

Factors associated with waiting for physiotherapy service: analysis from the Access and **Quality Improvement Program (PMAQ)**

Fatores associados à espera para o serviço de fisioterapia: análise a partir do Programa de Melhoria do Acesso e da Qualidade (PMAQ)

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Abstract

Introduction: Historically, the difficulty of referrals to specialized health services has been discussed. **Objective:** To analyze the factors associated with waiting time for specialized physio-therapy services. Methods: Cross-sectional, multilevel study, with secondary data, based on the external evaluation of the second cycle of the Access and Quality Improvement Program and the United Nations Development Program. The explanatory variables for the outcome "Estimated waiting time of users for specialized consultations - Physiotherapy" were grouped according to the characteristics of the family health teams and contextual factors. In the statistical analysis, Poisson's Multilevel Regression was used. A significance level of 5% was adopted (p < 0.05). Results: Observed association of the time of referral to physiotherapy with the health teams that receive support for the planning of the work process (n = 25.476; 83,4%; p < 0.0001), that the management provides information about the health situation (n = 26.505; 86.8%; p < 0.0016), receives support for the discussion of monitoring data (n = 24.149; 79,1%; p < 0.0001), receives permanent institutional support (n = 25.140; 82,3%; p < 0.0001), gets feedback from the evaluation carried out by the specialists (n = 22.801; 76,6%; p < 0.0001) and in the teams that are supported by the NASF physiotherapist (n = 5.666; 18,6%; p < 0.0001), with an association for the Gini Index (p < 0.044) and the HDI (p < 0.0001). Conclusion: The referral time to the specialized physiotherapy service was shown to be associated with both system organization and management factors, as well as contextual variables.

Keywords: Healthy surveys. Physiotherapy. Primary Health Care. Socioeconomic factors.

Resumo

Introdução: Historicamente, discute-se a dificuldade de encaminhamentos para o serviço especializado de saúde. Objetivo: Analisar os fatores associados ao tempo de espera para os serviços especializados de fisioterapia. Métodos: Estudo transversal, multinível, realizado a partir do Programa de Melhoria do Acesso e da Qualidade e do Programa das Nações Unidas para o Desenvolvimento. Adotou-se a variável desfecho: tempo estimado de espera dos usuários para atendimento especializado de consultas de fisioterapia. Na análise estatística, utilizouse a regressão multível de Poisson e adotou-se nível de significância de 5% (p < 0,05). **Resultados:** Observou-se associação do tempo de encaminhamento para fisioterapia com as equipes de saúde que recebem apoio para o planejamento do processo de trabalho (n = 25,48; 83,4%; p < 0,0001), como também para a gestão que disponibiliza informações sobre a situação de saúde (n = 26,55; 86,8%; p < 0,0016), recebe apoio para a discussão dos dados de monitoramento (n = 24,149; 79,1%; p < 0,0001), recebe apoio institucional permanente (n = 25,14; 82,3%; p < 0,0001) e obtém retorno da avaliação realizada pelos especialistas (n = 22,80; 76,6%; p < 0,0001). Nas equipes que são apoiadas por fisioterapeutas do Núcleo de Apoio à Saúde da Família (n = 5,67; 18,6%; p < 0,0001), verificou-se associação entre o Índice de Gini (p < 0,044) e o Índice de Desenvolvimento Humano (p < 0,0001). **Conclusão:** O tempo de encaminhamento para o serviço especializado de fisioterapia mostrou-se associado tanto com fatores de organização e gestão do sistema quanto com variáveis contextuais.

Palavras-chave: Inquéritos epidemiológicos. Fisioterapia. Atenção Primária à Saúde. Fatores socioeconômicos.

Introduction

The process of organization and construction of the Unified Health System (SUS) is marked by a significant increase in coverage and carried out through health care networks, in which Primary Health Care (PHC) is the preferred gateway to the system and as the coordinator and ordinator of care.¹⁻⁵

Despite this organization of the system, there is a great difficulty in accessing specialized services. It is from PHC that referrals to specialized services are made. It is worth mentioning that the resoluteness of PHC can be associated with work management processes, training of professionals and physical structure of services, and that

the disorganization of the flow of users is directly related to a difficulty of access and, consequently, complaints.³ In addition to these factors, underfunding and poor integration between the levels of health care make it difficult to integrate care and generate an increase in the waiting time of users for specialized services.⁶

The term "waiting time" is used to designate the period in which people wait to get the health services they need. It is an important indicator, being used as a measure of performance and evaluation of the quality of health services in other countries such as Canada, the United Kingdom and New Zealand.⁷⁻⁹ One of the specialized services that generates a large queue is physiotherapy. According to Ferrer et al.,⁶ the lack of a system organization can have repercussions on a long waiting list for the specialized physiotherapy service and such problems may be related to the low resoluteness of PHC or even to a low training of the team regarding the criteria used for the referral of these users.

Currently, the waiting list of the specialized service is currently configured as one of the main "bottlenecks" of the SUS, with little integration between the levels of health care, which hinders the wholeness of user care and directly hurts one of its main principles. 2,6 In addition, the high number of patients on the waiting list for physiotherapy services at the secondary level generates dissatisfaction and questions from users about the resolution of the system. Identifying factors that contribute to the reduction of this condition may help to improve the service for users. Thus, this study aimed to analyze the factors associated with waiting time for physiotherapy services in the specialized service.

Methods

This is a study with a cross-sectional, multilevel and quantitative approach, based on secondary data from the external evaluation of the second cycle of the Access and Quality Improvement Program (PMAQ). The PMAQ analysis bank is composed of 29,778 family health teams, distributed in 5,041 municipalities. The data were collected in electronic forms, installed on tablets for registration and automated submission to the central server at the Ministry of Health. 8-11 The outcome was measured by the following variable of the PMAQ: "Estimated waiting time of users for specialized consultations - Physiotherapy (of users referred in the last three months)", with answers given in number of days.

The independent variables, selected at the level of Health Teams, were: support for the planning and organization of the work process; information that helps in the analysis of the health situation; support for the discussion of the monitoring data from the information system; institutional support; tool for risk and vulnerability classification; counter-referral; integrative and complementary practices; "Extended Family Health Centers (NASF) with a professional physiotherapist". The answers were categorized into "yes" or "no", with the exception of the counter-referral in which the answers were "yes, always", "yes, most of the time", "yes, few times" or "there is no feedback" (Chart 1).

This database was linked to another database, with aggregation level at the municipal level: the national census, conducted by the Brazilian Institute of Geography and Statistics (IBGE), whose data were compiled by the Brazilian agency of the United Nations Development Program (UNDP).

The PMAQ is a program that aims to induce the evaluation process in primary care. Developed by the federal government, it is implemented by 41 federal research and teaching institutions, led by the Oswaldo Cruz Institute Foundation (Fiocruz) and federal universities of Bahia (UFBA), Minas Gerais (UFMG), Pelotas (UFPel), Rio Grande do Sul (UFRGS), Rio Grande do Norte (UFRN) and Piauí (UFPI).8-11

Chart 1 - Characteristic and contextual variables of family health teams: general description and adaptation strategies to the analysis model

	Variable	le Question			
Dependent	Waiting time for physiotherapy	Estimated waiting time of users for specialized consultations - Physiotherapy (of users referred in the last three months).	Number of days		
	Support for the planning and organization of the work process	Does the team receive support for planning and organizing the work process?	Yes or No		
Independent (Contextual) Independent (Family Health Teams)	Information that helps in the analysis of health situation	Does management provide the team with information that helps in the analysis of the health situation?	Yes or No		
	Support for the discussion of the monitoring data from the information system	Does the team receive support for the discussion of the monitoring data from the information system?	Yes or No		
	Institutional support	Does the team receive ongoing institutional support?	Yes or No		
	Tool for risk and vulnerability classification	Did the management use any typification based on risk and vulnerability criteria to define the number of people under the team's responsibility?	Yes or No		
	Counter-referral	Does the primary care team get a feedback from the evaluation carried out by the specialists of the referred users?	Yes, always Yes, most of the time Yes, a few times There is no feedback		
	Integrative and complementary practices	Does the team offer the service of integrative and complementary practices for the users of the territory?	Yes or No		
	Extended Family Health Centers (NASF) with professional physiotherapist	Extended Family Health Centers (NASF) with professional physiotherapist.	Yes or No		
	Gini index	The sum of the income of all family members, divided by the number of residents.	Numerical variable, categorized by tertiles: Up to 0,49 From 0,50 to 0,55 Above 0,56		
	Human Development Index (HDI)	An index to measure inequality in the distribution of per capita income. It ranges from 0, when there is no inequality, to 1 when all income is concentrated in a single individual.	Numerical variable, categorized by tertiles: Up to 0,651 From 0,652 to 0,739 Above 0,739		

The program is divided into four phases. The first consists in the adherence-contracting of indicators and commitments; the second, in the development of the project to generate changes in the management of care provided by the teams; the third is the external evaluation, with evaluation of the population; and the fourth is the re-contracting with the delineation of new objectives and commitments with indicators.

In the present study, data were extracted from the second cycle of the PMAQ, which provides information regarding family health teams. From this, the variables of module II were selected, which brings information collected through an interview with a professional of the team. In addition to this information, contextual variables extracted from UNDP were analyzed, such as the Gini Index and the Human Development Index (HDI). Thus, the present study was based on a multilevel analysis, in which all variables with information about the health teams at the first level were considered.

In the second level, variables related to the socioe-conomic context were included, whose associations with the outcome variable were plausible from the theoretical point of view. Therefore, the Gini index was included, which in Brazil is used as a key index of the United Nations Millennium Development Goals, 12-14 serving to measure the degree of concentration of income in cities. Used as a measure of social inequality, it ranges from 0 to 1, and the closer to 1, the greater the inequality in the place. The other variable added was the HDI, because it is an important tool to evaluate the development of different places, which consists of the geometric mean of the sum of life expectancy at birth, education index and income index.

In the statistical analysis, multilevel modeling was used to evaluate the influence of health team and contextual variables on the dependent variable. In general, the contextual level can be considered as social aggregates, due to its effect on teams and population. Thus, team data is usually considered as the first level (innermost level) and the where they are located are considered as the second level (level outermost). 15-17

Descriptive analysis was performed to verify the cutoff points or criteria for categorization, and the metric variables were categorized into three strata based on tertiles. Association tests were performed, such as the Rao Scott chi-square test, between the outcome variable and all independent variables, selecting those with $p \leq 0.2$ to be included in the multiple regression. Initially, the

unadjusted prevalence ratios (PR) and their respective 95% confidence intervals were estimated. It is worth noting that the interpretation of PR followed a mean ratio model, according to the theoretical model. Then, a Poisson multilevel regression model was performed, including the variables of the different levels. The modeling was initiated by a null model to verify the feasibility of multilevel modeling and, subsequently, variables of all dimensions were included. Finally, the term of interaction between contextual and individual socioeconomic variables was created to analyze the presence of crosslevel interaction. A significance level of 5% (p < 0.05) was adopted.

Results

A total of 24,055 basic health units (BHU) and 29,778 health teams, distributed in 5,041 Brazilian municipalities, were evaluated in Cycle II of the PMAQ. The mean referral time to the specialized physiotherapy service was 26.28 days.

The descriptive analysis of the data can be found in Table 1, where the initial associations based on the bivariate analysis can also be observed, both of the variables at the team level and the contextual variables, showing an association of all the variables observed with the time of referral to the specialized physiotherapy service.

In the multilevel modeling, it is observed that in both model 1, model 2 and final model, all variables remain associated with the outcome of the study, with the exception of places with a Gini index higher than 0.56. In the final model, a 5% increase in referral time to the specialized physiotherapy service can be observed in places where the team does not receive support for planning and organizing the work process: prevalence ratio (PR) = 1.05; confidence interval (CI) = 1.03-1.09. There was also a 4% increase in teams in which management does not provide information that helps in the analysis of the health situation (PR = 1.04; CI = 1.01-1.08); a 5% increase in teams that do not receive support for the discussion of monitoring data from the information system (PR = 1.05; CI = 1.02-1.08); a 15% increase in teams that do not receive permanent institutional support (PR = 1.15; CI = 1.13-1.17); a 26% increase in the teams that obtain a feedback from the evaluation carried out by the specialists of the referred

users (PR = 1.26; CI = 1.23-1.30); and a 10% increase in the teams that are not supported by the NASF physiotherapist (PR = 1.10; CI = 1.08-1.13) (Table 2). As for contextual variables, we observed an association of

the outcome variable with the HDI (PR = 2.19; CI = 1.97-2.43) and association of the Gini Index only in places with intermediate index (Gini from 0.50 to 0.55) (PR = 1.09; CI = 1.00-1.19), as shown in Table 2.

Table 1 - Relation between the outcome "time of referral to physiotherapy" (in days) and the independent variables of the study

Variable		Referral time to physiotherapy			
variable	Average (IC 95%)	p-value	PR (IC 95%)		
Does the team receive support	t for planning and organizing the work p	rocess?			
Yes	26.13 (25.49-26.78)	-	1		
No	30.40 (28.66.32.14)	< 0.0001	1.07 (1.05-1.09)		
Does the management provide	e the team with information that helps in	the analysis of the health situa	ation?		
Yes	26.41 (25.77-27.04)	-	1		
No	29.24 (27.27-31.31)	< 0.0001	1.14 (1.12-1.16)		
Does the team receive support	t for the discussion of the monitoring dat	a from the information system	?		
Yes	26.09 (25.43-2.75)	-	1		
No	29.61 (28.11-31.11)	< 0.0001	1.05 (1.03-1.06)		
Does your team receive ongoi	ng institutional support?		•		
Yes	25.33 (24.70-25.96)	-	1		
No	35.31 (33.30-37.32)	<0.0001	1.22 (1.20-1.24)		
Did the management use any t responsibility?	typification based on risk and vulnerabili	ty criteria to define the numbe	r of people under the team's		
Yes	25.94 (25.19-26.70)	-	1		
No	29.45 (28.21-30.69)	< 0.0001	1.03 (1.01-1.04)		
Does the primary care team ge	et a feedback from the evaluation carried	out by the specialists of the re	eferred users?		
Yes, always	21.58 (19.86-23.30)	-	1		
Yes, most of the time	22.56 (21.49-23.63)	<0.0001	1.08 (1.07-1.05)		
Yes, a few times	30.09 (29.12-31.07)	< 0.0001	1.19 (1.17-1.21)		
There is no feedback	27.18 (25.84-28.52)	< 0.0001	1.33 (1.31-1.37)		
Does the team offer the service	e of integrative and complementary prac	tices for the users of the territo	ory?		
Yes	42.92 (40.93-44.91)	-	1		
No	22.56 (22.01-23.12)	<0.0001	1.04 (1.03-1.05)		
Extended family health centers	s (NASF) with physiotherapist				
Yes	23.91 (23.17-24.65)	-	1		
No	37.04 (33.93-40.15)	< 0.0001	1.14 (1.12-1.17)		
Gini Index	•		•		
Up to 0.49	21.47 (20.74-22.20)	-	1		
From 0.50 to 0.55	24.53 (23.54-25.53)	0.863	1.00 (0.95-1.07)		
Above 0.56	35.85 (34.42-37.28)	0.008	0.90 (0.84-1.97)		
Human Development Index			•		
Up to 0.651	12.59 (12.24-12.93)	-	1		
From 0.652 to 0.739	21.21 (20.47-21.96)	< 0.0001	1.39 (1.32-1.47)		
Above 0.739	46.82 (45.27-48.38)	< 0.0001	1.96 (1.82-2.11)		

Note: PR = prevalence ratio; CI = confidence interval.

Table 2 - Analysis of the Poisson multilevel regression for the time of referral to the specialized physiotherapy service and the independent variables of the study

Variable	Null model	Model 1		Model 2		Final model	
Variable	Null model	PR (95%IC)	p-value	PR (95%IC)	p-value	PR (95%IC)	p-value
1 st Level (Teams)							
Does the team receive	support for planni	ng and organizing th	e work proc	ess?			
Yes	-	1	-	1	-	1	-
No	-	1.07 (1.05-1.09)	< 0.001	1.05 (1.03-1.09)	< 0.001	1.05 (1.03-1.09)	< 0.001
Does management pro	vide the team with	n information that hel	ps in the an	alysis of the health s	ituation?	•	-
Yes	-	1	-	1	-	1	-
No	-	1.14 (1.12-1.16)	< 0.001	1.04 (1.01-1.08)	0.015	1.04 (1.01-1.08)	0.016
Does the team receive	support for the dis	cussion of the monit	oring data fr	om the information	system?	•	-
Yes	-	1	-	1	-	1	-
No	-	1.05 (1.03-1.06)	< 0.001	1.05 (1.02-1.08)	0.001	1.05 (1.02-1.08)	0.001
Does the team receive	ongoing institution	nal support?		-		-	
Yes	-	1	-	1	-	1	-
No	-	1.22 (1.20-1.24)	<0.001	1.15 (1.13-1.17)	< 0.001	1.15 (1.13-1.17)	< 0.001
Did the management uresponsibility?	se any typification	based on risk and vu	ulnerability o	riteria to define the	number of p	people under the tea	ım's
Yes	-	1	-	1	-	1	-
No	-	1.03 (1.01-1.04)	< 0.001	0.97 (0.96-0.99)	< 0.001	0.97 (0.96-0.99)	< 0.001
Does the primary care	team get a feedba	ck from the evaluatio	n carried ou	it by the specialists o	of the referre	ed users?	
Yes, always	-	1	-	1	-	1	-
Yes, most of the time	-	1.08 (1.07-1.05)	< 0.001	1.08 (1.06-1.11)	< 0.001	1.08 (1.06-1.11)	< 0.001
Yes, a few times	-	1.19 (1.17-1.21)	< 0.001	1.16 (1.14-1.20)	< 0.001	1.17 (1.14-1.19)	< 0.001
There is no feedback	-	1.33 (1.31-1.37)	< 0.001	1.26 (1.23-1.30)	< 0.001	1.26 (1.23-1.30)	< 0.001
Does the team offer the	e service of integra	tive and complemen	tary practice	es for the users of th	e territory?	-	-
Yes	-	1	-	1	-	1	-
No	-	1.04 (1.03-1.05)	< 0.001	1.01 (1.00-1.03)	0.075	1.02 (1.00-1.04)	0.026
Extended Family Healt	h Centers (NASF) v	vith physiotherapist	•	•	-	•	-
Yes	-	1	-	1	-	1	-
No	-	1.14 (1.12-1.17)	< 0.001	1.11 (1.08-1.14)	< 0.001	1.10 (1.08-1.13)	< 0.001
2 nd Level							
Gini Index							
Up to 0.49	-	-	-	-	-	1	-
From 0.50 to 0.55	-	-	-	-	-	1.09 (1.00-1.19)	0.044
Above 0.56	-	-	-	-	-	0.98 (0.86-1.07)	0.610
Human Development I	ndex		-	-	-	-	-
Up to 0.651	-	-	-	-	-	1	-
From 0.652 to 0.739	-	-	-	-	-	1.40 (1.30-1.52)	< 0.001
Above 0.739	-	-	-	-	-	2.19 (1.97-2.43)	< 0.001
Random effects							
Variance (95%CI)	0.053 (0.048-0.057)	0.056 (0.054-0.058)	-	0.043 (0.040-0.048)	-	0.056 (0.054-0.058)	-
LR test	< 0.001	<0.001	_	< 0.001	_	< 0.001	_

Note: For all models, n = 29.778; CI = confidence interval; LR Test = likelihood ratio test (x^2 , p-value).

Discussion

This study proposed a multilevel analysis to identify which factors are associated with the waiting time for the specialized physiotherapy service, observing factors at the health team level and contextual factors. An association was found between the time of referral to physiotherapy and the health teams that receive support for the planning and organization of the work process in those in which the management provides information about the health situation, when the team receives support for the discussion of the monitoring data from the information system, in the teams that receive permanent institutional support, in those that obtain feedback from the evaluation carried out by the specialists of the referred users and in those that are supported by the NASF physiotherapist, with association also for the Gini Index and the HDI.

It is noticed that there was an association between organization, planning and management criteria with a shorter waiting time. The management work of PHC professionals broadens the participation of professionals at this level of care and tends to strengthen ties with regulatory centers. 18 It is also observed that an organized PHC system with management capacity in regulation can produce more information and qualifications that subsidize decision-making, while low qualification can limit conditions that could be decisive in PHC and generate excessive queues and increased waiting time. 18,19 Considering the potential of Health Care Networks, which are developed based on a set of elements in which PHC functions as a communication center for specialized services, support systems, logistics and governance, a good management and organization of primary services would contribute to a better resolution of health conditions. 19,20

The positive result found for a shorter referral time in the teams that obtain feedback from the evaluation carried out by the specialist confirms the importance of good communication between the health levels for a better offer of their services. The main element for the integration of health networks is an effective referral and counter-referral system, understood as a mechanism for mutual referral of patients between the different levels of complexity of services. The Ministry of Health defines this system as one of the key elements of reorganization of work practices that must be guaranteed by family health teams.²¹ The referral happens when a service

of lower complexity refers patients to a service of greater complexity, accompanying them and marking their attendance. Counter-referral happens when the situation is resolved and the patient is referred again to the provenience service to continue their follow-up.²² The regulatory policy is based on the feasibility of comprehensive care, safeguarding quality and equity in health care, according to the needs of users, without losing sight of its epidemiological, sanitary and social plurality. The structuring of the regulatory complex emerges as a strategy to organize supply and demand in health, establishing commitments between managers, service professionals and users.²³

However, the studies of Protasio et al.²⁴ and Pereira et al.,²⁵ point to a discontinuity of the regulation process due to the low occurrence and effectiveness of the counter-referral action of the services referred and provided in primary care. This weakens the user's control mechanism within the network and decreases its adherence, hurting the principle of longitudinality of care, given that continuous monitoring of cases within the network is not carried out.

In the present study, it was observed that in the teams that were supported by NASF teams and that had a physiotherapist in the team, the waiting time for the specialized physiotherapy service was lower. Currently the NASF is the main form of insertion of the physiotherapist in the primary level of care. When evaluating data on the waiting list for physiotherapy at the secondary level in a Brazilian municipality, Ferrer et al.⁶ observed that 88% of the referrals were made by the medical specialty centers of the municipality, the main cases being osteoarthritis (36%), lumbago/lumbocyatalgias (21%) and tendinitis (15%). In addition, the physiotherapy team identified that 72% of the patients did not need the specialized physiotherapy service at that time.⁶

The presence of a physiotherapist in PHC can improve the dialogue between these professionals and the use of appropriate criteria for screening and referral to the specialized service, reducing the waiting list and, consequently, the waiting time. The physiotherapist has already been implemented as a first contact professional in the reality of other countries such as England, Scotland, Wales, United Kingdom, among others, in which a percentage of 86% of adequate referrals is observed. The physiotherapist has already been implemented as a first contact professional in the reality of other countries such as England, Scotland, Wales, United Kingdom, among others, in which a percentage of 86% of adequate referrals is observed.

Regarding contextual variables, a direct relationship was observed between HDI and waiting time, showing

that cities with higher development indices have a longer waiting time. This result may have occurred due to government policies aimed at increasing access, especially in PHC, through the Family Health Program. In this sense, and based on the principle of equity, municipalities with greater vulnerability and low HDI can receive greater investment in this sector.^{28,29} As for the Gini Index, an association was observed only among cities with better and intermediate indicators. Measures of inequality seem to be associated with health problems in studies involving large areas, in which the unit of analysis is country, because these are more influenced by national than state policies, in addition to what is observed in other studies in which income inequality is still uniform throughout Brazil, which makes it difficult to interpret. 13,14

Despite the results found, this study has some limitations because it is a survey of secondary data, acquired by public platforms and because a portion of the population is assisted by supplementary health, not entering the study statistics. However, this limitation does not minimize the plausibility of the study, which used data sources from the Brazilian government, since this is the means of indirectly assessing the quality of care of primary care services. In addition, this is a crosssectional study, which makes it impossible to infer a cause and effect relationship. Longitudinal studies may confirm the cause-and-effect relationship of some independent variables on the outcome of the study. Still, the theoretical explanatory model assumed in this study is reductionist, given the complexity of factors that affect the time of referral to the specialized service. However, such limitations do not invalidate the findings presented here. Further studies can complement these findings and deepen the discussion on the topic.

Conclusion

The length of referral to the specialized physiotherapy service was associated with both organizational and management factors of the system and contextual variables. Understanding the factors that most contribute to the continuity of the flow of users in the health care network can result in better indicators. The waiting time for physiotherapy care can have repercussions on functional gains or significant losses when it becomes

excessive. The organization of flows, in addition to the continuous communication and participation of first contact professionals in PHC, seems to contribute to the better quality of services.

Authors' contributions

SJCA was the creator of the project, having carried out the conception, analysis and interpretation of the data, and was responsible for writing the manuscript. CGS, GJBS and AGR contributed to the analysis and discussion of the data and revision of the manuscript. All authors approved the final version.

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