



Secular Trends in Information Communications Technology: Access, Use, and Attitudes of Young and Older Patients With Diabetes

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BACKGROUND | Advances in information communications technology (ICT) provide opportunities for enhanced diabetes care. Knowledge of the more acceptable communication modalities in patients of different ages will help to inform the direction of future innovations.

METHODS | An anonymous ICT survey (examining access and use of mobile phones, computers, tablets, and the Internet and attitudes toward e-mail, Web-based consultations, and online peer-support) was conducted at the Royal Prince Alfred Hospital Diabetes Centre in Sydney, Australia. Survey deployment occurred during 4-month periods in 2012 and 2017. Respondents were stratified by current age (<40 or ≥40 years).

RESULTS | A total of 614 unselected patients (20% with type 1 diabetes, 55% with type 2 diabetes, 13% with gestational diabetes mellitus, and 12% with an undisclosed type of diabetes) completed the survey. Access to ICT increased from 89% in 2012 to 97% in 2017. The most commonly owned device was a mobile phone (87% ownership in 2017). Increase in mobile Internet usage in the <40 years of age subgroup was significant ($P = 0.04$). Significant increases in Internet access and smartphone feature use were observed in patients aged ≥40 years ($P \leq 0.001$ for all). Overall use of short message service (SMS, or text messaging) was high (90 and 80% for ages <40 and ≥40 years, respectively). Use of digital applications was low, even among the young (45% in 2017). Comfort with online consultations (40%) and support groups (32%) was also low.

CONCLUSION | Access to and acceptance and use of ICT is high, especially in those <40 years of age; however, the greatest increases were seen in those aged ≥40 years. High penetrance of mobile phones and text messaging in all age-groups would suggest that innovations involving an SMS platform have the greatest potential to enhance diabetes care.

The worldwide burden of diabetes is significant, and the number of people with type 2 diabetes is expected to exceed 600 million by 2045 (1). Innovative care models are urgently needed both to improve patient outcomes and to alleviate the workforce burden of this growing chronic disease. Technological progress in information communications technology (ICT) has resulted in the development of short message service (SMS, or text messaging), smartphone applications (apps), e-mail, Web-based consultations, and online peer support groups. All of these developments offer opportunities for enhanced diabetes care. However, studies have shown that ICT-based enhancement of care is not

guaranteed. In the setting of an underserved population of adults with type 2 diabetes, investigators of the Mobile Diabetes Detective randomized controlled trial (2) found that only half of their study participants regularly used computers or text messages; significant training and technical support was required for the study to proceed. Such data highlight the importance of a comprehensive understanding of a population's exposure to and acceptance of all available forms of communications technology.

Given the increasing burden of young-onset type 2 diabetes (3,4) and demonstrably poor engagement with health services (5), the digital revolution provides a great opportunity

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to reconnect these high-risk patients. Although younger age has been a predictor of eHealth use (6), a more detailed knowledge of preferred communication modalities for the purposes of health care delivery is an important prerequisite for the successful implementation of any ICT strategy. Improving engagement among younger patients is a worthy pursuit, but one also must not forget about the large cohort of older patients. The majority of patients with diabetes are middle-aged or older, and in theory, newer technologies may provide opportunities to overcome barriers to care such as geographical isolation and lack of access to information that may occur independent of a patient's age. Thus, again, better understanding of attitudes toward specific communication modalities in both younger and older patient cohorts would be informative.

Toward this end, a self-administered diabetes and technology survey was developed to explore access to digital devices, including mobile phones, tablets, and computers; use of SMS, smartphone apps, and the Internet; and attitudes regarding the use of ICT in the delivery of diabetes care. We surveyed the general population with diabetes in a metropolitan ambulatory care diabetes center and analyzed the responses provided.

The survey was conducted in 2012 and 2017. In 2012, Australia was experiencing a period of rapid uptake of mobile technology; the number of adults who owned a smartphone increased from 4.25 million to 8.67 million in the 12 months ending in June 2012 (7). In 2017, Australia was approaching the point of smartphone saturation; an estimated 88% of the adult population owned a smartphone at that time (8). Analysis of survey responses from 2012 and 2017 provide a contemporary insight into the effects of the mobile technology revolution on both our younger and older patient cohorts.

Methods

Participants and Recruitment

All patients attending the Royal Prince Alfred (RPA) Hospital Diabetes Centre for routine clinic appointments were invited to complete an anonymous diabetes and technology survey during the period of interest. The survey was conducted during two separate time periods; period 1 was from January to April 2012, and period 2 was from March to June 2017. For logistical reasons, a 4-month survey administration time frame was chosen in 2012 and again in 2017. The survey was intended to provide an unselected snapshot of clinic attendees at the time. There were no specific exclusion criteria.

A total of 300 patients responded in period 1 out of a pool of 1,815 patients reviewed during that time, for a response rate of

16.5%. A total of 314 patients responded in period 2 out of a pool of 1,960 patients reviewed during that time, for a response rate of 16.0%. Patients who completed a survey during period 1 were asked not to complete a survey in period 2.

Study Setting

Based in Sydney, Australia, the RPA Hospital Diabetes Centre is a secondary and tertiary ambulatory care center that routinely assists in the management of patients with type 1 diabetes, type 2 diabetes, and gestational diabetes mellitus (GDM). Patients ranging in age from 16 to 85 years and beyond are regularly reviewed by the Centre staff.

Survey Tool

A paper-based, self-administered survey tool was developed for use in the RPA Hospital Diabetes Centre in 2011 (Supplementary Figure S1). The survey tool was validated by experienced clinical staff and ICT data managers at the Centre. The survey was designed to gain an understanding of patient access to and use of ICT as well as their attitudes toward technology in a general context and in a diabetes-specific context.

Statistical Analysis

Descriptive and inferential statistical analyses were undertaken using SPSS Version 24 (IBM, Armonk, N.Y.). Because technology historically has been adopted more readily by the younger generations (9,10), the data sets were dichotomized according to age (<40 vs. ≥40 years of age). Comparative analyses of access to, use of, and attitudes toward technology in 2012 and 2017 were undertaken using Pearson χ^2 testing. Statistical significance was accepted at the level of $P = 0.05$.

Secondary analyses on the basis of sex and type of diabetes were performed, and the results of these analyses are reported in the supplementary materials. Because a significant increase was seen in the number of respondents with GDM in 2017, a post hoc analysis of respondents with versus those without GDM was undertaken for that year's survey.

Results

Patient Characteristics

Table 1 outlines characteristics of the 614 survey respondents. Overall, there was a relatively even split between male and female respondents, but there were more male respondents in period 1 and more female respondents in period 2. The increase in female respondents can be attributed to the

TABLE 1 Characteristics of Survey Respondents

	Overall (n = 614)	2012 (n = 300)	2017 (n = 314)
Sex			
Male	303 (49.3)	174 (58.0)	129 (41.1)
Female	300 (48.9)	120 (40.0)	180 (57.3)
Not disclosed	11 (1.8)	6 (2.0)	5 (1.6)
Age-group, years			
<20	10 (1.6)	8 (2.7)	2 (0.6)
20 to <30	47 (7.7)	14 (4.7)	33 (10.5)
30 to <40	129 (21.0)	35 (11.7)	94 (29.9)
40 to <50	75 (12.2)	33 (11.0)	42 (13.4)
50 to <60	115 (18.7)	71 (23.7)	44 (14.0)
60 to <70	140 (22.8)	83 (27.7)	57 (18.2)
≥70	85 (13.8)	49 (16.3)	36 (11.5)
Not disclosed	13 (2.1)	7 (2.3)	6 (1.9)
Type of diabetes			
Type 1 diabetes	123 (20.0)	61 (20.3)	62 (19.7)
Type 2 diabetes	337 (54.9)	189 (63.0)	148 (47.1)
GDM	80 (13.0)	1 (0.3)	79 (25.2)
Don't know	54 (8.8)	34 (11.3)	20 (6.4)
Not disclosed	20 (3.3)	15 (5.0)	5 (1.6)
Language spoken at home			
English	447 (72.8)	230 (76.7)	217 (69.1)
Other language	141 (23.0)	58 (19.3)	83 (26.4)
Not disclosed	26 (4.2)	12 (4.0)	14 (4.5)

All values are n (%).

inclusion of more patients with GDM in period 2. Approximately 31% of respondents were <40 years of age in the combined 2012 and 2017 cohorts. A higher proportion of respondents were <40 years of age in period 2 than in period 1 (41 vs. 19%). Again, this increase can be attributed to the inclusion of more patients with GDM in period 2. English was the predominant language spoken at home for 73% of respondents. Additionally, 20% of respondents identified as having type 1 diabetes, 55% reported having type 2 diabetes, and 13% reported having GDM.

Technology Access

Patients' access to core forms of ICT (i.e., computer, tablet, mobile phone, and the Internet) is presented in Table 2. Between 2012 and 2017, statistically significant increases in access were reported for tablets (additional 41% access, $P < 0.001$) and the Internet (additional 15% access, $P < 0.001$). Irrespective of patient age, the most commonly owned device during both survey periods was the mobile phone. Mobile phone ownership rates for our cohort were 83% in 2012 and 87% in 2017.

In both 2012 and 2017, survey respondents who were <40 years of age reported greater access to computers, tablets, mobile phones, and the Internet than those who were ≥40 years

of age. In the subgroup of respondents who were <40 years of age, the tablet was the only device for which a statistically significant increase in access was observed (additional 44% access in 2017, $P < 0.001$). The use of other technologies in the younger cohort was high at baseline, and use did not significantly change in period 2. Access to ICT in the subgroup of respondents ≥40 years of age increased between survey periods; 87% of older respondents reported access to at least one form of technology in 2012 and this increased to 95% in 2017 ($P < 0.01$).

Technology Use

A summary of smartphone feature use is presented in Table 3. After phone calls (90%), the most frequently used feature was found to be SMS (84%). In the younger patient cohort, mobile Internet usage was significantly higher in period 2 than in period 1 (87 vs. 74%, $P = 0.04$). Nonetheless, the increase in smartphone feature use observed in period 2 was primarily driven by those ≥40 years of age. Significant increases in use of all smartphone features were observed in the subgroup of respondents who were ≥40 years of age ($P \leq 0.001$ for all features). Smartphone app usage was reported by approximately half of the study cohort. App usage rates were higher in the younger patient subgroup during both survey periods. However, stagnation of

TABLE 2 Self-Reported Access to Core Forms of ICT in 2012 and 2017, Stratified by Current Respondent Age

Form of ICT	Year	Overall		Respondents <40 Years of Age		Respondents ≥40 Years of Age	
		Proportion With Access	P	Proportion With Access	P	Proportion With Access	P
Computer	2012	0.73	0.45	0.95	0.09	0.68	0.70
	2017	0.76		0.84		0.70	
Tablet	2012	0.15	<0.001	0.25	<0.001	0.13	<0.001
	2017	0.56		0.69		0.46	
Mobile phone	2012	0.83	0.21	0.96	0.28	0.80	0.27
	2017	0.87		0.91		0.84	
Internet access	2012	0.74	<0.001	0.93	0.59	0.69	0.001
	2017	0.89		0.96		0.84	
No technology	2012	0.11	<0.001	0	NA	0.13	<0.01
	2017	0.03		0		0.05	

NA, not applicable.

app uptake was observed in this demographic; 61% of younger patients reported smartphone app use in 2012 versus 54% in 2017 ($P = 0.46$). An increase in the uptake of apps between 2012 and 2017 was observed in the older patient subgroup (20 vs. 38%, $P < 0.001$).

An overview of technology-related behaviors, including health-related Internet searching and use of personal blood glucose monitoring in 2012 and 2017 is presented in Supplementary Table S1. Use of the Internet to search for health information increased over time (50% in period 1 vs. 74% in period 2, $P < 0.001$). Higher proportions of young respondents reported this behavior than their older counterparts. Although not universal, ownership and regular use of a personal blood glucose meter was common

in both 2012 (81%) and 2017 (89%). Despite high levels of ownership, only a minority of respondents (14% in 2012 and 25% in 2017) reported having ever connected their personal blood glucose meter to a computer to download (and print out) data from their devices. Those patients who had downloaded data reported higher levels of comfort with the use of technology in management of their diabetes (81 vs. 63%, $P = 0.001$).

Attitudes Toward Technology

Patient attitudes toward technology and its application in the setting of diabetes management are summarized in Table 4. Approximately 90% of respondents <40 years of age during both survey periods reported being either comfortable or

TABLE 3 Mobile Phone Feature Use in 2012 and 2017, Stratified by Current Respondent Age

Mobile Phone Feature	Year	Overall		Respondents <40 Years of Age		Respondents ≥40 Years of Age	
		Proportion Using Feature	P	Proportion Using Feature	P	Proportion Using Feature	P
Phone calls	2012	0.83	0.02	0.96	0.08	0.80	0.001
	2017	0.90		0.87		0.93	
SMS	2012	0.59	<0.001	0.96	0.21	0.49	<0.001
	2017	0.84		0.90		0.80	
Mobile Internet	2012	0.31	<0.001	0.74	0.04	0.25	<0.001
	2017	0.69		0.87		0.54	
Other apps	2012	0.28	<0.001	0.61	0.46	0.20	<0.001
	2017	0.45		0.54		0.38	

TABLE 4 Respondents' Comfort With Technology and Technology-Based Support in 2012 and 2017

Technology/ Technology-Based Support	Year	Overall		Respondents <40 Years of Age		Respondents ≥40 Years of Age	
		Proportion Who Are Comfortable or Very Comfortable	<i>P</i>	Proportion Who Are Comfortable or Very Comfortable	<i>P</i>	Proportion Who Are Comfortable or Very Comfortable	<i>P</i>
Technology in general	2012	0.58	<0.001	0.89	0.86	0.50	0.001
	2017	0.78		0.91		0.68	
Technology in diabetes	2012	0.60	<0.001	0.87	1.00	0.53	<0.02
	2017	0.75		0.87		0.66	
E-mail contact from the Diabetes Centre	2012	0.64	0.07	0.81	0.79	0.60	0.69
	2017	0.71		0.84		0.62	
Web-based diabetes consultation	2012	0.31	0.03	0.53	0.79	0.25	0.09
	2017	0.40		0.49		0.34	
Online diabetes support group	2012	0.23	0.01	0.36	0.91	0.19	<0.01
	2017	0.32		0.34		0.31	

very comfortable with technology in general. Despite high levels of comfort with technology in the younger cohort, levels of interest in Web-based diabetes consultation and online diabetes support groups were limited. The interest expressed by respondents <40 years of age remained stable over the two survey periods (~50% for Web consultation and 35% for online support groups).

Both comfort with technology and interest in online support groups were lower in the respondent subgroup ≥40 years of age. However, statistically significant increases in these areas were observed during survey period 2. With respect to comfort with technology, the percentage of older respondents expressing comfort increased from 50% in 2012 to 68% in 2017 (*P* = 0.001). With respect to online support groups, the percentage of older respondents expressing interest increased from 19% in 2012 to 31% in 2017 (*P* < 0.01). Interest in Web-based consultations (43% in 2017) and e-mail communications for clinical purposes (62% in 2017) did not significantly differ between survey periods for those aged ≥40 years.

Secondary Analyses

Male Versus Female

In comparing access to ICT of male and female respondents, no statistically significant differences were observed in either 2012 or 2017 (Supplementary Table S4a). Use of mobile phone features was similar within each time period for both sexes (*P* > 0.05 for all features; Supplementary Table S4b). The only significant difference observed between the sexes was in the level of comfort expressed for e-mail contact in

2017; 78% of female versus 62% of male respondents reported comfort with e-mail contact in this survey period (*P* = 0.005).

Type 1 Diabetes Versus Type 2 Diabetes

In comparing access of patients with type 1 diabetes and type 2 diabetes for the combined 2012 and 2017 cohorts, respondents with type 1 diabetes reported having significantly greater access to computers, mobile phones, and the Internet (Supplementary Table S5a). Looking specifically at the subgroup of patients <40 years of age, ICT access was high irrespective of diabetes type. However, access to mobile phones was higher in young respondents with type 1 diabetes than in young respondents with type 2 diabetes (98 vs. 83%, *P* = 0.02) (Supplementary Table S6a). Like their younger counterparts with type 1 diabetes, older respondents with type 1 diabetes reported significantly higher access to mobile phones than older respondents with type 2 diabetes (97 vs. 80%, *P* = 0.004). Older respondents with type 1 diabetes also reported greater access to the Internet than older respondents with type 2 diabetes (90 vs. 76%, *P* = 0.04).

When comparing use of mobile phone features, no statistically significant differences were observed between young respondents with type 2 diabetes and young respondents with type 1 diabetes (*P* > 0.05 for all smartphone features; Supplementary Table S6b). Older respondents with type 1 diabetes reported greater use of SMS and mobile Internet than older respondents with type 2 diabetes (*P* < 0.05 for both SMS and mobile Internet; Supplementary Table S6b).

Although attitudes toward technology differed between younger and older respondents, there were no significant differences between young respondents with type 1 and young respondents with type 2 diabetes, nor were there significant differences between older respondents with type 1 diabetes and older respondents with type 2 diabetes (Supplementary Table S6c).

GDM Versus non-GDM (<40 Years of Age)

Because the vast majority (95%) of patients with GDM were <40 years of age, we performed a post hoc analysis and compared patients with GDM who were <40 years of age with patients with type 1 and type 2 diabetes who were <40 years of age (Supplementary Tables S7a–S7c). Overall, patients with GDM who were <40 years of age demonstrated minor differences with respect to access to, use of, and attitudes toward technology when compared to patients with type 1 or type 2 diabetes who were <40 years of age. Specifically, those with GDM reported greater access to tablets than age-matched respondents with either type 1 or type 2 diabetes (79 vs. 56%, $P = 0.005$). Additionally, more respondents with GDM reported being comfortable with the use of technology in their diabetes management (92 vs. 79%, $P = 0.04$), and more respondents with GDM reported being comfortable with e-mail contact from the Diabetes Centre (91 vs. 74%, $P = 0.01$).

Discussion

Patients attending the RPA Hospital Diabetes Centre report generally high levels of access to ICT; in 2017, 97% of all survey respondents reported having access to at least one form of ICT. Overall, access to ICT was highest for respondents who were <40 years of age. Nevertheless, the greatest changes seen throughout the study were in the older age-groups. Increases in access to all forms of technology and an increase in the level of comfort with technology were observed in the age-group ≥ 40 years of age. Access to mobile phones is prevalent in both younger and older patients, and the use of SMS is widespread. Although app use is increasing in older age-groups, overall usage rates remain low. Paralleling the low app usage rate of older respondents, only about half of respondents <40 years of age reported using smartphone apps. Interestingly, <50% of patients reported being comfortable with Web-based diabetes consultation, and fewer still were comfortable with online peer support. Relatively minor differences were observed in analyses by sex and diabetes type. This finding suggests that age remains a major determinant of technology use.

These data provide optimism for the future use of ICT in diabetes care, especially among the younger cohort. Increases in access to and more favorable attitudes toward ICT

in older age-groups over the past 5 years will be encouraging to those working in the area given the high burden of diabetes seen in the older adult population. In addition, our results suggest that new innovations in the ICT space should be directed toward a mobile phone-based platform; the continued high penetrance of mobile phone ownership makes this the platform with the greatest potential reach.

Our data suggest that SMS-based systems have greater acceptability than smartphone applications. Over the past 5 years, a plethora of apps to facilitate diabetes self-management have been released for iPhone and Android devices. Despite developer interest in this space, it is intriguing to observe stagnation of app uptake in our young cohort between 2012 and 2017 and only a limited increase in uptake of apps in our older cohort during the same period. Market research conducted by Localytics, a company specializing in analytics and marketing in the mobile space, has shown that, although many people download apps to their phones, retention rates and use drop to 20% by 90 days (11). Our data are in accordance with these observations. Clearly, any beneficial self-management solution is required to maintain patient engagement for more than 3 months. Therefore, it is unlikely that a diabetes self-management smartphone app will be able to produce long-lasting results as a stand-alone program.

The popularity and widespread familiarity of text messaging is worthy of note. In our 2017 survey, >80% of both young and older adult respondents reported using SMS on a regular basis. During the past 15 years, there has been considerable interest in harnessing text messaging to improve various aspects of chronic disease management, including engagement with self-care, medication adherence, and attendance at clinical follow-up appointments (12–14). Clinical trials have been undertaken in both developed and developing nations over time frames spanning from weeks to months. Some studies have used a unidirectional communication strategy, whereas others have used a bidirectional strategy. Although significant heterogeneity of study design has been observed, systematic reviews have generally concluded that there have been positive outcomes observed for text-based interventions (12–15). Many projects have been undertaken on a small scale as proof-of-principle studies. However, evidence is accumulating that SMS-based interventions are cost-effective and therefore suitable for deployment at large scale (16). Moving forward, it would seem reasonable to take advantage of our patient cohort's familiarity with mobile technology and test an SMS-based support strategy to facilitate improved patient engagement with self-care and clinical follow-up.

From a clinician's perspective, Web-based consultations and online diabetes support groups and forums would seem to

be reasonable tools to facilitate patient engagement and care. Indeed, Vimalananda et al. (17) and McDonnell (18) have noted patient support for these interventions in other clinical settings. In contrast to these studies, our cohort expressed relatively low general acceptance for Web-based consultations and peer support. Acceptance may have been higher if a remote or rural community were surveyed because respondents from such areas may have had prior exposure to such experiences. The advent of infrastructure to support telehealth may also improve acceptance, and this could be explored further.

Our study had notable strengths and some limitations. Given that the study was undertaken across two distinct time frames using identical methodology and was conducted at the same Diabetes Centre, valid comparisons can be made across the two time-specific cohorts.

One limitation of our survey is the response rate of 16.3%. In this setting, one may ask whether we have been able to capture a representative sample of our clinic population and whether our results have been affected by nonresponse bias. We acknowledge differences in sex balance and age composition between the 2012 and 2017 survey cohorts. Given that the survey was anonymous and questionnaires were completed voluntarily by patients attending the Centre, it was not possible to control for imbalances in the sex or age of patients who completed questionnaires. Nevertheless, we believe an adequate response rate in each age category was observed during each of the survey periods (see Supplementary Tables S2 and S3).

Response rates were higher in the younger than in the older age-groups in the 2017 survey period. It is conceivable that our observed increase in technology access and use in the older age-groups may be an overestimate if a significant nonresponse bias was present.

We also acknowledge that significantly more patients with GDM completed the 2017 survey than the 2012 survey. This difference reflects a change in the way in which patients with GDM are reviewed at our Centre. In 2012, most patients with GDM were reviewed in a hospital antenatal clinic located outside the Diabetes Centre. Surveys were not administered outside the Diabetes Centre, so few patients with GDM had an opportunity to complete questionnaires in 2012. Because of growth in the number of patients with GDM, in 2017, GDM review clinics were routinely held in the Diabetes Centre. Because all patients attending the Centre were given the opportunity to complete a questionnaire, a greater number of patients with GDM completed questionnaires in 2017. Although there were significant differences between patients with GDM and those with other types of diabetes

aged <40 years, the positive finding of a secular trend of increased tablet use was still seen in the non-GDM population. Therefore, it is unlikely that the imbalance of GDM in the different time cohorts could substantially explain this finding.

Finally, we recognize that literacy, privacy, and data security are important factors that may affect the uptake and use of ICT, and we acknowledge that our survey did not specifically explore these areas. In the Australian setting, the federal government recently introduced a personal electronic health record system for Australian citizens. At the time of its launch, >10% of the population had opted out of the electronic record system. Common concerns expressed by those who opted out included uncertainty regarding who could access the medical information stored online and fears of data hacking by nefarious agents. Moving forward, it will be important to address privacy and data security concerns to improve the robustness of ICT-based systems and ensure widespread access that is both safe and secure. An individualized approach is likely to be most effective because differing levels of literacy within communities will require different applications of available technology.

Conclusion

For older adult patients, there have been significant increases in access to, use of, and more favorable attitudes toward ICT, particularly in the context of diabetes care over the study period. For younger adults with diabetes, changes have been small over time on the background of a high baseline level of use and acceptance. The high penetrance of mobile phone technology and the widespread use of SMS across all age-groups would suggest that the greatest promise for health care interventions would be to use these specific technologies. The efficacy of apps would appear to be limited, and there is still a low acceptance of Web-based consultations and online peer support. Thus, health care interventions using these technologies are not likely to have a large impact in the present environment. Our data would support the development of text-based innovations to enhance diabetes care, especially in the young, but also for a growing group of older patients.

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DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

AUTHOR CONTRIBUTIONS

T.L.M. contributed to the study design, coordinated the study as principal investigator, and drafted the manuscript. M.I.C. contributed to the study design, assisted in data collection, and reviewed the manuscript. L.M. contributed to the statistical analysis and reviewed the manuscript. T.A. contributed to data collection and analysis and reviewed the manuscript. M.M. contributed to the study design and reviewed the manuscript. D.K.Y., S.M.T., T.W., and J.W. contributed to the study design and interpretation of data and reviewed the manuscript. All authors approved the manuscript for submission. T.L.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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