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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Determinants of change in polypharmacy status in Switzerland: the population-based CoLaus study

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Abstract
Objectives This study aimed to assess the prevalence, the change, and the determinants of change in polypharmacy in a population-based sample.
Methods Baseline (2003–2006) and follow-up (2009–2012) data are from 4679 participants aged between 35 and 75 years (53.5% women, mean age 52.6 ± 10.6 years) from the population of Lausanne, Switzerland. Polypharmacy was defined by the regular use of ≥5 drugs. Four categories of change were defined: *never* (no polypharmacy at baseline and follow-up), *initiating* (no polypharmacy at baseline but at follow-up), *maintaining*, or *quitting*.
Results Polypharmacy increased from 7.7% at baseline to 15.3% at follow-up. Cardiovascular drugs were the most prescribed medicines at baseline and follow-up. Gender, age, obesity, smoking, previously diagnosed hypertension, or diabetes or dyslipidemia were significantly and independently associated with initiating and maintaining polypharmacy.
Conclusion In a population-based sample, prevalence of polypharmacy doubled over a 5.6-year period. The main determinants of initiating polypharmacy were age, overweight and obesity, smoking status, and previously diagnosed cardiovascular risk factors.

Keywords Polypharmacy · Determinants · Trends · General population · Switzerland

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Introduction

In recent years, there has been a substantial increase in the prescribing of regular medicines in general populations [1]. Subsequently, prevalence of polypharmacy, referred as the simultaneous intake of five or more medications, has been increasing [2] not only among the elderly but also in other ages [3].

Polypharmacy is driven by the increase in age and multimorbidity [4]. Given the current aging of the population and the number of drugs needed to treat age-associated multimorbidity, it is expected that the prevalence of patients on polypharmacy will continue to increase. Polypharmacy can increase the risk of drug-disease interaction in addition to drug-drug interactions; however, polypharmacy may, in many cases such as multimorbidity, be entirely appropriate and inevitable [5–7].

Although polypharmacy has become more widespread in recent years, determinants of change in polypharmacy status in longitudinal study are not well studied. Thus, this study aimed (1) to assess the prevalence and the change of

polypharmacy and (2) to examine the determinants of change in polypharmacy status as initiation or quitting.

Materials and methods

Study population and design

The CoLaus study is an ongoing prospective survey investigating the biological and genetic determinants of cardiovascular risk factors (CVRFs) and cardiovascular disease (CVD) in the population of Lausanne, Switzerland. The study was approved by the Institutional Ethics Committee of the University of Lausanne (decision reference 33/09). Detailed descriptions of the study design have been reported elsewhere [8]. A simple, non-stratified random sample of the Lausanne population aged between 35 and 75 years was drawn. Inclusion criteria were (a) written informed consent and (b) willingness to take part in the examination and to provide blood samples. Recruitment began in June 2003 and ended in May 2006 and included 6733 participants, with a participation rate of 41%. The baseline evaluation included an interview, a physical exam, blood sampling, and a set of questionnaires. As illustrated in supplemental Fig. 1, of the initial 6733 participants, 6184 (91.8%) provided extended data on their medicines. The follow-up visit was similar to the baseline evaluation and was performed between April 2009 and September 2012, 5.5 years on average after the baseline, and included 5064 participants (75.2% of the initial sample), 4679 of which (69.5% of the initial sample) had complete medication data at baseline and follow-up.

Lifestyle and clinical and biological parameters

Lifestyle factors, CVD, and medication status were assessed by questionnaire. Smoking status was categorized into never, former, and current as reported. Educational level was categorized as low (obligatory school or apprenticeship), medium (high school), or high (university degree). Height and weight were assessed with the participants in light clothes and without shoes using a Seca® scale; body mass index (BMI) was categorized as normal ($18.5 < BMI < 25$ kg/m^2), overweight ($25 \leq BMI < 30$ kg/m^2), and obese (≥ 30 kg/m^2). As the number of underweight ($BMI \leq 18.5$ kg/m^2) participants was small, they were included in the normal weight group.

Blood pressure was measured thrice on the right arm, after a rest of at least 10 min in the seated position using an Omron® HEM-907 automated oscillometric sphygmomanometer. The average of the last two blood pressure measurements was used for analyses.

Venous blood samples were drawn after an overnight fast. Clinical chemistry assays were performed at the central laboratory of the University Hospital of Lausanne (CHUV). Total cholesterol, HDL-cholesterol, triglycerides (TGs), and glucose were measured using commercial reagents; low-density lipoprotein (LDL-C) was calculated using the Friedewald formula if TG < 4.6 mmol/L.

For each condition (hypertension, dyslipidemia, or diabetes), three categories were defined: (1) absent (neither reported nor newly diagnosed at the baseline examination), (2) reported by the participant, and (3) newly diagnosed at the baseline examination among participants not reporting the condition (supplemental Fig. 2). Newly diagnosed hypertension was defined as a systolic BP (SBP) ≥140 mmHg and/or a diastolic BP (DBP) ≥90 mmHg [9]. Newly diagnosed dyslipidemia was defined as a total cholesterol >6.5 mmol/L and/or LDL-cholesterol >4.1 mmol/L and/or triglycerides >2.0 mmol/L [10]. Newly diagnosed diabetes was defined as a fasting plasma glucose >7 mmol/L [11].

Definitions of polypharmacy and polypharmacy changing status

Participants indicated which medicines they were currently taking. Medicines were coded according to the Anatomical Therapeutics Chemical (ATC) Classification System of the World Health Organization. Medicines were considered if they existed in the ATC; only medications listed in the official Swiss pharmacopeia (compendium.ch) were considered. Other complementary medicines such as non-official phytotherapies, dietary supplements (i.e., shark cartilage, Bach's flowers), or homeopathy were not considered. Polypharmacy was defined as the use of five or more medicines, including OTC drugs, regardless if a medicine contained one or more effective drugs (i.e., fixed dose combinations) [12].

Changing of polypharmacy status was defined as never (no polypharmacy at baseline and follow-up), initiation (no polypharmacy at baseline but at follow-up), quitting (polypharmacy at baseline but not at follow-up), and maintaining (polypharmacy at baseline and follow-up).

Statistical analysis

Statistical analysis was performed using Stata software version 14.1 (Stata Corp., College Station, TX, USA). Descriptive results were expressed as mean ± standard deviation (SD) or as the number of participants (percentage). Bivariate analysis was performed using chi-squared test for categorical variables and Kruskal-Wallis non-parametric test for age. Multivariate analysis was performed using multinomial (polytomous) logistic regression, and results were expressed as multivariate-adjusted relative risk ratios (RRRs) and 95% confidence interval (CI). Models were adjusted for gender, age groups ([35–50[, [50–65[, and [65–75]), BMI categories (normal, overweight, and obese), educational level

(low, middle, high), marital status (living in couple, living alone), country of birth (Switzerland vs. other), smoking categories (never, former, current), being physically active (yes vs. no), hypertension (never, previously diagnosed, and newly diagnosed), dyslipidemia (never, previously diagnosed, and newly diagnosed), and diabetes (never, previously diagnosed, and newly diagnosed). Statistical significance was considered for a two-tailed test with $P < 0.05$.

As some drugs could combine several pharmacologically different active substances, we ran several sensitivity analyses by checking ATC codes corresponding to combinations of different active substances (supplementary Table 1), excluding combinations of vitamins and minerals (ATC codes A11A, A11C, A11D, A11E, A11G¸ A11J, A12AX, B03AD, and B03AE). As ATC codes were defined with a maximum of five letters in the baseline survey, the same categorization was applied in the follow-up. Categories of "polyactive substances" were defined similarly to polypharmacy, i.e., 0–4 and 5 or more active substances. The same procedure was applied to define categories of change in polyactive substances: never (no polyactive substances at baseline and follow-up), initiation (no polyactive substances at baseline but at follow-up), quitting (polyactive substances at baseline but not at follow-up), and maintaining (polyactive substances at baseline and follow-up). Age-adjusted analyses were conducted using standardization based on the Lausanne population distribution for 2003, obtained from the Canton statistical office http://www.stat.vd.ch/Default.aspx?DocID=7818&DomId=2783. As some age groups initially present at baseline no longer existed at follow-up, calculations were based on age range 40–75, which is common for both baseline and follow-up periods. As no information was available regarding the total number of comorbidities, we used the number of medicines at baseline (categorized into three groups 0–1, 2–3, and 4 or more) as a proxy for adjustment. Two analyses were performed: one on polypharmacy and another on polyactive substances.

Results

Selection and characteristics of participants

The demographic, clinical and functional characteristics of the participants included and excluded are summarized in Supplemental Table 2. Excluded participants were more frequently men, not born in Switzerland, obese, current smokers, and with lower education.

Prevalence of medicines and polypharmacy

Prevalences of polypharmacy status and of the main drugs at baseline and follow-up (FU) are summarized in Table 1. Polypharmacy increased from 7.7% at baseline to 15.3% at follow-up. Cardiovascular drugs were the most prescribed medicines, both at baseline and follow-up; among cardiovascular drugs, hypolipidemic drugs and statins were the most frequent ones.

Table 1 Evolution of polypharmacy status and of the main drugs at baseline (2003–2006) and follow-up (2009–2012), CoLaus study, Switzerland, 4679 participants

	Baseline	Follow-up	*P* value
Polypharmacy			
5+ medicines	360 (7.7)	714 (15.3)	<0.001
Cardiovascular	1015 (21.7)	1780 (38.0)	<0.001
Hypolipidemic drugs (C10)	535 (11.4)	1003 (21.4)	<0.001
Statins (C10AA, C10B)	459 (9.8)	838 (17.9)	<0.001
Other[a]	99 (2.1)	216 (4.6)	<0.001
Antivitamin K (B01AA)	52 (1.1)	109 (2.3)	<0.001
Antiaggregants	312 (6.7)	565 (12.1)	<0.001
Aspirin	301 (6.4)	520 (11.1)	<0.001
ARB (C09C, C09D)	238 (5.1)	623 (13.3)	<0.001
ACE inhibitors (C09A, C09B)	157 (3.4)	345 (7.4)	<0.001
Beta-blockers (C07)	163 (3.5)	426 (9.1)	<0.001
Calcium channel blockers (C08)	91 (1.9)	218 (4.7)	<0.001
Diuretics (C03)	55 (1.2)	163 (3.5)	<0.001
Other (C01, C02, C04)	6 (0.1)	81 (1.7)	<0.001
Antidiabetic drugs (A10)	151 (3.2)	265 (5.7)	<0.001
Oral antidiabetics	139 (3.0)	241 (5.2)	<0.001
Insulin (A10A)	27 (0.6)	61 (1.3)	<0.001
Drugs for the digestive tract	284 (6.1)	453 (9.7)	<0.001
Antiacids (A02)	194 (4.2)	341 (7.3)	<0.001
Drugs for constipation (A06)	31 (0.7)	66 (1.4)	<0.001
Other[a]	97 (2.1)	107 (2.3)	0.450
Vitamins and minerals (A11, A12)	217 (4.6)	596 (12.7)	<0.001
Analgesics	588 (12.6)	625 (13.4)	0.230
Anilides (N02BE)	77 (1.7)	106 (2.3)	0.025
NSAIDs (M01)	225 (4.8)	425 (9.1)	<0.001
Opioids (N02A)	28 (0.6)	61 (1.3)	<0.001
Psychiatric	610 (13.0)	770 (16.5)	<0.001
Antidepressants (N06)	429 (9.2)	503 (10.8)	<0.001
Anxiolytics (N05B)	178 (3.8)	243 (5.2)	<0.001
Hypnotics and sedatives (N05C)	130 (2.8)	227 (4.9)	<0.001
Antipsychotics (N05A)	41 (0.9)	53 (1.1)	0.104

Results are expressed as the number of participants (column percentage). Between-period comparison using Cochran's test for paired data

ARB angiotensin receptor blocker, *ACE* angiotensin-converting enzyme, *NSAID* non-steroidal anti-inflammatory drug

[a] Codes A01, A03, A04, A05, A07, and A09

Changes and determinants in polypharmacy status

The changes in the polypharmacy status and determinants of changes are presented in Supplemental Table 3 (bivariate analysis) and Table 2 (multivariate analysis). Four hundred fifteen

Table 2 Multivariate analysis of the factors associated with changes in polypharmacy (5+ medicines/day) status between baseline (2003–2006) and follow-up (2009–2012), CoLaus study, Switzerland, 4679 participants

	Initiation	*P* value	Quitting	*P* value	Maintenance	*P* value
Gender						
Woman	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Man	0.46 (0.36–0.59)	<0.001	0.34 (0.21–0.57)	<0.001	0.50 (0.36–0.69)	<0.001
Age group						
[35–50[	1 (Ref.)		1 (Ref.)		1 (Ref.)	
[50–65[	2.54 (1.93–3.34)	<0.001	2.53 (1.51–4.24)	<0.001	4.70 (2.91–7.61)	<0.001
[65–75]	4.65 (3.36–6.43)	<0.001	3.58 (1.86–6.88)	<0.001	8.96 (5.34–15.05)	<0.001
P value for trend	<0.001		<0.001		<0.001	
BMI categories						
Normal	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Overweight	1.70 (1.32–2.18)	<0.001	1.16 (0.73–1.85)	0.535	1.43 (1.00–2.04)	0.047
Obese	1.92 (1.41–2.63)	<0.001	1.08 (0.55–2.13)	0.824	1.96 (1.31–2.93)	0.001
P value for trend	<0.001		0.577		<0.001	
Education						
High	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Middle	1.06 (0.75–1.51)	0.743	0.98 (0.53–1.82)	0.952	1.97 (1.12–3.45)	0.018
Low	1.13 (0.83–1.55)	0.433	0.87 (0.49–1.53)	0.630	1.91 (1.13–3.21)	0.015
P value for trend	0.433		0.497		0.071	
Marital status						
Living alone	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Living in couple	0.92 (0.74–1.15)	0.481	0.67 (0.44–1.02)	0.059	0.83 (0.62–1.12)	0.222
Born in Switzerland						
No	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Yes	1.02 (0.81–1.29)	0.858	0.85 (0.55–1.31)	0.462	0.74 (0.54–1.00)	0.049
Smoking status						
Never	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Former	1.56 (1.21–2.01)	0.001	1.40 (0.88–2.24)	0.152	1.33 (0.96–1.86)	0.088
Current	2.22 (1.69–2.91)	<0.001	1.08 (0.62–1.88)	0.796	1.57 (1.07–2.31)	0.020
P value for trend	<0.001		0.570		0.019	
Physically active						
No	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Yes	0.91 (0.73–1.13)	0.396	0.86 (0.56–1.32)	0.490	0.94 (0.70–1.26)	0.686
Hypertension						
None	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Already known	2.71 (2.12–3.46)	<0.001	1.12 (0.67–1.88)	0.654	4.75 (3.39–6.65)	<0.001
Diagnosed at baseline	1.28 (0.92–1.77)	0.140	0.66 (0.33–1.32)	0.240	0.60 (0.32–1.14)	0.118
Dyslipidemia						
None	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Already known	1.40 (1.09–1.80)	0.008	1.69 (1.02–2.81)	0.043	3.41 (2.43–4.77)	<0.001
Diagnosed at baseline	1.03 (0.78–1.36)	0.828	1.57 (0.93–2.64)	0.091	1.31 (0.85–2.02)	0.220
Diabetes						
None	1 (Ref.)		1 (Ref.)		1 (Ref.)	
Already known	3.35 (2.24–5.01)	<0.001	1.66 (0.57–4.82)	0.350	5.64 (3.68–8.65)	<0.001
Diagnosed at baseline	2.62 (1.53–4.50)	<0.001	1.26 (0.29–5.41)	0.753	2.10 (1.03–4.30)	0.041

Results are expressed as multivariate-adjusted odds ratio and 95% confidence interval. Statistical analysis using polytomous logistic regression using the "never" group as reference and using all variables in the table as covariates

BMI body mass index

participants (9.6%) initiated; 263 (5.6%) maintained, and only 97 (2.1%) quitted polypharmacy, while 3868 (82.7%) were not on polypharmacy neither at baseline nor at follow-up.

Bivariate analysis showed gender, age, BMI categories, education level, living alone, smoking status, and known hypertension, dyslipidemia, and diabetes to be associated with a change in polypharmacy status. Multivariate analysis indicated that being male and older were associated with any change in polypharmacy status, while overweight and obesity were only associated with initiation and maintaining polypharmacy status. Smoking (current or former) was associated with the initiation of polypharmacy, but only current smoking was associated with maintaining polypharmacy status. Known hypertension was associated with initiating and maintaining polypharmacy status, while no association was found with hypertension diagnosed at baseline. Known dyslipidemia was associated with maintaining polypharmacy status, while no association was found with dyslipidemia diagnosed at baseline. Both known diabetes and diabetes diagnosed at baseline were associated with initiating or maintaining polypharmacy status.

Sensitivity analyses

The crude prevalence rates of polyactive substance use were 8.9 and 17.1% at baseline and follow-up, respectively. The corresponding age-standardized rates for polypharmacy were 8.6% at baseline and 9.6% at follow-up; for polyactive substances, the rates were 9.9 and 13.9%, respectively. The results of the multivariate analysis using change in polyactive substances are provided in supplementary Table 4. Similar associations were found as for polypharmacy.

When the analysis was adjusted for the number of medicines at baseline, similar results were obtained for polypharmacy regarding the determinants of initiation; for maintenance, significant associations persisted for age, BMI categories, and known hypertension, dyslipidemia, and diabetes, while for quitting, all determinants were no longer significant (supplementary Table 5). Finally, for polyactive substances, most determinants of initiation remained significant; for maintenance, significant associations persisted for age, BMI categories, and known hypertension and diabetes, while for quitting, all determinants were no longer significant (supplementary Table 6).

Discussion

In this study, we assessed the baseline determinants of changes in polypharmacy such as BMI, smoking, and presence of specific comorbidities, and we found an absolute increase from 7.7 to 15.3% in polypharmacy over 5.6 years.

Prevalence of medicines and polypharmacy

Cardiovascular drugs were the most prescribed medicines, both at baseline and follow-up. This finding is consistent with a study in a Scottish primary care population [13]. Indeed, cardiovascular drugs not only constitute the greatest part of medicines taken by the population but are also a strong predictor of polypharmacy [14].

Among cardiovascular drugs, hypolipidemic drugs and statins were the most frequent ones and their prevalence almost doubled between baseline and follow-up. Importantly, this increase in hypolipidemic drugs is lower than the increase in dyslipidaemia prevalence [15]. Nevertheless, this doubling of hypolipidemic drugs between baseline and follow-up, with one fifth of participants taking them, is in line with a study conducted in Ireland [1] and also with a wider acceptance of preventive medication for the general population [16]. Contrary to USA, there is no consensus regarding guidelines for cardiovascular prevention in Switzerland. Several equations are used. This lack of consensus could explain a lower statin prescription [17].

Changes and determinants in polypharmacy status

Polypharmacy literally doubled from 7.7% at baseline to 15.3% at follow-up, a finding also observed in the USA (8.2% in 1999–2000 to 15% in 2011–2012) [18]. Although some participants quitted polypharmacy, initiating polypharmacy was more than 4.5-fold more frequent than quitting. Male gender was significantly associated with a lower likelihood of initiating, quitting, or maintaining polypharmacy. A possible explanation is that men utilize less frequently preventive care services than women [19], which would preclude the timely detection of diseases and therefore their treatment. Nevertheless, the effect of gender in polypharmacy changes should be further explored.

Increased age was significantly and positively associated with initiating, quitting, or maintaining polypharmacy. The increased age-related morbidity is the most obvious explanation for the initiation and maintenance, while the avoidance of any possible drug-drug interaction as well as the limited life expectancy in older adults might explain the positive association with quitting, as discussed in a systematic review [20].

Increased body mass index and current smoking were significantly and positively associated with initiating and maintaining polypharmacy status. Also, similar to our finding, obese subjects had significantly more exposure to multiple drug treatments in population-based studies in Italy and Greece [21, 22]. This might be partly due to the increased number of cardiovascular risk factors among obese subjects [23], although other diseases such as arthrosis and sleep disorders might also contribute to the increased number of drugs in this group. Regarding smoking, in the Greek study, smokers

were almost three times more likely to take four or more drugs [22]. Again, a higher prevalence of smoking-associated diseases such as chronic obstructive pulmonary disease might contribute. Unfortunately, no data regarding non-cardiovascular diseases was collected in the CoLaus study to confirm these hypotheses. The most likely explanation is an increased occurrence of obesity-associated and smoking-associated pathologies and corresponding medication. Overall, our results suggest that quitting smoking and preventing obesity might be interesting solutions to decrease the prevalence of polypharmacy.

Consistent with the high prevalence of cardiovascular drugs, participants previously diagnosed with hypertension, dyslipidemia, and diabetes had a higher likelihood of initiating or maintaining polypharmacy status. Similarly, a study conducted in Spain showed that hypertension or dyslipidemia, combined with other medications for the treatment of diabetes or other cardiovascular pathologies, could be considered as a pattern of polypharmacy [24]. However, newly diagnosed risk factors had no effect (with the exception of newly diagnosed diabetes for initiation of polypharmacy). The association with maintenance of polypharmacy was expected, as cardiovascular risk factors need a chronic, lifetime treatment [25]. The fact that existing cardiovascular risk factors were also associated with initiating polypharmacy was less expected, but consistent with the fact that treatment escalation is frequently necessary to maintain acceptable levels. Conversely, only newly diagnosed diabetes was significantly associated with initiating polypharmacy, which is consistent with a longitudinal study in Netherlands indicating that diabetes was a strong predictor of polypharmacy [26]. Interestingly, most of the factors associated with polypharmacy (obesity, hypertension, dyslipidemia, and diabetes) are components of the metabolic syndrome. Hence, our results suggest that participants with metabolic syndrome would be at high risk of polypharmacy. Indeed, a cross-sectional study conducted in Nancy (France) showed people with metabolic syndrome to have a 3.17 higher likelihood of presenting with polypharmacy (≥4 drugs) [27].

Sensitivity analyses

A significant number of drugs contain several active substances; a sensitivity analysis was conducted taking into account the number of active substances rather than the number of drugs (pills) taken. Considering only the number of drugs might underestimate the effect of polypharmacy, and indeed, the prevalence rate of participants taking at least five active substances was higher by approximately 2% than the rate based on drugs. Hence, it is likely that most prevalence rates reported using the number of drugs (pills) are also underestimated, but the magnitude of the underestimation will depend on the availability of drugs with several active substances.

Interestingly, the main determinants of change in the number of active substances were similar to those for polypharmacy. The same findings were obtained after adjusting for the number of medicines at baseline; for instance, age, BMI categories, and known cardiovascular risk factors were positively associated with initiation and maintenance. Hence, our results suggest that, contrary to the prevalence rates, the determinants of polypharmacy and of polyactive substances are identical and that age and BMI categories are the main drivers of initiating and maintaining polypharmacy or polyactive substances. Given the aging and the increase in BMI of the worldwide population, our results suggest that the prevalence of polypharmacy or polyactive substances will considerably increase in the near future. Still, studies assessing both polypharmacy and polyactive drugs in the general population are missing, and it would be of interest that our results be replicated in other settings.

Strengths and limitations

The major strength of this study is that it is one of the few prospective studies assessing the determinants of change in polypharmacy in a population-based sample. This study has also some limitations. First, participation rate was low (41%), but in line with other epidemiological studies [28]. Second, recall bias might occur, as participants might have indicated only the most important medications. Hence, polypharmacy prevalences might be underestimated. Still, our results provide a conservative estimation of the already considerable prevalence (15% at follow-up) of polypharmacy in this group. Also, recent studies suggest that self-reported medication use closely relates with pharmacy records [29]; hence, recall bias might be reduced.

Conclusion

In a population-based sample, prevalence of polypharmacy doubled over a 5.6-year period. The main determinants of initiating polypharmacy were age, overweight and obesity, smoking status, and previously diagnosed cardiovascular risk factors.

Author contributions NA wrote most of the manuscript. PMV collected data, made the statistical analysis, and reviewed the manuscript for important intellectual content. JC designed the study and reviewed the manuscript for important intellectual content. PV and GW revised the manuscript for important intellectual content. PMV had full access to the data and is the guarantor of the study. All authors have read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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