	DENTAL PROPHYLAXIS	SUPERVISED RINSING	FLOSSING	PLAQUE INDEX NO. SURFACE	NEGATIVE CONTROL RINSE OR B/F*	MEAN GINGIVITIS INCLUSION CRITERIA	MEAN PLAQUE INCLUSION CRITERIA
Menaker & Ross,[13] 1981 (DOF†)	1980	United States	Y‡	Y	N§	2	V¶	2.00	2.00
Lamster and Colleagues,[14] 1983	1981	United States	N	Y	N	6	V/SW#	2.00	1.80
Gordon and Colleagues,[15] 1985	1981	United States	Y	Y	N	2	V/SW	2.00	1.80
DePaola and Colleagues,[16] 1989	1984	United States	Y	Y	N	2	H**	1.95	1.95
Overholser and Colleagues,[17] 1990	1987	United States	Y	Y	N	2	H	1.95	1.95
Mankodi and Colleagues,[18] 1989 (DOF)††	1988	United States	Y	Y	N	2	H	0.95	1.95
Charles and Colleagues[19] (2004)††	1988	United States	Y	Y	N	2	H	0.95	1.95
Mankodi and Colleagues,[20] 1990 (DOF)	1990	United States	Y	Y	N	2	H	1.95	1.95
Overholser and Colleagues,[21] 1992 (DOF)	1991	United States	Y	Y	N	2	V	1.95	1.95
Mankodi and Colleagues,[22] 1993 (DOF)	1992	United States	Y	Y	N	2	V	1.95	1.95
Sharma and Colleagues,[23] 1997 (DOF)	1995	Canada	Y	Y	N	2	H	1.95	1.95
Mankodi and Colleagues,[24] 1997 (DOF)	1995	United States	Y	Y	N	2	H	1.95	1.95
Charles and Colleagues,[25] 2001	1997	Canada	Y	N	N	6	H	1.75	1.75
Charles and Vincent,[26] 1999 (DOF)	1998	United States	Y	N	N	6	H	1.75	1.95
Sharma and Colleagues,[27] 2002	2000	Canada	Y	N	N	6	H	1.75	1.95
Barouth and Colleagues,[28] 2003	2000	United States	Y	N	N	6	H	1.75	1.95
Sharma and Colleagues,[29] 2004	2002	Canada	Y	N	Y	6	H	1.75	1.95

* B/F: Brushing and flossing.
† DOF: Data on file.
‡ Y: Yes.
§ N: No.
¶ Vehicle control.
# SW: Sterile colored water control.
** H: 5% Hydroalcohol control.
†† Gingival index was used in these 2 studies.

TABLE 1 (CONTINUED)

STUDY	YEAR STUDY INITIATED	COUNTRY	DENTAL PROPHYLAXIS	SUPERVISED RINSING	FLOSSING	PLAQUE INDEX NO. SURFACE	NEGATIVE CONTROL RINSE OR B/F*	MEAN GINGIVITIS INCLUSION CRITERIA	MEAN PLAQUE INCLUSION CRITERIA
Charles and Peng,[30] 2009 (DOF)	2004	Canada and United States	Y	N	N	6	H	1.75	1.95
Charles,[31] 2012 (DOF)	2005	United States	Y	N	N	2	H	1.75	1.95
Santos and Colleagues,[32] 2006	2005	Canada	Y	N	N	6	H	1.75	1.95
Santos and Colleagues,[33] 2012	2006	Canada	N	N	N	6	H	1.95	1.95
Charles and Colleagues,[34] 2013	2007	United States	N	N	N	6	H	1.75	1.95
Sharma and Colleagues,[35] 2010	2008	Canada	Y	N	N	6	H	1.75	1.95
Simmons and Colleagues,[36] 2010	2008	United States	N	N	Y	6	No negative control rinse	1.75	1.95
Cortelli and Colleagues,[37] 2012	2009	Brazil	Y	N	N	6	H	1.75	1.95
Cortelli and Colleagues,[38] 2013	2010	Brazil	Y	N	N	6	H	1.75	1.95
Junker and Colleagues,[39] 2012 (DOF)	2010	Canada	N	N	N	6	H	1.75	1.95
Lynch and Colleagues,[40] 2014 (DOF)	2010	Canada	N	N	N	6	H	1.95	1.95
Cortelli and Colleagues,[41] 2014	2012	Brazil	Y	N	N	6	H	1.75	1.95

site-level data available for external researchers to use (Figure 1).

Treatments included. If a study included more than 1 mechanical methods (MM)-only group, only groups having the same mechanical components as the mechanical methods with essential oil–containing mouthrinse (MMEO) group were included. The MMEO group included the same mechanical methods and 20 milliliters of EO mouthrinse, used twice daily for 30 seconds.

Inclusion criteria for original studies and data extraction. Table 1 summarizes the protocol characteristics for the included studies. The study populations included generally healthy men and women, 18 years or older, with at least 20 natural scorable teeth (teeth with facial and lingual surfaces that were not grossly carious, fully crowned, extensively restored, orthodontically banded, acting as abutments, or were third molars). The participants presented with mild to moderate levels of gingival inflammation and dental plaque but without signs of clinical periodontitis: MGI[44] of 1.75 or greater, or gingival index[45] (GI) of 0.95 or greater and Turesky Modification of the Quigley-Hein Plaque Index[46,47] (PI) of generally 1.95 or greater.

Outcomes. Analyses were defined based on outcomes or variables that determined the positive impact of the treatments. They were chosen based on the clinical relevance, which could help clinicians to better choose a preventive approach.

Primary outcome.

- Healthy site (yes or no): A site was defined as healthy (yes) if MGI scores were 0 or 1 at 6 months. A site was not defined as healthy (no) if MGI scores were 2, 3, or 4 at 6 months. Because the categorization of healthy sites as MGI of 0 or 1 is not compatible with any categorization of GI, the 2 studies using GI were excluded from the healthy site analysis. A GI score of 1 is equivalent to MGI scores of 1 and 2, and therein lies the difficulty in combining the GI with the MGI. The MGI affords an expansion of the scale

TABLE 2

Demographics and baseline characteristics across studies (all randomized studies).

PARAMETERS	MECHANICAL ONLY (N = 2,562)	MECHANICAL WITH MOUTHRINSE USE* (N = 2,544)	TOTAL (N = 5,106)
Age, y			
n	2,499	2,483	4,982
Mean (SD†)	34.7 (11.1)	34.6 (10.9)	34.6 (11.0)
Median	34.0	34.0	34.0
Minimum-Maximum	(17-73)	(17-74)	(17-74)
Sex, n (%)			
Male	930 (37.2)	956 (38.4)	1,886 (37.8)
Female	1,569 (62.8)	1,531 (61.6)	3,100 (62.2)
Race, n (%)			
White	1,415 (72.5)	1,438 (72.0)	2,853 (72.2)
Nonwhite	538 (27.5)	560 (28.0)	1,098 (27.8)
Smoker, n (%)			
Yes	485 (19.0)	443 (17.4)	928 (18.2)
No	2,072 (81.0)	2,100 (82.6)	4,172 (81.8)
Smokeless Tobacco Use, n (%)			
Yes	1 (< 1.0)	0	1 (< 1.0)
No	951 (99.9)	996 (100)	1,947 (99.9)
Baseline Mean Modified Gingival Index			
n	2,478	2,462	4,940
Mean (SD)	2.2 (0.2)	2.2 (0.2)	2.2 (0.2)
Median	2.1	2.1	2.1
Minimum-Maximum	(1.7-3.3)	(1.7-3.1)	(1.7-3.3)
Baseline Mean Gingival Index‡			
n	84	80	164
Mean (SD)	1.3 (0.2)	1.3 (0.2)	1.3 (0.2)
Median	1.2	1.2	1.2
Minimum-Maximum	(1.0-1.8)	(1.0-1.8)	(1.0-1.8)
Baseline Mean Plaque Index			
n	2,503	2,488	4,991
Mean (SD)	2.8 (0.4)	2.8 (0.4)	2.8 (0.4)
Median	2.8	2.7	2.8
Minimum-Maximum	(1.7-4.7)	(1.8-4.4)	(1.7-4.7)
Baseline % Healthy Sites			
n	2,478	2,462	4,940
Mean (SD)	2.3 (3.7)	2.3 (3.7)	2.3 (3.7)
Median	0.0	0.0	0.0
Minimum-Maximum	(0.0-30.8)	(0.0-27.8)	(0.0-30.8)
Baseline % Plaque-Free Sites			
n	2,503	2,488	4,991
Mean (SD)	2.6 (5.5)	2.6 (5.5)	2.6 (5.5)
Median	0.0	0.0	0.0
Minimum-Maximum	(0.0-43.2)	(0.0-42.4)	(0.0-43.2)

* Mouthrinse refers to marketed Listerine brand of fixed combination of 4 essential oils.
† SD: Standard deviation.
‡ Gingival index only applies to Mankodi and colleagues[18] and Charles and colleagues.[19]

at the lower end in order to reflect resolution of inflammation from the complete unit being involved to only a partial unit having inflammation.

Secondary outcomes.

- Percentage change in a participant's whole-mouth mean gingivitis score (MGI/GI) from baseline at 6 months.
- Plaque-free site (yes/no): A site was defined as plaque-free (yes) if PI scores were 0 or 1. A site was not defined as plaque-free (no) if PI scores were 2, 3, 4, or 5.
- Percentage change in a participant's whole-mouth mean plaque score (PI 2 or 6 surfaces) from baseline at 6 months.

Data analysis. ***Meta-analysis.*** For the analysis of healthy sites and plaque-free sites, by-study treatment effect and standard error (SE) estimates were obtained using a generalized linear model approach, using a logit link based on the odds of healthy or nonhealthy sites (or plaque-free or plaque sites). A model was fit by study, including terms for treatment and for baseline percentage of healthy (or plaque-free) sites as a covariate. This model was used to estimate the odds ratio (OR) and associated SE within each study.

The method of DerSimonian and Laird[48] was then used to generate a pooled overall estimate of the OR based on a random effects assumption, using the estimates for the within-study ORs and associated SEs. The corresponding estimate based on the fixed effects assumption was obtained similarly by combining the within-study estimates, using as weights the inverse of the squared within-study SEs. Forest plots were generated for healthy sites and plaque-free sites, with a confidence interval (CI) for each study, and an overall summary OR, and percentage change.

For percentage change from baseline in whole-mouth mean gingivitis and plaque scores, analyses were based on a model with percentage change at the participant level as the response and baseline mean score as a covariate. The method of DerSimonian and Laird[48] was then used to generate a pooled overall estimate of the between-treatment differences based on the random effects

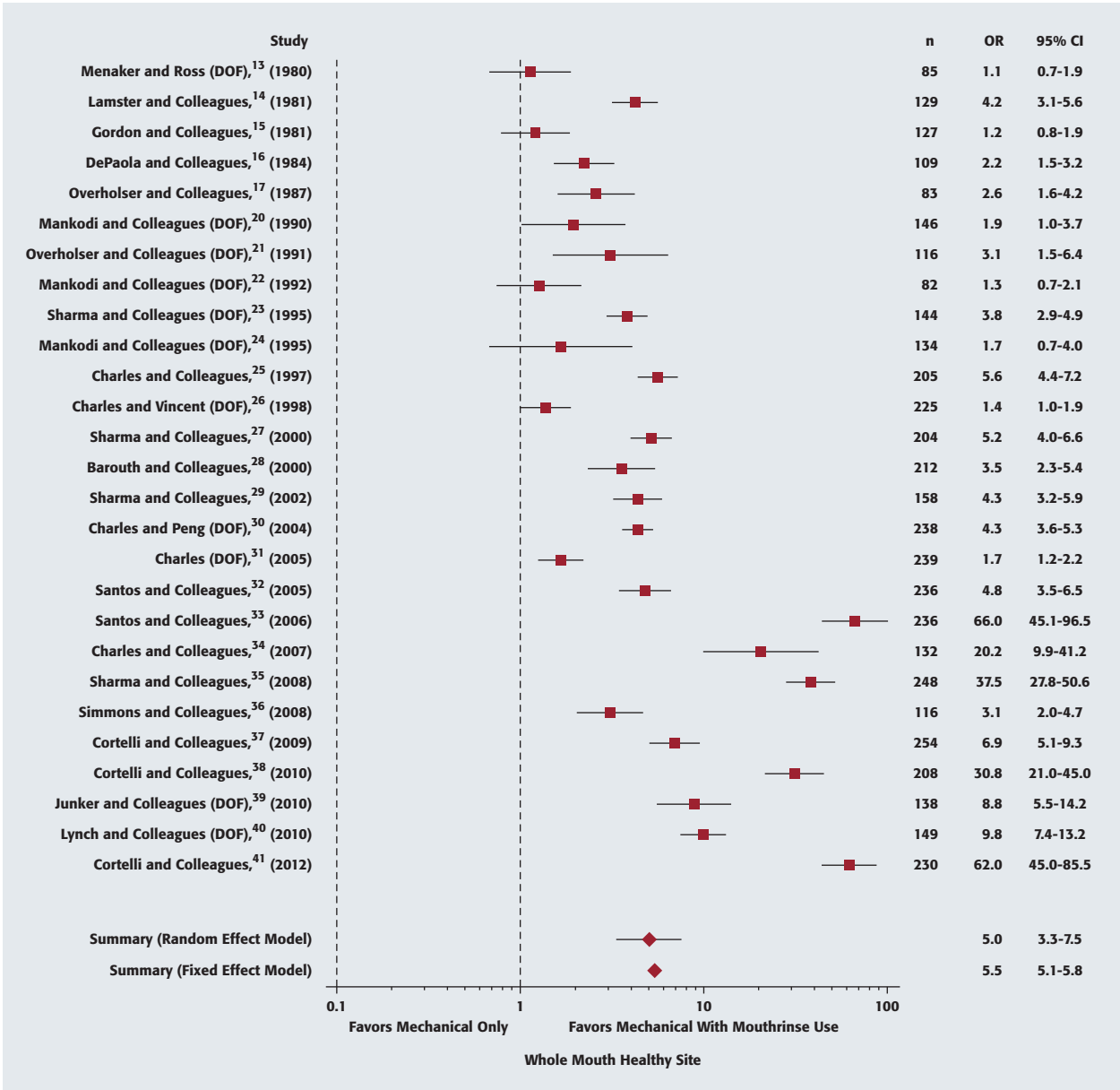

Figure 2. Odds ratios (OR) and 95% confidence intervals (CI) of whole-mouth healthy sites at month 6 intention-to-treat population. The years in parentheses represent the dates that the studies were initiated. DOF: Data on file.

assumption, using the individual study estimates and standard errors.

The statistical and clinical relevance of the specific study characteristics, that is, heterogeneity, were evaluated by exploring interactions between treatment and the following study characteristics: 6- versus 2-surface plaque index (plaque-free sites and percentage reduction in plaque), GI versus MGI (percentage reduction in mean GI or mean MGI), supervised versus unsupervised rinsing, dental prophylaxis versus no dental prophylaxis, flossing versus no flossing, study period, and study location.

Responder analysis. A responder analysis was conducted on the aggregated individual participant–level data to evaluate individual participant responses, using cumulative distribution of responder analysis graphs.[49] This responder analysis approach presents the proportion of responders over the entire range of possible cutoff points, visually. This allows clinicians to compare treatment groups at any response level that is valid for their

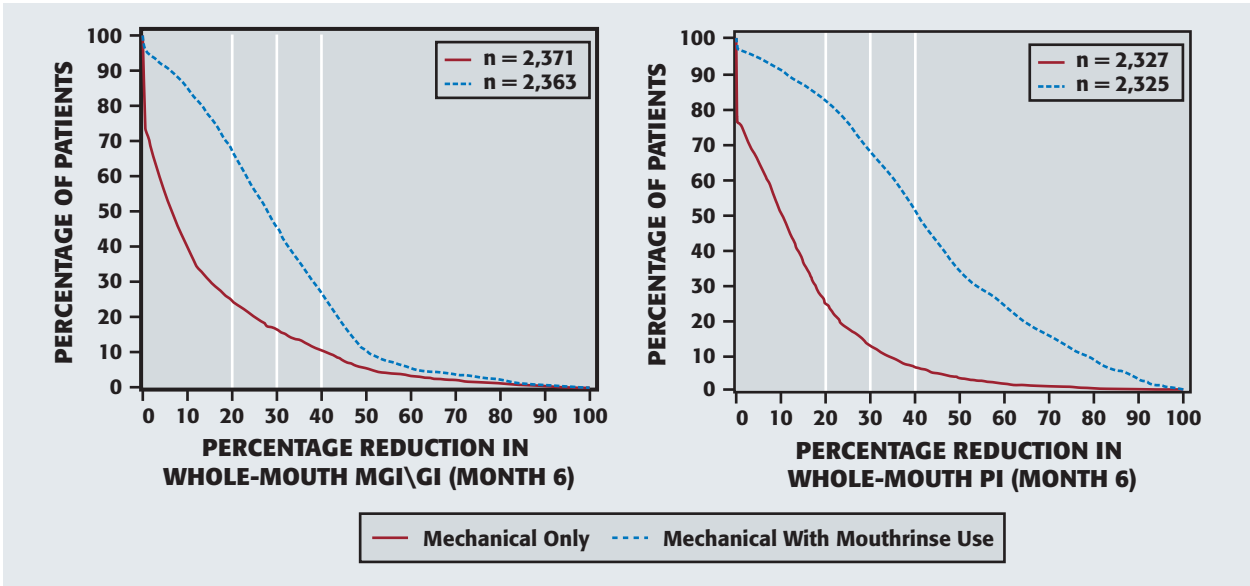

Figure 3. Responder analysis of percentage reduction of whole-mouth mean modified gingival index (MGI) and gingival index (GI) (27 studies) and whole-mouth plaque index (PI) (28 studies).

patient population. This visual display accompanies the analyses of percentage of healthy sites and percentage of plaque-free sites. In the context of healthy sites, for instance, the responder curve plots the proportion of participants within each treatment group achieving at least the given percentage of healthy sites, for all possible percentages of healthy sites (0-100%).

Assessment of risk of bias. Risk of bias in each of the included studies was evaluated per the principles of the *Cochrane Handbook for Systemic Reviews of Interventions*.[50] All studies were randomized trials. Specifically, in this context, we evaluated whether these studies were observer-masked and monitored after the Good Clinical Practice quality standard based on the International Conference on Harmonization guidelines for clinical research. These clinical studies were carefully designed and they contain detailed individual patient–level data including demography and baseline characteristics, patient disposition, outcomes, and adverse events.

RESULTS

Demography. The available demographic and baseline characteristics are provided in Table 2. Data from a total of 5,106 randomized participants were included in the meta-analysis set, of which 2,562 participants received MM treatment only and 2,544 participants received MMEO treatment. The mean age of the study population was 35 years, 72% of participants were white, 62% of participants were women, and 18% of participants were smokers (self-reported). Baseline clinical characteristics for all randomized participants by treatment group are provided in Table 2. Baseline means (standard deviations) for key clinical indexes assessed in the meta-analyses were MGI = 2.2 (0.2), GI = 1.3 (0.2), PI = 2.8 (0.4). There were no notable differences among treatment groups for any of the demographic or baseline characteristics.

Efficacy. Efficacy analyses were performed on the intention-to-treat populations across 29 clinical studies that fit the criteria for the meta-analysis, including 4,827 participants with postbaseline data (2,425 in the MM treatment group and 2,402 in the MMEO group).

The odds ratio of a healthy gingival site (27 studies) for participants in the MMEO treatment group at 6 months was 5.0, compared with participants in the control group (OR = 5.0; 95% CI, 3.3-7.5), from the random effects model (Figure 2). For the secondary outcome variable, percentage reduction from baseline in MGI/GI (n = 29 studies) at 6 months, the summary difference between percentage reductions and 95% CI were 16.0 (11.3-20.7). Responder curves for percentage reduction in whole-mouth mean MGI/GI and PI are presented in Figure 3. Responder analysis results showed that 66% of patients in the MMEO group and 24% patients in the MM group achieved a threshold of 20% reduction in MGI/GI. The responder curves for percentage of whole-mouth healthy sites are presented in Figure 4. Responder analysis results showed that for a threshold of 50% healthy sites, 44.8% of MMEO subjects and 14.4% of MM participants met this threshold (Figure 4).

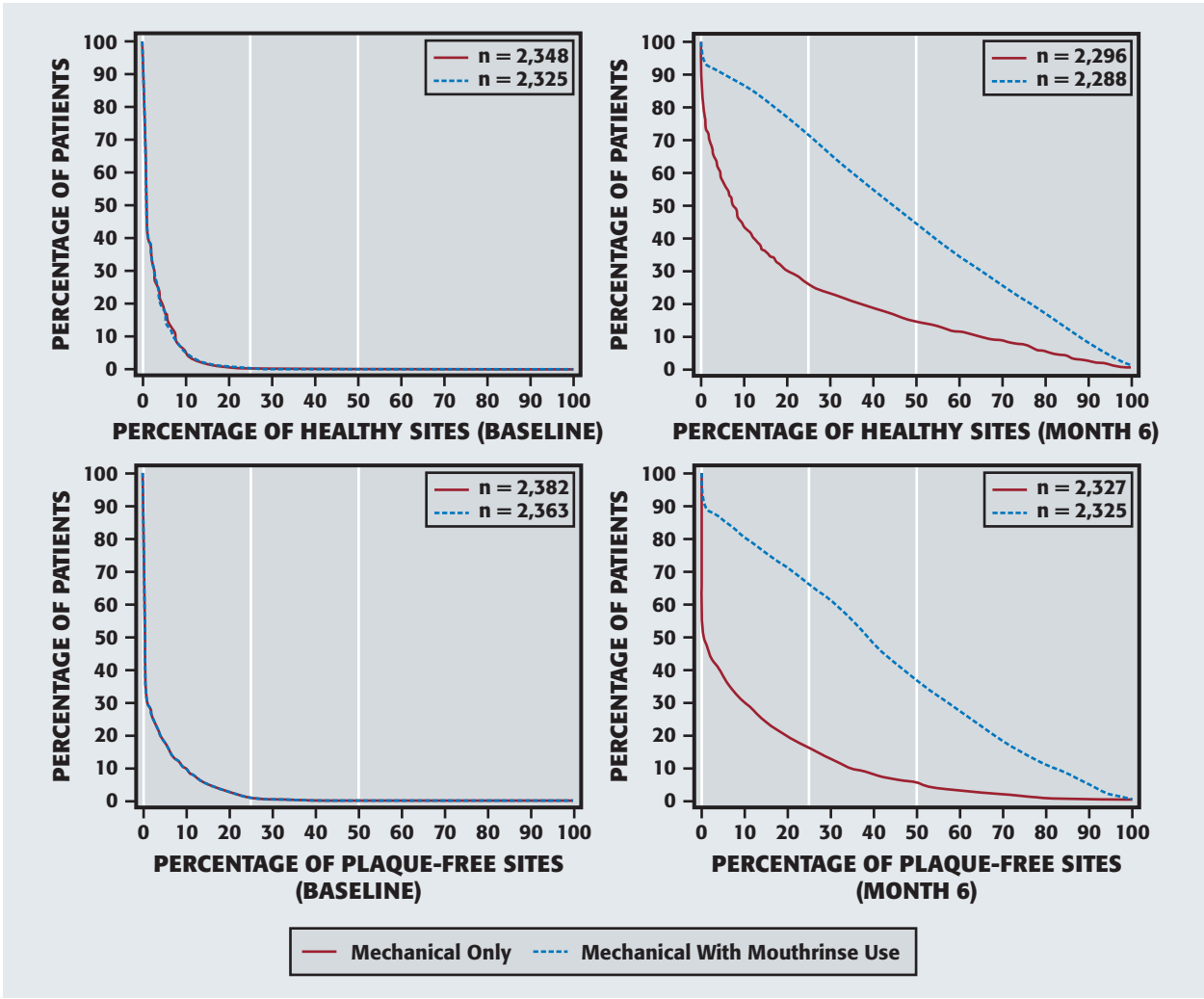

Figure 4. Responder analysis of percentage of whole mouth-healthy sites (27 studies) and plaque-free sites (28 studies) intention-to-treat population.

Twenty-eight of the 29 studies were included for the percentage of plaque-free sites (yes or no), because 1 study had only partial data available due to unreadable case reports. The summary OR of a plaque-free site for participants in the MMEO group compared with participants in the MM group, was 7.8 (95% CI, 5.4-11.2) from the random effects model. The study-specific ORs and confidence intervals for plaque-free sites are presented in Figure 5. For the variable percentage reduction from baseline in PI at 6 months, the summary percent reductions (95% CI) was 27.7 (22.4-32.9). Figure 3 provides the responder curve for percent reduction in whole-mouth mean PI, with 83% of MMEO participants achieving 20% reduction in PI from baseline after 6 months, compared with 25% of MM participants. Figure 4 provides the responder curves for mean percentage plaque-free sites, with 36.9% of MMEO participants experiencing at least 50% plaque-free sites after 6 months compared with 5.5% of MM participants.

Risk of bias in the original studies. Regarding risk of bias, all studies were conducted using a computer-generated randomization scheme with varying levels of fixed block sizes depending on the study size, all test products were administered by personnel not involved in participant enrollment or study assessments, and study test products were either group-coded (early studies) or individually coded and randomized. All 29 studies adhered to the same basic methodology and were monitored after the Good Clinical Practices and ICH guidelines for clinical research. There was a low risk of performance and detection bias because the key study personnel were masked to treatment assignment across all studies. The dropout rate in all studies was less than 10% and attrition was balanced across the

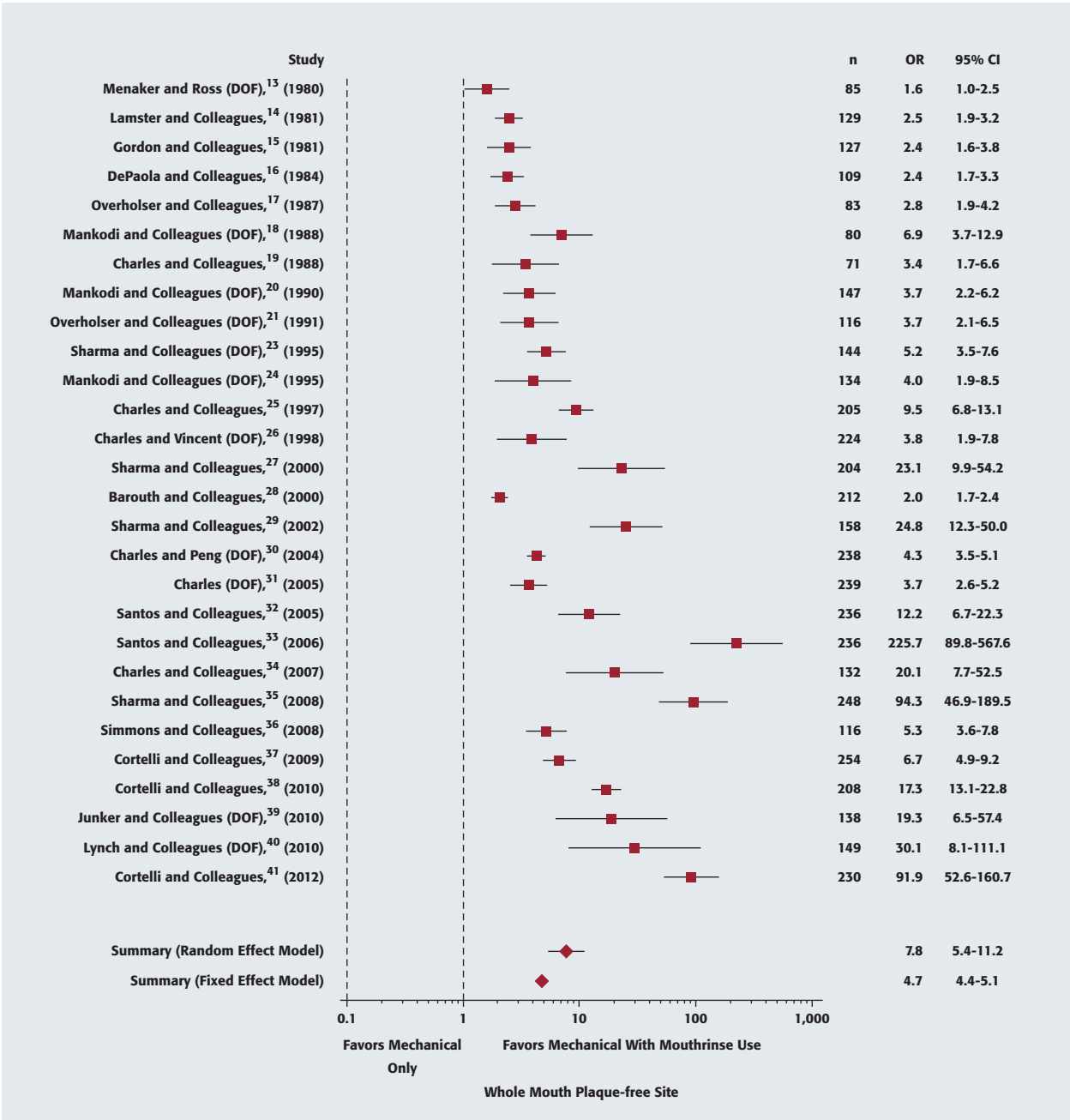

Figure 5. Odds ratios (OR) and 95% confidence intervals (CI) of whole-mouth plaque-free sites at month 6 intention-to-treat population. The years in parentheses represent the dates that the studies were initiated. DOF: Data on file.

treatment groups. All studies were funded by the manufacturer; all protocols and reports were available; all of the outcome variables (primary and secondary) were prespecified in study protocols.

Heterogeneity assessment. Heterogeneity was examined by assessing the interaction between treatment and each of the study characteristics separately. The study characteristics examined were supervision, baseline dental prophylaxis, flossing, study period, and location. In addition, we also considered—for the outcomes of change in MGI/GI—which measure was used; and for change in PI, the number of surfaces evaluated. Nearly all of these interactions were statistically significant and were therefore sources of heterogeneity.

For study characteristics, study period, study location, supervised rinsing, flossing, prophylaxis, and 6- versus

TABLE 3

Summary of random effects measures according to whether studies included flossing or baseline dental prophylaxis as part of the mechanical regimen.*

END POINT	FLOSSING REQUIRED (CI)†	FLOSSING NOT REQUIRED (CI)	PROPHYLAXIS (CI)	NO PROPHYLAXIS (CI)
Healthy Sites (Odds Ratio)	3.8 (2.7-5.2)	5.1 (3.3-8.0)	4.0 (2.5-6.4)	10.6 (4.3-26.1)
Percentage Reduction in Mean Gingival Index/Gingival Index (MMEO Mean–MM Mean)	16.4 (12.3-20.5)	16.0 (11.0-21.0)	15.1 (9.7-20.5)	19.4 (8.0-30.9)
Plaque-free Sites (Odds Ratio)	11.1 (2.4-50.7)	7.6 (5.2-11.1)	6.5 (4.4-9.7)	17.0 (5.2-55.1)
Percentage Reduction in Plaque Index (MMEO Mean–MM Mean)	34.6 (13.9-55.4)	27.1 (21.6-32.7)	26.8 (21.1-32.5)	30.8 (16.6-45.0)

* Random effects measures with 95% confidence intervals.
† CI: Confidence interval.

2-surface plaque were all closely related to each other. All supervised rinsing studies occurred before all unsupervised rinsing studies; study locations changed across time, all but 1 of the 2-surface PI studies were conducted before 1996 and all but 1 of the 6-surface studies were conducted after 1996. Because of the correlation among these characteristics, it is not clear whether the improvement in results could be attributed to a subset of these characteristics.

Treatment effects for plaque-free sites and percentage change of PI differed by whether flossing was part of the regimen or not (Table 3). The other outcomes did not differ by flossing. Also, for all outcomes, the separation between the MMEO and MM was larger for studies that did not include a baseline dental prophylaxis (Table 3). Therefore, the ORs for healthy sites and plaque-free sites were larger for studies with no baseline dental prophylaxis than those with prophylaxis. Similarly, the percentage change of MGI/GI and of PI was larger for studies without prophylaxis than those with a baseline dental prophylaxis treatment.

DISCUSSION

Summary of evidence. In addition to the classical percentage reduction in plaque and gingival indexes, this meta-analysis provides new information not only on adjunctive use of mouthrinses containing essential oil in achieving gingival health, but also relative to mechanical oral hygiene alone. All 32 long-term randomized clinical trials (published and unpublished) sponsored by the manufacturer were considered for inclusion in the analysis; 29 met the inclusion criteria of the meta-analysis protocol (one study did not contain a marketed EO rinse and 2 studies did not have individual-level data available).[13-41] Though not as comprehensive as doing an analysis of all potential studies, a meta-analysis of clinical studies available to manufacturers has important benefits. It is important to highlight that because of regulatory and ADA Seal of Acceptance requirements, these clinical studies are carefully designed and executed, and they contain detailed individual-level data including baseline characteristics, patient disposition, and outcomes. All 29 studies included in the meta-analysis were modeled after the same basic methodology.[42]

This is the first meta-analysis to perform a responder analysis in which sites were evaluated regarding presence and absence of disease, allowing the clinician to evaluate the level of response the participants had to treatment at 6 months. The rationale for daily use of antiplaque/antigingivitis mouthrinses is twofold: as an adjunctive component to mechanical oral hygiene regimens[29] for the control and prevention of plaque, gingivitis, and dental caries,[3] and as a method of delivering antimicrobial agents to mucosal sites throughout the mouth that harbor potentially pathogenic bacteria capable of recolonizing on supragingival and subgingival tooth surfaces.[51,52]

In the 2006 meta-analysis by Gunsolley,[11] 3 marketed mouthrinses containing chlorhexidine, cetylpyridinium chloride, or EO were determined to have beneficial antiplaque and antigingivitis effects when used long-term, and in conjunction with other oral hygiene measures such as brushing and flossing.

A systematic review and meta-analysis published by Van Leeuwen and colleagues[12] in 2011 compared the antiplaque and antigingivitis efficacy of EO and other mouthrinses, including 19 long-term studies that met the inclusion criteria. The authors showed that EO mouthrinses appear to be a good choice for long-term use as an antigingivitis agent. Finally, Gandini and colleagues[53] and Boyle and colleagues[3] presented quantitative assessments of published data regarding use of mouthrinse and risk of common oral conditions. Their analyses focused on large epidemiologic studies and revealed that there was a clear benefit from use in terms of reducing the risk of dental plaque, gingivitis, and caries and that there were no major adverse effects. Specifically, they found no statistically significant association between use of mouthwash containing alcohol and oral cancer risk.[53]

The present meta-analysis was designed to provide an alternative method to interpret clinical data and propose a benefit-based approach to clinical research and

practice, similar to what is applied in medicine, allowing the clinicians to use the responder analyses and ORs to evaluate the benefit expected for their patients.[48] This methodology is presented in the FDA guidance on patient reported outcomes as a method for assessing individual participant responses while avoiding the need to pick a responder criterion.

The results of the responder analyses suggest that after 6 months of use, clinicians could expect that approximately 45% of patients would have at least 50% of sites without gingivitis (MGI = 0 or 1) and approximately 37% of participants would have at least 50% of sites without plaque (PI = 0 or 1). In addition, the implementation of a long-term oral care routine that provides 7 times greater odds for plaque-free sites and 5 times greater odds for healthy sites can be compelling information for the clinician when educating patients on the appropriate oral care routine.

Strengths and limitations. This is the first meta-analysis of long-term clinical data to include responder analysis of published and unpublished results of the benefits provided by EO mouthrinses in achieving gingival health in addition to mechanical methods of oral hygiene. Because publication was not considered in the inclusion of studies, this analysis is not subject to publication bias. One of the limitations of the present study involves the noninclusion of data from other manufacturers and independent researchers, mostly because the site-level data of other published data are not publically available. However, to the best of our knowledge, there are only 3 other published reports of EO mouthrinses compared with placebo mouthrinses of 6 months duration that have been conducted by other researchers.[54-56] Those could not be included in the current publication due to a lack of site-level and individual participant-level data.

However, the meta-analysis presents a new approach to clinical research data in dentistry, with focus on achieving gingival health as a means of disease management. One of the main strengths shown here is the fact that data developed from over 30 years of research were generated by using the same clinical research method applied to the protocols of all studies, generating a unique database with over 5,000 participants, from 3 different countries, aged 18 years and older, both sexes, and with other demographic characteristics that reflect a diverse population.[13-41]

This analysis allowed for the identification and investigation of protocol differences and the exploration of heterogeneity of the treatment effect, thereby helping clarify the implications of any heterogeneity on the results. An implication of the analyses of heterogeneity appears to be that the studies that more closely mimic real world experience seem to produce larger estimates of the benefit of mouthrinses as part of daily oral hygiene.

CONCLUSIONS

This meta-analysis of 6-month clinical trials supports the clinically relevant benefit of daily use of EO mouthrinses for plaque and gingivitis reduction beyond MM oral hygiene by determining the percentage of plaque-free tooth surfaces and gingival sites that achieved health, the goals of preventive services.

Addition of daily rinsing with an EO mouthrinse to mechanical oral hygiene provided statistically significantly greater odds of having a cleaner and healthier mouth, which may lead to prevention of disease progression. Clinicians may find this novel format of data representation for a range of responses helpful in reaching decisions to manage plaque and gingivitis for all patients. ■

Dr. Araujo was a senior director, Scientific & Professional Affairs, Johnson & Johnson Consumer Companies, Skillman, NJ when this article was written. He now is vice president, Science Institute, American Dental Association, Chicago, IL.

Ms. Charles is a director, Clinical Research, Johnson & Johnson Consumer Companies, Morris Plains, NJ.

Dr. Weinstein is a director, Epidemiology, Janssen Research & Development, Raritan, NJ.

Mr. McGuire is a director, Biostatistics, Biometric & Clinical Data, Johnson & Johnson Consumer Companies, Morris Plains, NJ.

Dr. Parikh-Das is a manager, Clinical Research, Johnson & Johnson Consumer Companies, Morris Plains, NJ.

Ms. Du is a principal scientist, R&D Biometrics, Johnson & Johnson (China), Shanghai, China.

Dr. Zhang is a research manager, Scientific and Professional Affairs, Johnson & Johnson Consumer Companies, 185 Tabor Rd., Morris Plains, NJ 07950, e-mail JZhang1@its.jnj.com. Address correspondence to Dr. Zhang.

Dr. Berlin is a vice president, Epidemiology, Johnson & Johnson, Titusville, NJ.

Dr. Gunsolley is a professor, Virginia Commonwealth University, Richmond, VA.

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