



Regional comparison of self-reported late pregnancy cigarette smoking to mass spectrometry analysis

Eric S. Hall^{1,2,3} · Jennifer M. McAllister^{1,2,4} · Elizabeth A. Kelly^{1,5} · Kenneth D. R. Setchell^{2,6} · Vandana Megaraj⁶ · Kristine L. Jimenez⁶ · Nichole Nidey^{2,7} · James M. Greenberg^{1,2} · Scott L. Wexelblatt^{1,2,4}

Received: 7 October 2020 / Revised: 25 February 2021 / Accepted: 11 March 2021
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Abstract

Objective To report a more accurate prevalence estimate of late pregnancy nicotine exposures.

Study design A cross-sectional study during a 2-month period in 2019. Participants were women delivering in any of the six county maternity hospitals who consented to universal drug testing at the time of delivery as part of routine hospital admission.

Results Of 2531 tested samples, 18.7% tested positive for high levels of cotinine indicating primary smoking or other primary use of tobacco products. Together, 33.0% of the study population tested positive for nicotine exposure during late pregnancy compared to vital records which reported 8.2% cigarette smoking during the third trimester of pregnancy and 10.5% cigarette smoking at any time during pregnancy through maternal self-report.

Conclusion Captured vital birth smoking measures vastly underreport actual primary exposures to nicotine products. Vital birth data also fail to capture secondhand exposures which constitute a significant proportion of the population.

Introduction

Use of tobacco products during pregnancy is unsafe and is associated with increased risk for birth defects, stillbirth, and neonatal death [1, 2]. Additionally, the effects of

tobacco use during pregnancy have a far-reaching impact on most phases of childhood development [3]. Even second-hand smoke exposures during pregnancy have been associated with preterm birth, reduced birthweight, childhood cancer, and physician-diagnosed asthma [3, 4].

The 2003 revision of the US Standard Certificate of Live Birth introduced new measures of maternal cigarette smoking which capture the self-reported number of cigarettes smoked during each pregnancy trimester [5]. Live birth certificate-derived data, viewable using the Centers for Disease Control and Prevention WONDER online database, have been cited to describe smoking prevalence and trends among pregnant women in the USA [5–7]. According to these measures, reported cigarette smoking at any point in pregnancy has trended downward each year from 2014 to 2018 throughout the USA as well as in the State of Ohio and in Hamilton County, Ohio the setting for the current study (Table 1). The downward trend is also observed within each of these jurisdictions for third trimester smoking from 2016 to 2018 (the time frame for which the third trimester cigarette smoking data are available).

While the downward trends are encouraging, these figures may not accurately represent the true prevalence of perinatal tobacco exposures. Self-reported measures are susceptible to the effects of social pressure and recall bias

✉ Scott L. Wexelblatt
Scott.wexelblatt@cchmc.org

¹ Perinatal Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

² Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA

³ Translational Data Science and Informatics, Geisinger, Danville, PA, USA

⁴ Center for Addiction Research, University of Cincinnati College of Medicine, Cincinnati, OH, USA

⁵ Department of Obstetrics and Gynecology, University of Cincinnati College of Medicine, Cincinnati, OH, USA

⁶ Division of Pathology and Laboratory Medicine, Clinical Mass Spectrometry, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

⁷ Division of Biostatistics and Epidemiology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA

Table 1 Maternal self-reported rates of cigarette smoking at any time during pregnancy as well as during the third trimester of pregnancy, 2014–2018.

Year	Any cigarette smoking during pregnancy			Third trimester cigarette smoking		
	United States	Ohio	Hamilton County, OH	United States	Ohio	Hamilton County, OH
2014	7.9%	16.2%	12.4%			
2015	7.5%	15.2%	11.4%			
2016	7.2%	14.3%	11.4%	5.7%	11.4%	8.7%
2017	6.9%	13.8%	10.1%	5.4%	11.1%	7.9%
2018	6.5%	13.1%	9.7%	5.1%	10.6%	7.4%

[8–12]. Also, data collected for birth certificates are very specific and limited in scope referring only to smoking of traditional cigarettes without a mechanism to report use of any other nicotine delivery products [5, 13]. Over the past several years, e-cigarettes have rapidly gained popularity [14]. Marketing of e-cigarettes as a safer alternative to traditional cigarettes as well as the perception of e-cigarettes as a mechanism for smoking cessation have further encouraged their use, even during pregnancy [15, 16]. Other products such as little cigars and cigarillos are not subject to the same regulations or taxes as traditional cigarettes and are heavily marketed in African American and other communities as a less expensive alternative to cigarettes [17].

As a biomarker for nicotine, cotinine can be measured to detect primary as well as secondary tobacco exposures from any nicotine delivery device [18–20]. Cotinine measurement through mass spectrometry of urine has been established as reliable—though cotinine clearance has previously been reported as accelerated in pregnant women with a half-life as short as 8.8 h [21–23]. As a result, cotinine detection is useful for detecting nicotine exposures of pregnant women for the last 3–4 days prior to delivery [19]. In a previous single center study, we measured cotinine among pregnant women at the time of parturition to detect late pregnancy nicotine exposures. Although 8.6% of women self-reported use of cigarettes during the last trimester of pregnancy [13], mass spectrometry analysis detected high levels of cotinine indicating primary tobacco use in nearly double the number of women (16.5%). We identified an additional 7.5% of women with low-level exposures indicating secondhand exposure or less recent primary tobacco use [13].

Given these considerations, we sought to determine whether these encouraging self-reported trends truly indicate a decline in the rates of tobacco use during pregnancy or are they simply masking a shift in the use of cigarettes to other nicotine delivery products. Our objective was to validate previous findings demonstrating significantly higher rates of late pregnancy nicotine exposure than reported by vital birth data at a robust county level. Measuring a population level sample, we aimed to report a more accurate prevalence estimate of late pregnancy nicotine exposures.

Materials/subjects and methods

We conducted a cross-sectional study during the 2-month period, August and September 2019 within Hamilton County, Ohio—the urban county that includes Cincinnati. Urine collected from women delivering in any of the six maternity hospitals located within the county (regardless of each woman’s place of residence) was tested using mass spectrometry analysis for the detection of cotinine. Vital birth statistics including self-reported last trimester cigarette smoking data were obtained representing all deliveries at the same six hospitals during the study period. The two data sets (hospital laboratory data and vital birth records) represented the same cohorts of women who delivered at each maternity hospital during the study period. However, to protect patient privacy the data sets were separately de-identified prior to analysis and were therefore not linked at the individual person-level but compared in aggregate. We compared rates of self-reported smoking from the vital birth data set to high- and low levels of cotinine detected using mass spectrometry analysis. The study was approved by the Cincinnati Children’s Hospital Medical Center and Ohio Department of Health Institutional Review Boards. Data sets were de-identified and aggregated. Additionally, urine testing was universal, non-discriminatory, and results could not be linked back to an individual, therefore the study was granted a waiver of consent.

Laboratory data

All six of the maternity hospitals within the county obtain consent for universal drug testing at the time of delivery as part of routine hospital admission [24]. Historically, ~1% of women exercise their option to opt out of universal testing, in which case their infant has a urine toxicology test performed and undergoes a minimum 48-h observation for signs of drug withdrawal. Laboratory technicians split samples from each of the consented urine samples collected during the study period (1–2 ml) and transported the samples to Cincinnati Children’s Hospital Medical Center for mass spectrometry analysis. Split samples were blinded, except for the identity of the maternity hospital from where they were collected (obscured in this report) and samples

were tested independent from any clinical processes. In the case of multiple birth deliveries, only a single split sample was obtained from the mother. Using a cutoff informed by previous analyses suggesting that urinary cotinine levels in nonsmokers are always <100 ng/ml despite some instances of high levels of passive exposure, mass spectrometry results positive for cotinine were categorized as high- (≥ 100 ng/ml) or low-level (≥ 4 ng/ml and <100 ng/ml) exposures [25, 26]. Measures <4 ng/ml were considered below the LOQ and were not categorized as positive exposures. Cotinine calibration curves were linear over the concentration range of 2–250 ng/ml with a correlation coefficient of 0.99 or greater. The analytical recovery of cotinine from urine was >95%. Intra-assay and inter-assay imprecision of cotinine was <8% and <10% (expressed as coefficient of variation), respectively. High-level categorization was interpreted as active primary use of nicotine delivery devices during late pregnancy, while low-level categorization was interpreted as secondhand smoke exposures during late pregnancy or delayed exposures (3–4 days prior to delivery) subsequent to primary use. Measures ≥ 250 ng/ml exceeded the upper limit of precision detectable without additional sample dilution and testing and were reported simply as “ ≥ 250 ng/ml.”

Cotinine analysis by liquid chromatography tandem mass spectrometry (LC-MS/MS)

Cotinine was quantified as a component of a routine validated drug panel of 46 drugs of abuse in a College of American Pathologists and Clinical Laboratory Improvement Amendments certified laboratory. Cotinine and its conjugates were extracted from urine samples using a Hamilton Robotics MicroSTARlet paired with a Tecan SP IP8 automated solid phase extraction (SPE) processor. Urine samples were hydrolyzed by β -glucuronidase enzyme to obtain free (non-conjugated) cotinine in the presence of the stable-labeled internal standard, [$^2\text{H}_3$]cotinine and SPE performed. Cotinine was detected and quantified by LC-MS/MS with multiple reaction monitoring. All samples were analyzed with the LC20AD HPLC system (Shimadzu) coupled to the SCIEX QTRAP 4500 mass spectrometer (Sciex, Concord, Canada). Chromatographic separation of cotinine analytes was achieved on a 50×4.6 mm, Kinetex Phenyl-Hexyl Column (Phenomenex). A gradient mobile phase was used with a binary solvent system, which was ramped from 5% mobile phase B (methanol/0.1% formic acid) to 95% mobile phase A (water/10 mM ammonium formate) at a flow rate of 0.7 ml/min. The total run time was 7 min. The optimal signal for the analytes were achieved in positive ion mode with the use of the following instrument settings: Ionspray voltage (IS): 2500 v; Source temperature (TEM): 650 °C; Curtain Gas (CUR): 35 psi; Ion source gas

1 (GS1): 60 psi and Ion source gas 2 (GS2): 50 psi. The ion transitions monitored were selected as m/z 177 \rightarrow 80 and m/z 177 \rightarrow 98 representing the $[\text{M}+\text{H}]^+$ ion and its collision-induced fragment ion for cotinine and [$^2\text{H}_3$]cotinine, respectively. Data acquisition on the mass spectrometer was controlled by Analyst 1.6.2 software (Sciex, Concord, Canada). Data processing and quantification were performed with MultiQuant software version 3.0 (Sciex, Concord, Canada). The calibration curves were linear over the tested concentration range of 2–250 ng/ml with a correlation coefficient of 0.99 or greater. The limit of quantification (LOQ) was determined at 4 ng/ml.

Live birth data

Vital birth records representing deliveries in each of Hamilton County’s six maternity hospitals were obtained for the 2-month study period. We identified all singleton and first-in-set-order of multiple birth deliveries so that each delivering mother was represented once. Self-reported late pregnancy smoking status was determined using a self-reported number of cigarettes greater than 0 smoked on a typical day of the trimester during which delivery occurred (second trimester for infants born at 26 weeks gestation or less or third trimester for infants born at greater than 26 weeks gestation). Birth data also included each mother’s age, race, and ethnicity (recorded as Hispanic, non-Hispanic black, non-Hispanic white, and other or unknown), insurance (recorded as Medicaid or private), education (recorded as less than high school degree, high school degree, or at least some college), and residence within Hamilton county (yes/no). Tabulations derived from vital records which represent any subgroup with <10 individuals are not presented in this report in accordance with the Ohio Department of Health data use agreement.

Statistical analysis

For each hospital, last trimester nicotine use was represented by rates of (1) self-reported cigarette smoking from vital birth data, and (2) high-level, mass spectrometry cotinine detection from laboratory data. Although self-reported smoking and high-level cotinine variables were not linked at the individual person-level, the unmatched data sets represented the same cohorts of women who gave birth at each maternity hospital during the study period. We used two-sided chi-square tests to test for independence in positive detection for last trimester nicotine use (yes/no) and detection method (self-report/laboratory test). We also calculated Pearson correlation coefficients to examine the correlation between late pregnancy smoking rates and hospital demographic characteristics. All statistical analyses and calculations were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA) software.

Table 2 Population characteristics among women who delivered at each of the six de-identified maternity hospitals in Hamilton County.

Maternal characteristic	Maternity hospital						All
	1	2	3	4	5	6	
Women	670	546	826	277	134	423	2876
Married <i>N</i> , (%)	380 (56.7)	360 (65.9)	479 (58.0)	171 (61.7)	78 (58.2)	147 (34.8)	1615 (56.2)
Maternal age (median)	30	30	30	27	28.5	28	29
Maternal race and ethnicity							
Hispanic (%)	58 (8.7)	18 (3.3)	27 (3.3)	<10	<10	78 (18.4)	189 (6.6)
Non-Hispanic black (%)	127 (19.0)	110 (20.2)	211 (25.5)	<10	22 (16.4)	188 (44.4)	662 (23.0)
Non-Hispanic white (%)	434 (64.8)	403 (73.8)	559 (67.7)	259 (93.5)	104 (77.6)	142 (33.6)	1,901 (66.1)
Other or Unknown (%)	51 (7.6)	15 (2.7)	29 (3.5)	<10	<10	15 (3.6)	124 (4.3)
Insurance							
Medicaid (%)	222 (33.1)	143 (26.2)	285 (34.5)	109 (39.4)	44 (32.8)	311 (73.5)	1114 (38.7)
Private (%)	375 (56.0)	390 (71.4)	474 (57.4)	155 (56.0)	83 (61.9)	111 (26.2)	1588 (55.2)
Education (%)							
Less than high school degree (%)	73 (10.9)	23 (4.2)	74 (9.0)	24 (8.7)	10 (7.5)	128 (30.3)	332 (11.5)
High school degree (%)	155 (23.1)	110 (20.1)	191 (23.1)	89 (32.1)	22 (16.4)	119 (28.1)	686 (23.9)
Some college (%)	440 (65.7)	412 (75.5)	556 (67.3)	164 (59.2)	102 (76.1)	174 (41.1)	1848 (64.3)
County residence (%)	313 (46.7)	318 (58.2)	584 (70.7)	31 (11.2)	87 (64.9)	314 (74.2)	1647 (57.3)

Results

During August and September 2019, 2951 infants were born to 2876 mothers in the six Hamilton County delivery hospitals. Urine samples representing 2531 of those mothers (88.0%) were analyzed. Population demographics representing the mothers at each hospital as well as in total are presented in Table 2.

Of 2531 tested samples, 18.7% tested positive for high levels of cotinine indicating primary smoking or primary use of other tobacco products. An additional 14.4% tested positive for low levels of cotinine indicating recent passive exposure to nicotine, or several days lapsed from primary exposure. The bimodal distribution of mass spectrometry cotinine levels for the study cohort is presented in Fig. 1. Together, 33.0% of the study population tested positive for nicotine exposure during late pregnancy compared to 10.5% cigarette smoking at any time during pregnancy and 8.2% cigarette smoking during the third trimester of pregnancy through vital records maternal self-report (Table 3). Birth hospital-specific rates of high-level cotinine ranged from 9.9 to 29.9%. Low-level rates ranged from 10.2 to 22.6% and any exposure rates ranged from 20.2 to 52.5%.

Demographic patterns between hospitals significantly varied. Around 74% of patients at site 6 were Medicaid insured compared to an average of roughly 40% for the entire sample. Pearson analysis found positive correlation between the percent of women insured by Medicaid and all levels of nicotine exposure (low-level exposure correlation coefficient: 0.85, $p = 0.03$; high-level exposure correlation coefficient: 0.78, $p = 0.07$; any level exposure correlation coefficient: 0.84, $p = 0.03$).

Discussion

Despite reports of declining cigarette smoking among pregnant women determined by state and national vital records data, ~1 in 3 women in our study tested positive for exposure to nicotine during late pregnancy. More than twice as many women tested positive for high levels of late pregnancy nicotine exposure (indicating primary use of nicotine products) than reported third trimester smoking. These findings validate our previous analysis which was limited to a single delivery hospital in 2014–2015 [13]. Continued reliance on existing measures may result in providers and public health

Fig. 1 Distribution of study cohort mass spectrometry levels (ng/ml) among results testing positive for any level of cotinine. Cotinine level is on the bottom of the figure.

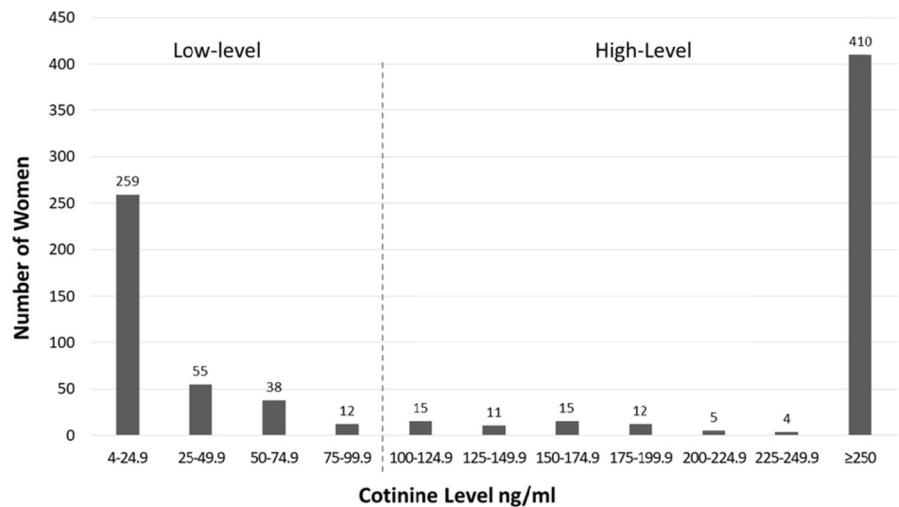


Table 3 Mass spectrometry laboratory results compared to self-reported smoking status as captured in vital birth records.

Measure	Maternity hospital						
	1	2	3	4	5	6	All
Vital birth records (<i>N</i>)	670	546	826	277	134	423	2876
Married <i>N</i> , (%)	380 (56.7)	360 (65.9)	479 (58.0)	171 (61.7)	78 (58.2)	147 (34.8)	1615 (56.2)
Self-reported any trimester smoking, <i>N</i> (%)	59 (8.8)	41 (7.5)	82 (9.9)	51 (18.4)	<10	59 (13.9)	301 (10.5)
Self-reported last trimester smoking, <i>N</i> (%)	43 (6.4)	32 (5.9)	63 (7.6)	42 (15.2)	<10	49 (11.6)	235 (8.2)
Mass spectrometry tested, <i>N</i> (capture rate %)	635 (94.8)	496 (90.8)	693 (83.9)	265 (95.7)	141 (105.2)	301 (71.2)	2531 (88.0)
Low-level exposure, <i>N</i> (%)	65 (10.2)	62 (12.5)	107 (15.4)	38 (14.3)	24 (17.0)	68 (22.6)	364 (14.4)
High-level exposure, <i>N</i> (%)	63 (9.9)	82 (16.5)	153 (22.1)	62 (23.4)	22 (15.6)	90 (29.9)	472 (18.7)
Any exposure, <i>N</i> (%)	128 (20.2)	144 (29.0)	260 (37.5)	100 (37.7)	46 (32.6)	158 (52.5)	836 (33.0)
High-level by mass spectrometry compared to last trimester self-reported smoking (chi-square), <i>p</i>	0.02	<0.0001	<0.0001	0.02	0.002	<0.0001	<0.0001

officials underestimating the significant ongoing use of nicotine during pregnancy and to under resource prenatal cessation programs or other interventions.

The tremendous public health burden of tobacco use on maternal, infant, and women’s health outcomes makes it imperative that tobacco and nicotine use is both identified and addressed. In addition to the immediate adverse outcomes associated with tobacco use in pregnancy, women who use tobacco have an increased risk of cardiovascular disease, malignancy including breast, lung, and colon cancer, and progression of cervical intraepithelial neoplasm. Both active and passive exposure to tobacco smoke can increase the chance of stillbirth, low birthweight, birth defects, and respiratory problems in babies. There is an increased risk of childhood illnesses such as respiratory infections, otitis media, and cancer with tobacco exposure, and conditions including asthma and obesity as also associated with in utero tobacco exposure. Long-term childhood outcomes including learning and neurobehavioral issues are also negatively impacted by tobacco exposure [27].

Electronic nicotine delivery systems including e-cigarettes, hookah pens, mod or pod systems, vape pens, and vaporizers have become more widely available and combined with the ongoing use of hookahs and cigars make up the chosen form of nicotine use outside of cigarettes by pregnant women. Overall prevalence of nicotine containing product use in a cohort of pregnant women from the first wave of the national Population Assessment of Tobacco and Health Study is highest for cigarettes (13.8%), followed by e-cigarettes (4.9%), hookah (2.5%), and cigars (2.3%), and below 1% for all other products [28].

In our study, we found a positive correlation between women with Medicaid insurance and nicotine exposure in their infants. Recent reports have demonstrated similar findings in the general population. The prevalence of any tobacco product use among individuals with Medicaid insurance is nearly twice that of those with private insurance [29]. This knowledge is important in identifying women who use tobacco and nicotine products during pregnancy because there are known interventions that have proven

efficacy. The United States Preventative Services Task Force (USPSTF) concludes with high certainty that the net benefit of behavioral interventions for tobacco cessation on perinatal outcomes and smoking abstinence in pregnant women who smoke is substantial [30]. Based on 86 studies done in 2013, the USPSTF found that behavioral interventions in pregnant women are effective at improving rates of smoking cessation as well as perinatal health outcomes (decreased incidence of low birthweight and preterm birth) and higher cessation rates compared to controls who did not receive any intervention [30]. The USPSTF also concludes with high certainty that the benefit of behavioral interventions and pharmacotherapy for tobacco cessation in non-pregnant women who use tobacco is substantial [30]. Identification of maternal tobacco use early in pregnancy not only allows for maternal interventions to assist with cessation but also interventions that assist women in the postpartum period and beyond.

Lack of reliable identification of women who use tobacco or nicotine containing substances may be due to many factors including social pressure, fear of admitting the use of a harmful substance during pregnancy, and recall bias in reporting, but may also result from limitations in data collection. Questions narrowly focused on cigarette use only or reliance on what women believe to be the definition of “current tobacco use” without further clarification may lead to less accurate measures. Insufficient questions at follow up appointments to ascertain if women who were not using nicotine in earlier pregnancy have resumed use, and an attitude by health care workers that women “should not be smoking in pregnancy so why do we bother asking them” may also contribute to less accurate data. Use of an objective marker of nicotine exposure would allow women to be identified early in pregnancy and accurately allowing patient centric plan to be developed to aggressively assist with cessation.

Limitations

Across the county, urine was not tested for about 12% of women who delivered during the study period. Some samples were not obtained due to precipitous deliveries, emergency cesarean sections, or human error. One site had a 105% capture rate resulting from a triage process implemented for prenatal testing in which all maternal urine is collected and tested, even if not admitted, and in which some women may have had more than one urine tested. Site 6 had the lowest capture rate resulting from a shortage of collection materials for a 3-day period during the study. Neither of these capture rate anomalies are likely to bias the overall site or study results. Although previous analyses indicate that nonsmokers’ cotinine concentrations are

unlikely to exceed 100 ng/ml, we could not distinguish with certainty between primary or secondary exposures concentrations in the low-level range. Low-level exposure values may result from cessation of primary smoking several days prior to hospitalization, low use of primary smoking, or secondary smoke exposure. Finally, to maintain privacy, we could not link individual-level attributes (race/ethnicity, insurance, education) to de-identified urine samples.

Conclusion

Captured vital birth statistics smoking measures vastly underreport exposures to nicotine products as demonstrated through universal testing of maternal urine with mass spectrometry. Future studies are needed to identify how data collection measures and patient demographics may influence self-report of exposure to inform future interventions/education/data collection.

Acknowledgements This study includes data provided by the Ohio Department of Health, which should not be considered an endorsement of the study or its conclusions. This work was supported by a grant from Chiesi Farmaceutici and by a gift from Amgis Foundation Inc. Although both organizations provided financial support, neither participated in study design, data collection, data analysis and interpretation, or manuscript preparation.

Compliance with ethical standards

Conflict of interest SLW and ESH have been consultants for Braeburn Pharmaceuticals. SLW is on the Abbott Nutrition speaker’s bureau. All other authors have no competing interests.

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