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Research Article

The Burden and Risk Factors of Hyperglycaemia in Pregnancy in Uganda: A Cross-Sectional Study

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Abstract

Aims: Hyperglycaemia in pregnancy (HIP) is a major determinant of maternal and offspring adverse outcomes, but there are little data from sub-Saharan Africa. This study examined the burden and risk factors of HIP in Uganda.

Materials and Methods: We collected data sociodemographic, anthropometric and clinical data from approximately 4000 pregnant women attending antenatal clinics in Uganda. Oral glucose tolerance test performed at 24-28 weeks gestation to screen for hyperglycaemia. Prevalence was defined as the number of participants diagnosed with HIP as a proportion of the total number of participants enrolled into the study, during the study period. Univariable and multivariable Poisson regression models were fitted to calculate prevalence ratios for association between risk factors and the outcome.

Results: Using the 2013 WHO criteria, 8.5% (95% CI: 7.7-9.4%) of the women had HIP. In multivariable analyses, older maternal age (>30 years) and mid-gestation obesity were the key factors associated with hyperglyceamia; other factors, such as HIV infection, were less important.

Conclusions: This study reveals a high prevalence of HIP in Uganda, with obesity an important contributor. Cost-effective interventions are urgently needed to mitigate this major health threat in Africa, where the rates of obesity are increasing.

Keywords: Hyperglycaemia in pregnancy; gestational diabetes; risk factors; obesity; sub-Saharan Africa

Introduction

Hyperglycaemic disorders are common in pregnancy, and are associated with increased risk of adverse outcomes in the mother and child. The International Diabetes Federation (IDF) estimates that 16.2% of live births are born to mothers with hyperglycemia in pregnancy (HIP) [1]. The majority of these (84%) have gestational diabetes mellitus (GDM), while the remainder are classified as having diabetes in pregnancy (DIP), either preexisting type 1 or type 2 diabetes which pre-dates pregnancy or is first identified during testing in the index pregnancy. Significant variations (from 1% to 28%) in the prevalence of GDM have been reported across the world. While this may reflect the fact that certain populations (such as African American, Hispanic, South-East Asian and indigenous Australian women) have increased susceptibility to GDM [2], it is also a result of differences in the screening and diagnostic criteria that have been used [3]. In general, the burden of GDM parallels the prevalence of obesity, impaired glucose tolerance and type 2 diabetes in the population [4].

It is thought that the highest burden of HIP is in low- and middle-income countries (LMIC), particularly in sub-Saharan Africa (SSA) [1]. However data on HIP in SSA are limited and, in most cases, screening is either not performed or done sub-optimally. A recent review showed that only 10% of countries in SSA had published data on HIP,[5] although HIP is likely to become an even greater health challenge in Africa in parallel with the rapidly increasing prevalence of type 2 diabetes. Most studies, which have largely come from South Africa and Nigeria, have been small and employed variable methodologies and diagnostic criteria [5-7]. Thus, GDM prevalence reported across countries has ranged from as low as 0% in Tanzania [8], to as high as 46% in Djibouti [9]. Even in the same country, in South Africa, there is wide variability in prevalence estimates, ranging from 2% to 27% [10,11]. Similarly, although some of the classical factors (such as maternal age, obesity or GDM in a previous pregnancy) have been reported to be important, the strength of these associations or other local factors have not been rigorously examined [7].

The profound genetic heterogeneity and unique environmental exposures, such as endemic infections and malnutrition, are likely to influence how HIP is expressed in Africa, and we cannot assume that the HIP risk factors and presentation follow Western stereotypes [12]. For example, some studies have shown a high prevalence of GDM among HIV-infected pregnant women. Moreover, the limited data from Africa suggest that type 2 diabetes occurs at young age and in relatively lean individuals [13,14] who predominantly display postprandial hyperglycaemia on oral glucose tolerance test (OGTT) [15-17], compared to high-income countries.

We undertook a large study of pregnant women attending antenatal care at a number of urban and peri-urban health facilities in Uganda in order to accurately document the prevalence of GDM, its risk factors (both traditional and emerging), and the contribution of fasting and postprandial hyperglycaemia.

Materials and Methods

Setting

A cross-sectional study was conducted across five hospitals in urban and peri-urban areas in Uganda, specifically Entebbe municipality (Entebbe Grade B Hospital), Kampala city (St Francis Hospital Nsambya, Uganda Martyrs Hospital Rubaga, and Kawempe Referral Hospital), and Masaka municipality (Masaka

Regional Referral Hospital).

Study population

Study participants were pregnant women aged 18 years or older and between 24 and 28 weeks of gestation, enrolled from antenatal clinics at the five hospitals between 13th June 2018 and 31st October 2019. Women who were already known to have diabetes, unable to give informed consent, or had significant medical conditions, e.g. heart failure, renal disease, severe anaemia, or preeclampsia were excluded from the study, as were those with multiple pregnancy.

Sample size

A minimum sample size of 2305 pregnant women was required in order to be able to estimate an anticipated GDM prevalence of 10% [5-7] according using the International Association of Diabetes and Pregnancy Study Group (IADPSG) criteria, with precision of +/-1.5% and a significance level of 5%. We also assumed a response rate of 80% and adjusted for a design effect of 1.2

Data collection

Standardised questionnaires were used to collect data on socio-demographic and lifestyle factors (including age, level of education, smoking status and alcohol use). Questionnaires also covered family, medical (including HIV status) and reproductive history (parity, gravidity and complications in prior pregnancies). Weight, height, waist circumference, hip circumference, and mid-upper arm circumference were measured using calibrated Seca scales, stadiometer, and flexible tape measures. After 30 minutes of rest, three blood pressure measurements, with 5 minutes' rest in between, were collected. These measurements were taken with the participant in a seated position, from the right arm when possible (otherwise collected on the left arm in those with conditions that precluded the use of the right arm), using portable sphygmomanometers (OMRON-Healthcare-Co HEM-7211-E-Model-M6; Kyoto, Japan). We used the computed mean of the last two blood pressure readings for the analysis. Body mass index (BMI) was calculated as weight in kg divided by height in meters squared in women whose weight and height measurements were taken during pregnancy.

Following an overnight fast (at least 8 hours), all women underwent an oral glucose tolerance test (OGTT); following collection of fasting venous blood sample, 82.5 g glucose monohydrate (equivalent to 75g anhydrous glucose) dissolved in 250 ml of water was administered orally, and repeat venous blood samples were taken after 1 hour and 2 hours. Samples for glucose measurement were immediately centrifuged, and plasma stored on ice. All samples were analysed centrally at the MRC/UVRI and LSHTM Clinical and Diagnostics Laboratory in Entebbe, within 4 hours of collection, or stored at -80 $^{\circ}$C for subsequent analysis.

Definitions

Based on existing literature, the following were considered as potential HIP risk factors: maternal age (greater than 30 years), obesity, multiparity, history of smoking, history of alcohol drinking, hypertension, history of macrosomia, family history of diabetes, low education attainment and HIV infection. BMI was categorised into underweight, normal, overweight and obese groups according to WHO recommendations [18]. Hypertension was defined as systolic BP≥140 mmHg or diastolic BP≥90 mmHg, or being on antihypertensive medication [19].

HIP was diagnosed according to WHO 2013 criteria [20] as either GDM: fasting glucose ≥5.1 and ≤6.9 mmol/L or 1 HR glucose ≥10.0 mmol/L or 2HR glucose ≥8.5 and <11.0 mmol/L; or DIP: fasting glucose ≥7.0 mmol/L or 2HR ≥11.1 mmol/L. Participants found with HIP (whether GDM or DIP) were referred for appropriate clinical management.

Statistical analysis

The objective of this research was to determine the prevalence of, and risk factors for HIP. Social demographics, family history and reproductive history characteristics of the participants were summarized to assess distributions, missingness and data sparsity**.** Categorical variables were summarized using frequencies and proportions. For continuous variables, the mean, median, interquartile range and standard deviation were used to summarize the variables based on the distribution. The chi-square and Fisher's exact test were used to assess the association between the categorical variables and the outcome, HIP. The one-way ANOVA was used to compare means between the two groups (HIP and Non-HIP) for normally distributed continuous variables, and the Wilcoxon Rank Sum (Mann–Whitney) Test was used for non-normally distributed continuous variables. Covariates were included in the subsequent multivariable analysis if significant differences ($P<0.05$) in means, medians and proportion were observed between the two groups.

Univariable and multivariable Poisson regression models with robust standard errors were used to compute crude and adjusted prevalence ratios for the association between each of the explanatory variables and the outcome. The likelihood ratio test was used to test for potential linear trends in association of maternal level of education, age categories and BMI categories with the outcome. A final multivariable Poisson regression model with robust standard errors was then fitted to estimate the adjusted prevalence ratios for different explanatory variables in relation to the outcome (HIP). All tests were done at 5% level of significance and analysis was done using Stata version 17.

Ethical considerations

The research project was approved by the research and ethics committee of Uganda Virus Research Institute (approval GC/127/19/04/625) and Uganda National Council for Science and Technology (approval HS2340). All participating women gave informed written consent.

Patient and public involvement

Patients, community representatives and policy makers are engaged at different stages of our research including formulating research questions. We have community advisory groups to facilitate our engagement with the community.

Results

General characteristics

We identified a total of 4796 women who were between 24 and 28 weeks of gestation. Of these, 958 were excluded because they did not satisfy the other eligibility criteria or had incomplete data (Figure 1). A total of 3838 women were included in the final analyses, and their characteristics are shown in Table 1. Their mean age was 26.6 (SD 5.5) years. 3.6% of the women were HIV positive. Of the 3838 participants, 3511 were normoglycaemic and 327 (Prevalence: 8.5%; 95% confidence interval (CI): 7.7-9.4%) had hyperglycaemia. Of the hyperglycaemic cases, 280 (85.6%) and 47 (14.4%) were graded as GDM and DIP, respectively (Figure 1).

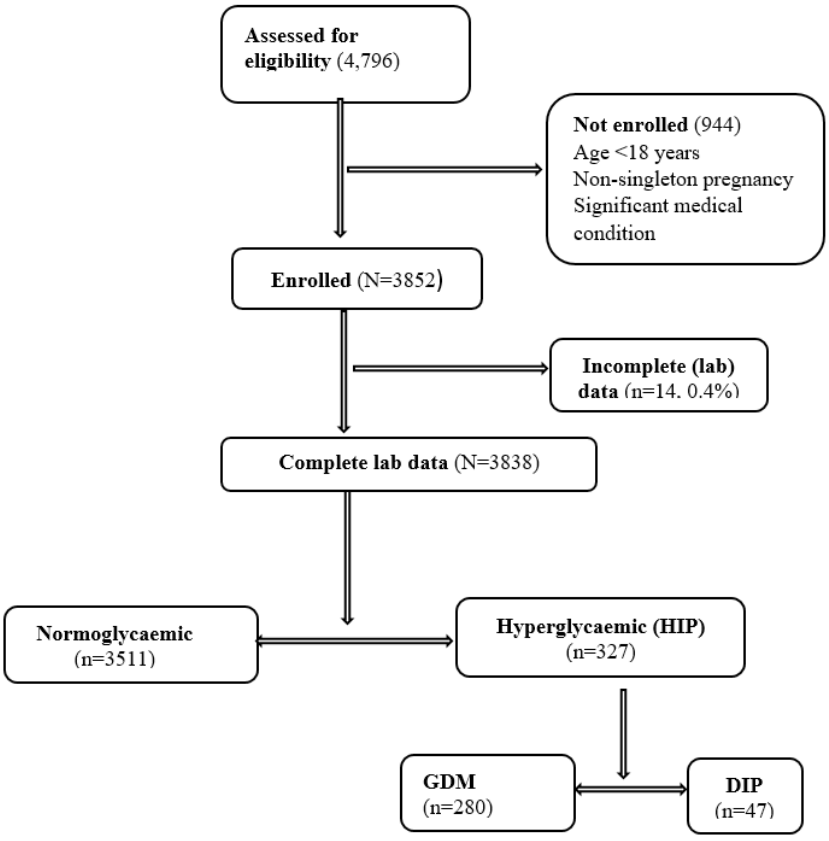

Figure 1: Participants flow diagram in the study.

Variable	All participants n=3838	Hyperglycaemic n=327 (8.5%)	Non-Hyperglycaemic n=3511(91.4%)	P-value
MUAC (cm), Median(IQR)	28.5 (26.1 – 31.5)	31.0 (27.8– 34.4)	28.3 (26-31.1)	<0.001
Gravidity, Median(IQR)	2 (1 – 3)	3 (2 - 4)	2 (1 – 3)	<0.001
Parity, Median(IQR)	1 (0 – 2)	1 (0 – 3)	1 (0 – 2)	<0.001
Health facility, n(%)				
Public	2296 (59.8)	141 (43.1)	2155 (61.4)	
Private	1542 (40.2)	186 (56.9)	1356 (38.6)	<0.001
Hypertension, n(%)				
Yes	34 (0.9)	4 (1.2)	30 (0.9)	0.53
HIV status				
Positive	137 (3.6)	19 (5.8)	118 (3.4)	0.022
History of macrosomia (birth weight > 4kgs), n(%)				
Yes	415 (18.9)	60 (26.1)	355 (18.1)	0.003
Age groups (years), n (%)				
18-24	1538 (40.1)	83 (25.4)	1455 (41.4)	
25-29	1234 (32.2)	94 (28.8)	1140 (32.5)	
30-34	672 (17.5)	84 (25.7)	588 (16.8)	
35 and above	394 (10.3)	66 (20.2)	328(9.4)	<0.001
BMI, n(%)				
Below 25	1350 (35.2)	68 (20.8)	1282 (36.5)	
Overweight (25-30)	1453 (37.9)	99 (30.3)	1354 (38.6)	
Obese (30+)	1032 (26.9)	160 (48.9)	872 (24.9)	<0.001
Maternal highest level of education, n(%)				
Primary	721 (18.9)	57 (17.5)	664 (19.1)	
Secondary	1706 (44.9)	135 (41.5)	1571 (45.2)	
Post-secondary	593 (15.6)	43 (13.2)	550 (15.8)	
University	784 (20.6)	90 (27.7)	694 (19.9)	0.011
Family history of diabetes, n(%)				
Yes	935 (26.3)	99 (32.1)	836 (25.7)	0.014
History of smoking, n(%)				
Yes	37 (1.0)	7 (2.1)	30 (0.9)	0.023
History of alcohol use, n(%)				
Yes	828 (21.6)	74 (22.6)	754 (21.5)	0.63
Number of risk factors, median(IQR)	3 (1-4)	4 (2-5)	3 (1-4)	<0.001
Number of risk factors, n(%)				
0 -1	1016 (26.5)	58 (17.7)	958 (27.3)	
2- 3	1612 (42.0)	101 (30.9)	1511 (43.0)	
4-5	959 (25.0)	127 (38.8)	832 (23.7)	
≥6	251 (6..5)	41 (12.5)	210 (6.0)	<0.001

SD: Standard Deviation, IQR: Interquartile Range, BMI: Body Mass Index, MUAC: Mid Upper Arm Circumference, Number of risk factors: this was defined as having one or more of the risk factors maternal age (greater than 30 years), obesity, multiparty, history of smoking, history of alcohol drinking, hypertension, history of macrosomia, family history of diabetes, low education attainment and HIV infection.

Table 1: Maternal baseline characteristics.

Risk factors for HIP

The prevalence of HIP was higher among women from private hospitals than those from public hospitals. Hyperglycaemic mothers were on average older, and had higher median mid upper-arm circumference and higher median BMI, compared to non-hyperglycaemic participants; 48.9% of the hyperglycaemic participants were obese, compared to 24.9% in those who did not have HIP (Table 1). Women with HIP were more likely to have a family history of diabetes and had higher median gravidity. They were also more likely to have higher education attainment, and to be smokers, compared to women who did not have HIP. The prevalence of hypertension was similar among women with HIP and those with normoglycaemia. In contrast, the prevalence of HIV infection was higher among women with HIP than in those without HIP (Table 1).

Final multivariable model results were based on the 3,526 (92%) participants who had complete data for the variables included. Participants who were excluded from the final analysis model due to missing data had similar sociodemographic characteristics to those that were included (Supplementary Table 1). In adjusted analyses, there was strong (P<0.001) evidence of an association between BMI and HIP after adjusting for HIV status, gravidity, age group, education, family history of diabetes, and smoking history. The adjusted prevalence ratio of being hyperglycaemic comparing obese participants to those with BMI below 25 kg / m^2 was 2.07 (95% CI: 1.54 – 2.79). Similarly, each additional increase in age level category was strongly associated with the risk of HIP (P=0.007), adjusting for HIV status, gravidity, BMI, education, family history of diabetes and participant's history of smoking (aPR:1.21, 95% CI: 1.05 – 1.40). Health facility type was strongly associated with the risk of HIP (P=0.001), adjusting for HIV status, gravidity, BMI, education, family history of diabetes and participant's history of smoking. The adjusted prevalence ratio of being hyperglycaemic comparing participants in private health facilities to those in public facilities was 1.51 (95% CI: 1.19 – 1.92).

There was evidence (P=0.015) of an association between smoking history and HIP after adjusting for other variables in the model. The prevalence of hyperglycaemia was 2.27 times greater for participants with a history of smoking compared to those without no smoking history, controlling for other variables in the model (aPR:2.27, 95% CI: 1.17-4.39). HIV status, gravidity, Parity, family history of diabetes, and maternal highest level of education were not associated with HIP after adjusting for other variables in the final model (Table 2).

Based on the final multivariable regression model, the likelihood ratio test showed evidence against linearity of BMI (p=0.023), but not for maternal education (p=0.185), and age (p=0.666). BMI was therefore retained as categorical in the final model, whilst a single estimate for a one-level increase was fitted for the other variables i.e maternal education and age.

Variable	Univariable model			Multivariable model		
	Crude PR	95% CI	P-value	Adjusted PR	95% CI	P-value
Gravidity	1.18	1.12 – 1.24	<0.001	0.98	0.85– 1.13	0.811
Parity	1.20	1.13-1.29	<0.001	1.06	0.90-1.26	0.440
HIV status						
Negative	ref	ref		ref	ref	
Positive	1.67	1.08 -2.56	0.020	1.54	0.97-2.43	0.067
Health Facility						
Public	ref	ref		ref	Ref	
Private	1.96	1.59-2.42	<0.001	1.51	1.19-1.92	0.001
Prevalence ratio per additional level of age-category. (18 – 24, 25-29,30-34 and greater or equal 35 years)	1.47	1.35-1.63	<0.001	1.21	1.05-1.40	0.007
Grouped BMI, kg/m^2						
Below 25	ref	ref		ref	ref	
Overweight (25-30)	1.35	1.00 – 1.83		1.08	0.79 – 1.47	
Obese (30+)	3.08	2.35 – 4.04	<0.001	2.07	1.54 – 2.79	<0.001
Prevalence ratio per additional level of maternal education (primary, secondary, Post-secondary, and university)	1.13	1.02-1.25	0.017	1.00	0.88 -1.11	0.691
Family history of diabetes						
No	ref	ref		ref	ref	
Yes	1.33	1.06 - 1.67	0.014	1.07	0.85-1.34	0.576
History of smoking						
No	ref	ref		Ref	ref	
Yes	2.25	1.14 – 4.42	0.019	2.27	1.17-4.39	0.015

PR: Prevalence Ratio, 95% CI: 95% Confidence Interval, BMI: Body Mass Index. Adjusted model: Adjusted for gravidity, HIV status, and maternal highest level of education, age group, family history of diabetes, smoking history and BMI (Kg/m2).

Table 2: Univariable and multivariable robust Poisson regression analysis of risk factors for HIP

HIP detection by fasting vs 1hr and 2hr glucose

Among women who had HIP, hyperglycaemia would have been detected with fasting glucose measurement alone, without the need for 1hr and/or 2hr OGTT samples, in 75.5% of the cases. Fasting blood glucose performed equally well at identifying HIP across the different categories of BMI or age groups (Supplementary Table 2). 4.9% of the women with HIP had hyperglycaemia only at 1hr, 13.9% had hyperglycaemia only at 2 hr time point during the OGTT; 5.8% had elevated glucose values at both 1 and 2hr time points in the OGTT (Supplementary Table 2 and Supplementary Fig. 1).

Discussion

In this study, we have shown that hyperglycaemia is common among pregnant women in Uganda. The majority of the cases (85.6%) had GDM. The traditional risk factors, notably increasing age and BMI, were the strongest predictors of HIP in this setting; HIV infection was less important as a risk factor. Three quarters of HIP cases were detected with fasting blood glucose testing alone.

The prevalence of GDM in this study is consistent with more recent estimates from other countries in SSA; for example, a prevalence of 8.4% was reported in Tanzanian urban women [21], while in Johannesburg, South Africa, the prevalence was 9.1% [22]. These reflect a high burden in countries that currently have relatively young and lean populations. Importantly, this burden is likely to increase sharply because increasing numbers of women in SSA are entering pregnancy at older age, and the prevalence of obesity in the region is increasing rapidly, particularly among women of childbearing age [23]. HIP will therefore become a major challenge in a continent where it is currently not prioritised, and resources severely limited.

There continues to be much debate about what is the right approach for screening and management of HIP, particularly in LMIC. In most countries, when GDM screening is done, this is restricted to "high-risk" women. The risk stratification is mostly based on data from high-income countries rather than locally derived evidence. Reassuringly, our data and others [5,6] show that the major risk factors for HIP in SSA are generally similar to those in high-income countries. The impact of potential local determinants appears to be small. For example, early studies, mostly from high-income countries, showed that HIV-infected women had a high prevalence of GDM [24]. In our study, while univariate analysis was consistent with this association, multivariate analysis, and other data from SSA [25], do not support HIV as an important independent risk factor for HIP. This lack of association may reflect recent trends to use antiretroviral therapy with less toxic metabolic side effects. Also, the prevalence of HIV was fairly low, so our study was not adequately powered.

The fact that the major drivers of HIP in SSA are similar to those observed in developed countries should make it easier for countries in SSA to adopt low-cost interventions that have been shown to be effective in other regions, such as those targeting obesity. It is, however, crucial to also note important differences in expression of these risk factors. For example, we observed that obesity and HIP were more common in women with high education attainment and higher socioeconomic status, while in high-income countries these risk factors are typically more prevalent in the less educated and lower socioeconomic status groups. Adapting/targeting potential interventions in SSA would need to take these local contexts into account. Additionally, because of low levels of health literacy/awareness and poor record keeping in SSA, determining risk factors accurately poses a challenge; for this reason, the International Federation of Gynecology and Obstetrics recommends universal testing in LMIC settings [26,27].

Similarly, most countries in SSA, particularly in rural areas, will not have the capacity to undertake screening based on OGTT. In our study, the majority of HIP cases (75.5%) would have been detected if the fasting blood glucose was the only test used. This supports use of fasting blood glucose as a simple and practical screening approach in resource-poor settings [28]. However, the fact that nearly 25% of women with HIP would have been missed if fasting glucose alone was measured, because they had isolated elevation of the one- or two-hour glucose levels (a finding supported recent observations in Nigeria [29]), remains a concern. This is in accord with increasing evidence from epidemiological studies in non-pregnant populations that suggest that a significant proportion of dysglycaemia in Africa is expressed through abnormalities in postprandial glucose concentrations, and that use of fasting blood glucose alone would fail to detect a substantial fraction of individuals with diabetes [17]. The natural history of such isolated postprandial hyperglycaemia, including its relationship to complications, is unclear and needs further investigation. Nonetheless, these observations will need taking into account when local strategies for screening and treating hyperglycaemia in pregnancy are considered.

Our study has a number of strengths. It is the largest one of its kind in a SSA population and included pregnant women across the spectrum of socioeconomic status from a number of hospitals is Uganda, with a good participation rate. Even after excluding participants with missing data (whose characteristics were not dissimilar to those included), the study had sufficient power to answer the key research questions. We employed rigorous methodology and standardized protocols, including centralised laboratory testing. An important limitation of the current study is its cross-sectional nature and therefore it cannot inform causal links or define outcomes of HIP in the region (which is being addressed in another study).

Conclusions

Our study addressed a major evidence gap on HIP burden and risk factors in SSA. We report a relatively high prevalence of HIP in Uganda, and that obesity is a major contributor. This is likely to increase sharply in the near future, as more and more women become pregnant at higher BMI and older age, the key HIP risk factor. More effort will be required to improved detection, understand outcomes, and develop appropriate HIP management strategies in Uganda and other countries in sub-Saharan Africa.

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Contributors: MJN had the initial idea and developed the conceptual framework. BKN, IS, AA, IS and EW did the data analysis. BKN and IS drafted the manuscript. All authors contributed to the design or data collection, and commented on drafts and revisions.

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