Past physical activity and age-related macular degeneration: the Melbourne Collaborative Cohort Study

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ABSTRACT

Background/aims To assess the association between past physical activity and early, intermediate and late age-related macular degeneration (AMD) in a community-based cohort study in Melbourne, Australia.

Methods Diet and lifestyle information was recorded at baseline (1990–1994) and total recreational activity was derived from walking, vigorous and non-vigorous exercise. At follow-up (2003–2007), digital macular photographs were graded for early, intermediate and late AMD. Data were analysed using multinomial logistic regression controlling for age, sex, smoking, region of descent, diet and alcohol. Effect modification by sex was investigated.

Results Out of 20 816 participants, early, intermediate and late AMD were detected at follow-up in 4244 (21%), 2661 (13%) and 122 (0.6%) participants, respectively. No association was detected between past total recreational physical activity and early, intermediate or late AMD. Frequent (≥3 times/week) and less frequent (1–2 times/week) vigorous exercise were associated with lower odds of intermediate and late AMD in univariable models. After controlling for confounders, there was evidence of effect modification by sex and frequent vigorous exercise was associated with a 22% decrease in the odds of intermediate AMD (95% CI 4% to 36%) in women, but no association was found for men.

Conclusions Past frequent vigorous exercise may be inversely related to the presence of intermediate AMD in women. Further studies are needed to confirm whether physical activity and exercise have a protective effect for AMD.

INTRODUCTION

A growing body of evidence supports a positive influence of physical activity (PA) on successful ageing, namely lowering morbidity and mortality, maintaining physical and cognitive functions and improving biomarkers of ageing.[1 2] Age-related macular degeneration (AMD) is the most common cause of severe vision loss in people over the age of 50 living in developed countries.[3]

Apart from general lifestyle and nutritional advice there is no specific treatment to avert AMD, or prevent progression from earlier to later stages of AMD. In light of current demographic trends, the number of people living with AMD is projected to increase considerably.[4] Thus, there is a large and unmet need to identify modifiable risk factors for the development and progression of AMD. Regular exercise has been shown to increase antioxidant enzyme activity and increase resistance to oxidative stress which is thought to be one of the key components in the pathogenesis of AMD.[5 6] In the absence of disability, PA represents a lifestyle choice that is modifiable for many older persons.

The current evidence regarding the influence of recreational PA on AMD is inconclusive; some studies show a protective association,[7–9] while others show no association.[10 11] Studies involving objective detection of AMD have ranged in size from 888 to 10 890 participants, lacking statistical power to detect associations with the later stages of AMD, especially when investigating effect modification. The majority of studies measured PA at the same time as AMD detection, allowing the possibility of reverse causality between exposure and outcome.

Against this background, we assessed the association of past PA, particularly vigorous exercise, with the presence of early, intermediate and late AMD in men and women from a single large cohort study.

MATERIALS AND METHODS

Study population

The Melbourne Collaborative Cohort Study is a prospective cohort study of 41 514 participants (24 469 women) living in Melbourne, Australia. Caucasian volunteers aged between 40 and 69 years were recruited in randomly selected census districts. At baseline (1990–1994), participants attended clinics where demographic, lifestyle and dietary information were collected and anthropometric measurements were performed. Fundus photography was performed at follow-up visits between 2003 and 2007. The study protocol was approved by the Human Research and Ethics Committees of The Cancer Council Victoria and the Royal Victorian Eye and Ear Hospital, and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants after explanation of the nature of the study.

Exposure measures

Structured questionnaires were administered at baseline to obtain demographic and lifestyle information. Smoking history was documented as never, former or current. Food intake was estimated using

a self-administered 121-item food frequency questionnaire, specifically developed for the Melbourne Collaborative Cohort Study[12] and used to calculate the Mediterranean diet score, a sex-specific scale based on intakes of vegetables, fruit and nuts, legumes, cereal, fish, meat products, dairy products, olive oil and alcohol.[13] Scores range from zero (indicating a poorer diet) to nine (indicating a healthier diet). Individual energy intake was calculated from Australian food composition tables.[12] Those with total energy intake below the 1st and above the 99th centile of the baseline population for each sex were considered to have potential measurement error and were excluded from the analyses.

Age at the time of AMD detection was categorised as <60, 60 to <70 and ≥70 years old. Region of descent was dichotomised into Northern European descent (Australia, New Zealand, England, Ireland, Scotland, Wales or Latvia) and Southern European Descent (Italy, Greece or Malta). The highest level of education attained was categorised as less than primary school completion, some high or technical school, high or technical school completion and completion of a degree or diploma.

To assess the participants' levels of average recreational PA during the preceding 6 months, participants were asked three questions at baseline: (1) On average (eg, over the last 6 months), how many times a week do you walk for recreation or exercise?; (2) On average (eg, over the last 6 months), how many times a week do you exercise vigorously for a period of at least 20 min? ('vigorously' means making you sweat or feel out of breath, and includes such activities as swimming, tennis, netball, athletics and running); and (3) On average (eg, over the last 6 months), how many times a week do you engage in less vigorous exercise for recreation, sport or health and fitness purposes, which did not make you sweat or feel out of breath (and includes such activities as bike riding, dancing, etc). The response options for each of the three questions were none, 1–2 times/week and ≥3 times per week. The responses were converted into metabolic equivalent of task (MET) minutes in order to calculate total recreational activity. It was assumed that participants exercised for 30 min per session and were active for the median number of days possible in each category. Walking was assigned a value of 3.5 METs, non-vigorous exercise was assigned a value of 5.5 METs and vigorous exercise was assigned a value of 8 METs in line with values published in the *Compendium of Physical Activities*.[14] Total recreational activity was categorised as 0, >0 to <500, 500 to <1000 and >1000 MET-minutes to reflect the recommendation of the US Department of Health and Human Services that adults be active for 500–1000 MET-minutes per week.[15]

Detection of AMD at follow-up

Digital fundus photography was performed at follow-up and graded using the 'OptoLite/OptoMize Pro' software (Digital HealthCare Image Management Systems, Cambridge, UK) as previously described.[16] Photographs were assessed by examiners who were masked to baseline characteristics. For this analysis, AMD was defined according to the Beckman classification.[17] Participants were classified according to features in the area 6000 μm in diameter centred on the fovea in the worse affected eye. Individuals with drusen 63–124 μm in size without pigmentary abnormalities in either eye were classified as having early AMD. Individuals with drusen 63–124 μm in size accompanied by pigmentary abnormalities, or drusen ≥125 μm with or without pigmentary abnormalities in the absence of late AMD in either eye were classified as having intermediate AMD. Those with choroidal neovascularisation or geographic atrophy (≥175 μm hypopigmentation with visible choroidal vessels) in either eye were classified as having late AMD. Those who had no AMD-related macular changes, or changes considered normal for ageing (<63 μm drusen or pigmentary abnormalities only) were classified as having no AMD. If only one eye was graded for a particular subject, that subject was omitted from analyses unless late AMD was detected in that eye.

Statistical methods

We investigated the relationship between AMD and total recreational activity using multinomial logistic regression. Associations are presented as odds as indicated for relative risk ratios from multinomial logistic regression models. The relationship between vigorous exercise and AMD was modelled separately as we hypothesised that the physiological effect of vigorous exercise may be different to that of walking and non-vigorous exercise. Age, sex, smoking status and region of descent were included in each model to control for confounding. A directed acyclic graph was drawn for the causal relationship between PA and AMD to identify any additional confounding variables. Along with the covariates already mentioned, education, body composition, genetics, diet and alcohol were included in the directed acyclic graph as they have previously been associated with the risk of AMD.[18–21] Interactions between PA and sex were explored as exercise and PA patterns differ considerably between the sexes and interaction by sex has previously been reported when investigating the association between cardiovascular risk factors and AMD.[20 22 23]

Less than 0.1% of the 21 132 subjects who attended follow-up and had retinal images assessed for AMD had missing data on baseline exposures, thus complete case analyses were conducted.

Statistical analyses were performed using Stata/IC V.12.1 (StataCorp LP, College Station, Texas, USA).

RESULTS

Of the 41 514 participants seen at baseline, 32% (n=13 274) did not attend the follow-up wave including 4808 who had died or moved away (figure 1). Of the follow-up population, 79.3% (n=22 402) had fundus photographs taken, of which 94% (n=21 132) could be graded. After exclusions based on confounding macular pathology precluding AMD grading, poor quality or missing photographs, extreme energy intake values or missing PA or smoking data, a total of 20 816 participants were included in the final analyses (figure 1). The median time between baseline and fundus photography for these participants was 11.3 years (IQR 10.5–12.2, range 8.5–16.4). Included participants were younger, less likely to be of Southern European descent and more likely to be involved in PA than participants not included in the analyses (table 1).

Early, intermediate and late AMD were detected at follow-up in 4244 (21%), 2661 (13%) and 122 (0.6%) participants, respectively.

Baseline measurements and PA

For the participants eligible for inclusion in this study, the age at the time of photography ranged from 47 to 85, with a median of 64 years (IQR 57–72). Only 8% (n=1752) of the participants were current smokers and almost a third (n=6472) were former smokers (table 1).

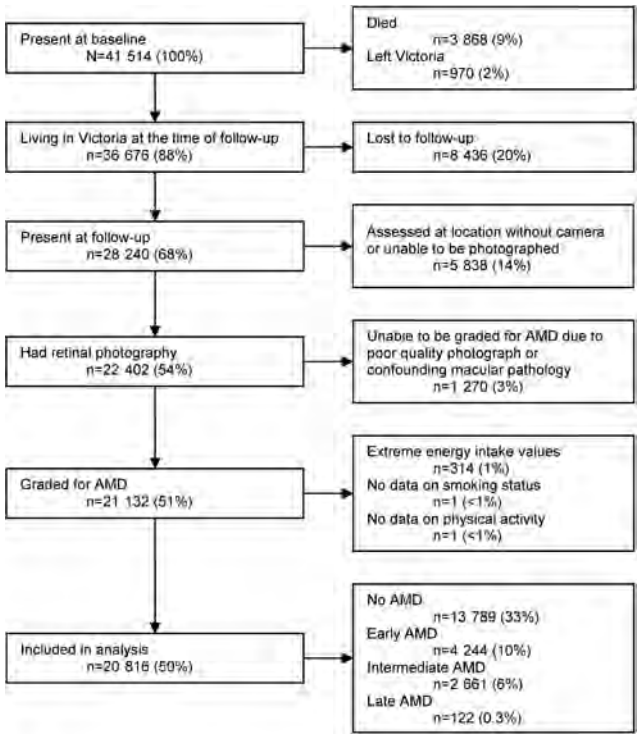

Figure 1 Flow chart of participants in the Melbourne Collaborative Cohort Study, Australia 1990–2007. AMD, age-related macular degeneration.

The distribution of baseline characteristics across total recreational activity categories and vigorous exercise categories is given in online supplementary tables S1a and S1b, respectively. Almost a third of all men (n=2497, 30%) and a quarter of all women (n=3116, 25%) exercised vigorously at least once per week. Those who were older, were current smokers, or had low diet scores reported being less active. Those who were of Northern European descent or had attained higher education levels were more likely to be active. Of those included in this study, 4244 (20.4%) were classified as having early AMD, 2661 (12.8%) were classified as having intermediate AMD and 122 (0.6%) had late AMD.

PA and AMD

Examination of a directed acyclic graph suggested that body composition and education could be omitted from the analyses without biasing the causal pathway between PA and AMD. Diet and alcohol were seen to be a source of potential bias and were added to the models along with age, sex, smoking status and region of descent (see online supplementary figure S1).

Total recreational activity

Lower odds of intermediate AMD were observed for the most active individuals in an unadjusted model (table 2). After adjustment for confounders, there was no evidence of an association between total recreational activity and early, intermediate or late AMD (table 3). Sex was not observed to modify the effect of total recreational activity.

Vigorous exercise

Frequent (≥3 times/week) and less frequent (1–2 times/week) vigorous exercise was associated with lower odds for both intermediate and late AMD in an unadjusted model (table 2).

Table 1 Baseline demographics for participants from the Melbourne Collaborative Cohort Study included and not included in this analysis

	Included n=20 698 n (%)	Not included n=28 816 n (%)
Sex		
Male	8281 (40)	8764 (42)
Female	12 535 (60)	11 934 (58)
Age at baseline (years)		
40 to <50	7948 (38)	5199 (25)
50 to <60	6926 (33)	6586 (32)
60 to 69	5942 (29)	8913 (43)
Smoking*		
Never	12 592 (60)	11 227 (54)
Former	1752 (8)	2936 (14)
Current	6472 (31)	6525 (32)
Region of descent		
Northern European	18 034 (87)	13 150 (64)
Southern European	2782 (13)	7548 (36)
Highest level of education*		
Less than primary school	643 (3)	2322 (11)
Some high/technical school	9195 (44)	11 739 (57)
Completed high/technical school	4688 (23)	3888 (19)
Degree or diploma	6290 (30)	2740 (13)
Mediterranean diet score*		
0–3	4634 (22)	5163 (25)
4	4338 (21)	4387 (21)
5	4853 (23)	4771 (23)
6	4064 (20)	3823 (19)
7–9	2927 (14)	2508 (12)
Total recreational activity (MET-minutes)*		
0 (none)	3990 (19)	5242 (25)
>0 to <500	4171 (20)	4155 (20)
500 to <1000	8133 (39)	8152 (39)
1000 to 2550 (most active)	4522 (22)	3149 (15)
Vigorous exercise*		
None	15 203 (73)	17 602 (85)
1–2 times/week	3014 (14)	1589 (8)
≥3 times/week	2599 (12)	1497 (7)

*Missing data for those not included in analysis: smoking (n=10), education (n=9), Mediterranean diet score (n=46), total recreational activity (n=9) and vigorous exercise (n=9).

There was evidence of effect modification by sex and after controlling for confounders, frequent vigorous exercise was associated with lowered odds of intermediate AMD in women but not in men (table 4). For both men and women, frequent vigorous exercise was not associated with early or late AMD (table 4).

DISCUSSION

Using the world's largest single study of AMD conducted in a Caucasian population, we demonstrated a protective association of past frequent vigorous PA with intermediate AMD for women, controlling for a number of confounders. This finding has important public health implications, at least for women who constitute the largest group affected by AMD.

This protective association is in keeping with a number of studies assessing the impact of PA on AMD in Caucasian populations including the Tromsø study which demonstrated a protective association for women but not men.[7–9 23] Studies that

Table 2 Univariable multinomial logistic regression models for AMD and physical activity*

	Early AMD RRR (95% CI)	Intermediate AMD RRR (95% CI)	Late AMD RRR (95% CI)
Total recreational activity (MET-minutes)			
0 (none)	1.00	1.00	1.00
>0 to <500	1.00 (0.89 to 1.11)	0.96 (0.84 to 1.09)	1.09 (0.63 to 1.96)
≥500 to <1000	0.98 (0.89 to 1.08)	0.97 (0.86 to 1.08)	1.21 (0.72 to 2.01)
1000 to 2550 (most active)	0.67 (0.87 to 1.07)	**0.87 (0.76 to 0.99)**	1.02 (0.57 to 1.84)
Vigorous exercise			
None	1.00	1.00	1.00
1–2 times/week	1.01 (0.92 to 1.11)	**0.86 (0.76 to 0.97)**	**0.47 (0.25 to 0.90)**
≥3 times/week	0.94 (0.85 to 1.04)	**0.76 (0.66 to 0.87)**	**0.37 (0.17 to 0.80)**

Estimates with p values ≤0.05 are shown in boldface.
*Participants with no AMD are the reference.
AMD, age-related macular degeneration; RRR, relative risk ratio.

show no association in Caucasian populations have been smaller (n≤2810) and may have lacked statistical power to detect any effect of PA.[10 11] In our study, the number of cases of late AMD was relatively small compared with early and intermediate AMD which might explain why the association of vigorous exercise with late AMD did not remain statistically significant after controlling for confounders such as age and smoking status.

PA is difficult to capture, and in this study only recreational PA was measured which under-represents total PA. Advances in activity tracking devices and developments in retinal imaging will no doubt improve the ability to capture the exposure and allow more accurate investigation into the impact of PA on AMD in the future. Strengths of our study include the large sample size from a single study, the reliable and valid assessment of AMD, the assessment of PA preceding the assessment of AMD, investigation of modification by sex and the extensive assessment of diet. Levels of PA were captured a minimum of 8.5 years prior to fundus photography and we believe that past

Table 3 Multivariable multinomial logistic regression for AMD and total recreational activity*

	Early AMD		Intermediate AMD		Late AMD	
	Cases	RRR (95% CI)	Cases	RRR (95% CI)	Cases	RRR (95% CI)
Total recreational activity (MET-minutes)						
0 (none)	818/3437	1.00	532/3151	1.00	21/2640	1.00
>0 to <500	856/3610	1.04 (0.93 to 1.17)	537/3291	0.96 (0.84 to 1.10)	24/2778	1.02 (0.56 to 1.85)
≥500 to <1000	1651/7025	1.05 (0.95 to 1.16)	1056/6430	0.97 (0.86 to 1.09)	52/5426	1.09 (0.65 to 1.84)
1000 to 2550 (most active)	919/3578	1.07 (0.95 to 1.19)	536/3578	0.94 (0.82 to 1.08)	25/3067	1.20 (0.66 to 2.20)
Age at photography (years)						
48 to <60	1609/6314	1.00	659/5364	1.00	3/4708	1.00
60 to <70	1687/6106	**1.09 (1.00 to 1.18)**	794/5213	**1.26 (1.13 to 1.41)**	9/4428	3.34 (0.90 to 12.37)
70 to 85	948/5613	**0.58 (0.53 to 0.64)**	1208/5873	**1.82 (1.64 to 2.02)**	110/4775	**40.8 (12.9 to 128.8)**
Sex						
Male	1401/7175	1.00	1054/6828	1.00	52/5826	1.00
Female	2843/10 858	**1.44 (1.34 to 1.55)**	1607/9622	**1.15 (1.05 to 1.25)**	70/8085	1.09 (0.74 to 1.59)
Smoking						
Never	2697/10 974	1.00	1554/9831	1.00	64/8341	1.00
Former	1209/5547	0.93 (0.86 to 1.01)	886/5224	**1.12 (1.02 to 1.23)**	39/4377	1.13 (0.74 to 1.72)
Current	338/1512	0.88 (0.78 to 1.01)	221/1395	1.07 (0.92 to 1.26)	19/1193	**2.90 (1.70 to 4.95)**
Region of descent						
Northern European	3557/15 695	1.00	2232/14 370	1.00	107/12 245	1.00
Southern European	687/2338	**1.50 (1.35 to 1.65)**	429/2080	**1.36 (1.20 to 1.53)**	15/1666	0.87 (0.50 to 1.53)
Mediterranean diet score						
0–3	908/4011	1.00	562/3665	1.00	31/3134	1.00
4	907/3730	1.10 (0.99 to 1.22)	546/3369	1.05 (0.92 to 1.20)	28/2851	0.99 (0.59 to 1.66)
5	1008/4201	1.07 (0.96 to 1.18)	642/3835	1.08 (0.96 to 1.23)	24/3217	0.73 (0.43 to 1.26)
6	834/3563	1.03 (0.92 to 1.15)	533/3262	1.04 (0.91 to 1.19)	17/2746	0.60 (0.33 to 1.10)
7–9	587/2528	1.01 (0.89 to 1.14)	378/2319	1.04 (0.90 to 1.20)	22/1963	1.11 (0.63 to 1.96)

Cases indicate the number of cases/number of cases and controls.
Estimates with p values ≤0.05 are shown in boldface.
*Participants with no AMD are the reference. Adjusted for age, sex, smoking status, region of descent and Mediterranean diet score.
AMD, age-related macular degeneration; RRR, relative risk ratio.

Table 4 Multivariable multinomial logistic regression for AMD and vigorous exercise*

	Early AMD		Intermediate AMD		Late AMD	
	Cases	RRR (95% CI)	Cases	RRR (95% CI)	Cases	RRR (95% CI)
Vigorous exercise men						
None	964/4965	1.00	775/4776	1.00	44/4045	1.00
1–2 times/week	197/987	0.97 (0.81 to 1.15)	121/911	0.93 (0.75 to 1.14)	5/795	1.12 (0.44 to 2.87)
3 times/week	240/1223	0.95 (0.81 to 1.12)	158/1141	1.01 (0.84 to 1.23)	3/986	0.61 (0.19 to 1.99)
Vigorous exercise women						
None	2126/8101	1.00	1257/7232	1.00	61/6036	1.00
1–2 times/week	435/1665	0.98 (0.87 to 1.11)	231/1461	0.98 (0.84 to 1.14)	5/1235	0.53 (0.21 to 1.33)
≥3 times/week	282/1092	0.97 (0.84 to 1.12)	119/929	**0.78 (0.64 to 0.96)**	4/814	0.76 (0.27 to 2.11)
Age at photograph						
48 to <60	1609/6314	1.00	659/5364	1.00	3/4708	1.00
60 to <70	1687/6106	1.08 (1.00 to 1.17)	794/5213	**1.25 (1.12 to 1.40)**	9/4428	3.23 (0.87 to 12.0)
70 to 85	948/5613	**0.58 (0.53 to 0.63)**	1208/5873	**1.80 (1.62 to 2.00)**	110/4775	**38.5 (12.1 to 121.9)**
Smoking						
Never	2697/10 974	1.00	1554/9831	1.00	64/8341	1.00
Former	1209/5547	0.93 (0.86 to 1.01)	886/5224	**1.12 (1.02 to 1.23)**	39/4377	1.14 (0.75 to 1.73)
Current	338/1512	0.88 (0.77 to 1.00)	221/1395	1.08 (0.92 to 1.26)	19/1193	**2.85 (1.67 to 4.86)**
Region of descent						
Northern European	3557/15 695	1.00	2232/14 370	1.00	107/12 245	1.00
Southern European	687/2338	**1.47 (1.33 to 1.62)**	429/2080	**1.35 (1.20 to 1.52)**	15/1666	0.81 (0.46 to 1.41)
Mediterranean diet score						
0–3	908/4011	1.00	562/3665	1.00	31/3134	1.00
4	907/3730	1.10 (0.99 to 1.22)	546/3369	1.05 (0.93 to 1.20)	28/2851	1.00 (0.59 to 1.68)
5	1008/4201	1.07 (0.97 to 1.19)	642/3835	1.08 (0.96 to 1.23)	24/3217	0.75 (0.44 to 1.29)
6	834/3563	1.04 (0.93 to 1.16)	533/3262	1.04 (0.91 to 1.19)	17/2746	0.63 (0.34 to 1.14)
7–9	587/2528	1.02 (0.91 to 1.15)	378/2319	1.04 (0.90 to 1.20)	22/1963	1.18 (0.68 to 2.08)

Cases indicate the number of cases/number of cases and controls.
Estimates with p values ≤0.05 are shown in boldface.
*Participants with no AMD are the reference. Adjusted for age, sex, smoking status, region of descent and Mediterranean diet score.
AMD, age-related macular degeneration; RRR, relative risk ratio.

levels of PA are a greater indicator of long-term exercise habits than those captured at the time of AMD detection.[24]

The main shortcoming is the considerable loss to follow-up which partly reflects the natural attrition to competing risks of ill health and death to be expected in this age range. Variation in the risk of ill health and death associated with differing levels of PA is to be expected, and bias stemming from survivorship cannot be ruled out. This may account in part for the effect modification by sex. Men are at greater risk of death prior to assessment compared with their female counterparts.[25] The surviving men are healthier on average than those who have died and are less likely to develop AMD. Patterns of PA may be associated with unmeasured behaviours which have not been taken into account in this analysis and could confound the observed association. In addition, the lack of detail in the assessment of PA may limit our study and several assumptions were employed to calculate total recreational activity. The use of self-reported PA has a number of limitations; participants may under-report or over-report their PA and this has been reported as a greater problem in the elderly.[26] Differential bias will likely result from overestimation of exercise frequency, leading to attenuation of the association between AMD and frequent exercise. Unmeasured changes in PA in the period leading up to the follow-up assessment may also be important, but this is unlikely to be the case as AMD development and progression is a slow process over several decades.[27] No comment can be made about disease incidence or progression, although approximation by extrapolation of prevalence by age to the cohort at baseline indicates that the percentage with late-stage AMD would have likely been low (0.07% with late AMD). Thus, for the majority of subjects, it is unlikely that inactivity resulted from visual impairment secondary to AMD.

In conclusion, we found that frequent vigorous exercise had a protective association with intermediate AMD for women after controlling for common AMD risk factors which further supports the public health message of staying active throughout life.

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Contributors All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: RPF. Acquisition, analysis or interpretation of data: all authors. Drafting of the manuscript: MBM and RPF. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: MBM. Administrative, technical or material support: AMH. Study supervision: RPF, JAS, AK, RHG.

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