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IONIZED AND TOTAL MAGNESIUM LEVELS CHANGE DURING REPEATED EXERCISE IN OLDER ADULTS

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Abstract: *Background:* Magnesium is essential for health and performance. Sub-optimal levels have been reported for older persons. In addition, physical exercise is known to temporally decrease magnesium blood concentrations. *Objective:* To investigate these observations in conjunction we assessed total (tMg) and ionized magnesium (iMg) concentrations in plasma and whole blood, respectively, during 4 consecutive days of exercise in very old vital adults. *Design:* 68 participants (age 83.7±1.9 years) were monitored on 4 consecutive days at which they walked 30-40km (average ~8 hours) per day at a self-determined pace. Blood samples were collected one or two days prior to the start of exercise (baseline) and every walking day immediately post-exercise. Samples were analysed for tMg and iMg levels. *Results:* Baseline tMg and iMg levels were 0.85±0.07 and 0.47±0.07 mmol/L, respectively. iMg decreased after the first walking day (-0.10±0.09 mmol/L, p<.001), increased after the second (+0.11±0.07 mmol/L, p<.001), was unchanged after the third and decreased on the final walking day, all compared to the previous day. tMg was only higher after the third walking day compared to the second walking day (p=.012). In 88% of the participants, iMg levels reached values considered to be sub-optimal at day 1, in 16% of the participants values were sub-optimal for tMg at day 2. *Conclusion:* Prolonged moderate intensity exercise caused acute effects on iMg levels in a degree comparable to that after a bout of intensive exercise. These effects were not associated with drop-out or health problems. After the second consecutive day of exercise, levels were returned to baseline values, suggesting rapid adaptation/resilience in this population.

Key words: Older adults, consecutive exercise days, micronutrients, reference values.

Abbreviations: ANOVA: Analysis of variance; BMI: Body mass index; HR: heart rate; iMg: ionized magnesium; LH: Lithium heparine; Mg: magnesium; Rpm: Revolutions per minute; tMg: total magnesium.

Introduction

Magnesium (Mg) is an essential micronutrient for general health and physical performance (1). Research has shown that magnesium deficiency can amongst others lead to muscle weakness, neuromuscular dysfunction, and muscle cramping (2-7).

Magnesium deficiency may be more prevalent in older adults because it is known that the age- related reduction in bone mass results in a reduction of the magnesium body reserves (8). Besides, magnesium absorption decreases with age (9). Additionally, use of medicines, including the widely used proton pomp inhibitors, may increase the risk of hypomagnesemia (10).

It should be noted that circulating Mg represents < 1% of total body reservoirs and therefore is not a perfect predictor of the body magnesium status. Nevertheless, total serum magnesium is the mostly used clinical representative of the magnesium status (11).

Previous studies observed a transient decrease in blood magnesium concentrations, during and immediately after exercise in trained young adults (12-15), indicating redistribution between Mg pools in the body. In the case of elderly, where baseline magnesium levels may already be low, a post-exercise drop could result in in plasma hypomagnesemia (< 0.70 mmol/L for tMg and < 0.46 mmol/L for iMg) (16, 17). However, whether magnesium blood concentrations in older adults decrease after exercise is unknown. In addition, the effect of consecutive days of exercise on magnesium blood levels in older adults is unknown.

Earlier studies that investigated the relationship between magnesium blood levels and exercise were mainly focussed on healthy young and middle aged adults, while studies in the older adults are lacking. Therefore, we included a large unique group of active older adults, with an age above 80 years old.

The aim of this study was to assess blood magnesium levels in a vital group of older adults aged > 80 years old and to investigate the effect of (repeated) exercise on ionized (whole blood) and total magnesium (plasma) levels. Moreover, we explored factors that could predict low magnesium levels and the exercise induced decrease in magnesium. We hypothesized that the older adults were low in total and ionized magnesium levels and showed a decrease in magnesium levels after prolonged moderate intensity exercise.

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Materials and methods

Study population

We selected 72 male and 22 female walkers who participated in the 2016 edition of the Nijmegen Four Days Marches, a large annual four-day walking event taking place in the Netherlands (http://www.4daagse.nl/en/). Exclusion criteria were known diabetes and/or renal dysfunction. The study was approved by the Medical Ethical Committee of the Radboud university medical center (CMO registration number: 2007/148), and all participants gave written informed consent prior to participation. This study was conducted in accordance with the Declaration of Helsinki.

Study procedure

The study took place in the summer season, i.e. July. Actual climatological conditions are specified in the results section. Measurements were performed before the start of the event ('baseline'), and at four consecutive walking days. Baseline measurements, including registering participant characteristics and collection of a blood sample, were performed in our field laboratory at the event location one or two days prior to the first walking day, between 09:30 AM and 04:00 PM. A 24 hour recall for dietary intake was done a few weeks before the start of the event.

Every walking day, immediately before the start of the march, participants' body weight was measured. Thereafter, participants walked 30 or 40 km, at a self-selected pace, starting between 4:00 and 8:00 AM. Every day, participants registered their fluid intake using a diary. Directly after finishing, post-exercise body weight was determined, a blood sample was taken (see below for details) and a set of questionnaires was completed. Heart rate was measured during the first walking day using a 2-channel ECG chest band system (Polar Electro Oy, Kempele, Finland). Mean heart rate during exercise was calculated as the average heart rate, excluding the values derived directly before the start and after the finish. Heart rate was used to estimate exercise intensity as percentage of (expected) maximal heart rate: Intensity = (Measured HR / Expected maximal HR) * 100%, with Expected max HR = 208 - (0.7 * Age) (18).

Baseline measurements

At baseline, body weight (Seca 888 scale, Hamburg, Germany) and body height were determined and body mass index (BMI) was calculated. Thereafter, resting heart rate and blood pressure were measured using an automated sphygmomanometer (M5-1 intellisense, Omron Healthcare, Hoofddorp, The Netherlands) after 5 minute supine rest.

Blood samples

Blood samples were taken at baseline and post-exercise at the four consecutive walking days. Participants were seated for 5 min after which a venous blood sample was taken from the cephalic vein. Blood was collected in lithium-heparin (LH) tubes (3.5 ml LH PSTTM II and 4.0 ml LH 17 IU/mL, Becton-Dickinson, Vianen, The Netherlands). The LH PSTTM II samples were centrifuged at 3000G for 8 minutes at 22 degrees and plasma was stored at -20 °C. Plasma samples were analysed for their total magnesium concentrations (Dimension Vista 1500, Siemens Healthcare, Erlangen, Germany). For measurement of ionized magnesium status, a fraction of the whole blood sample collected in the LH 17 IU/mL vacutainer was immediately analysed using the Stat Profile pHOx Plus M analyzer (Nova Biomedical, Waltham, MA, USA) according to the manufacturers' recommendations.

Furthermore, a part of the whole blood sample collected in the LH 17 IU/ml vacutainer was used for direct analyses of plasma haemoglobin and haematocrit concentrations (Rapidpoint 400, Siemens Healthcare, Erlangen, Germany). Relative changes in plasma volume were calculated from blood haematocrit and haemoglobin concentrations using Dill and Costill's equation (19).

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences 22.0 (IBM SPSS version 22.0, Armonk, New York, USA), and the level of significance was set at $p < 0.05$. Data are presented as mean ± SD unless indicated otherwise. The Kolmogorov-Smirnov test was used to examine the normality of the data distribution. Data was normally distributed. Parametric tests were used for analysis.

Total and ionized magnesium data were analysed using repeated measures ANOVA for the effect of consecutive days (5 levels; baseline, day 1 till day 4), with a post hoc Bonferroni correction when there was a main effect for consecutive days.

A backward linear regression was used to analyse which variables contributed significantly to the observed baseline total and ionized magnesium levels. In addition, a backward linear regression was also used to analyse which variables contributed significantly to the observed decrease ionized magnesium after the first day of exercise.

Results

Participant characteristics

Twenty-six of our participants did not finish the 4 Day Marches due to various reasons (e.g. knee problems, back problems, time consuming and the heat). The characteristics of the remaining 68 participants who completed all 4 days are shown in table 1.

Exercise characteristics

Exercise was performed under warm ambient conditions, with a significant increase in humidity ($p < .001$) and with significant varying wet bulb globe temperature (WBGT) between a minimum of 15 °C (in the early morning) and a maximum of 29 °C during the four days ($p < .001$) (table 2).

Table 1
Participant characteristics

	Participants (n = 68)
Characteristics	
Age (years)	83.7 ±1.9
Body composition	
Height (cm)	168.9 ± 7.3
Weight (kg)	71.0 ± 10.0
BMI (kg/m^2)	24.8 ± 2.7
Cardio characteristics	
Resting heart rate (bpm)	66.6 ± 13.5
Systolic pressure (mmHg)	147.2 ± 14.0
Diastolic pressure (mmHg)	81.8 ± 10.3
Dietary intake	
Energy intake (kCal)	1990 ± 477
Total protein (En%)	16.6 ± 4.3
Total fat (En%)	33.8 ± 7.7
Total carbohydrates (En%)	43.8 ± 7.6
Fibre (g)	22.2 ± 6.7
Calcium (mg)	964 ± 368
Magnesium (mg)	336 ± 99
Walking distances per day	
Walking 30 km	n = 65
Walking 40 km	n = 3

Means ± SD are shown. BMI: Body mass index; Dietary intake values are estimated with a 24 hour recall; En%: Energy percentage of that macronutrient of total energy intake.

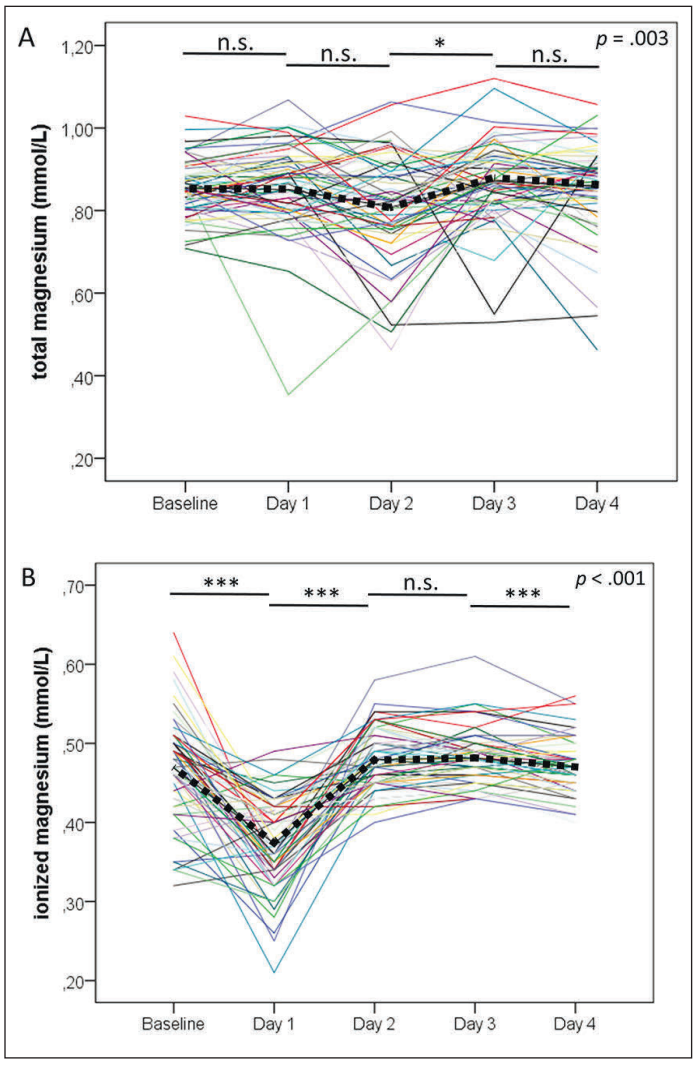
Walking exercise intensity assessed as percentage of estimated maximal heart rate, for all participants was 76 ± 11 %, with an average heart rate of 108 ± 15 bpm (table 3). Based on this criterion, the exercise was classified as moderate intensity (20). Plasma volume decreased after the first day of walking with -2.2 ± 10.1% (p = .035) and increased during the other exercise days (p = .206, p < .001 and p < .001, respectively). Fluid intake varied with 3.9 ± 1.5 L on the first day, 3.8 ± 1.4 L on the second day, 3.8 ± 2.6 L on the third day and 2.0 ± 1.1 L on the last exercise day (table 3).

Total and ionized magnesium at baseline

Average baseline levels of tMg (0.85 ± 0.07 mmol/L) and iMg (0.47 ± 0.07 mmol/L) were above the reference value (figure 1). None of the participants had tMg levels below reference value, while 23 participants (34%) had iMg levels below reference value (table 4). The average ratio between ionized and total magnesium was 0.55.

A multiple backward regression was run to predict baseline tMg and iMg values from gender, age, body composition, resting heart rate, energy intake and dietary intake. None of these variables statistically significantly predicted baseline tMg or iMg levels (p > .05).

Figure 1
Total (A) and ionized (B) magnesium concentrations (mmol/L) for all 68 participants



Lines represent every single participant, dotted line represents the average magnesium concentration. P values represent a repeated measures ANOVA for the effect of days. Significant differences between days are presented with horizontal lines, with n.s. non-significant, * p < 0.05, ** p < 0.01, and *** p < 0.001.

Exercise response

Both tMg and iMg levels changed significantly during the four consecutive walking days (p = .003 and p < .001, respectively) (figure 1).

tMg did not change after the first and second walking day compared to baseline and the previous day (p = 1.00 and p = .086 respectively). After that, a significant increase in tMg (+ 0.07 ± 0.15 mmol/L, p = .012) was measured at day 3 compared to day 2. tMg remained stable after the fourth day of exercise,

Table 2
Ambient conditions at day 1 to day 4

	Day 1	Day 2	Day 3	Day 4	Asymp. Sign.
Minimum WBGT (°C)	15	18	17	18	
Maximum WBGT (°C)	27	29	26	25	
Mean WBGT (°C)	22.2 ± 4.9	24.4 ± 4.0	22.5 ± 3.4	21.4 ± 2.8	
Friedman Test Mean Rank WBGT	2.25	3.89	2.25	1.61	< .001
Minimum humidity (%)	45	35	55	65	
Maximum humidity (%)	90	80	95	95	
Mean Humidity (%)	62.5 ± 18.6	56.1 ± 18.3	73.9 ± 14.6	85.4 ± 11.2	
Friedman Test Mean Rank Humidity	1.93	1.18	3.11	3.79	< .001

WBGT: wet bulb globe temperature. Asymp. Sign P values refer to an Intra-group Friedman ANOVA test for the effect of days.

Table 3
Exercise characteristics presented for all participants at day 1 to day 4

		Day 1	Day 2	Day 3	Day 4	Asymp. Sign.
Walking						
	Exercise duration (hours:minutes)	8:11 ± 1:06	8:28 ± 1:05	7:55 ± 1:13	7:53 ± 1:25	< .001
	Speed (km/h)	3.8 ± 0.5	3.7 ± 0.5	3.9 ± 0.6	4.0 ± 0.7	< .001
	Fluid intake (L)	3.9 ± 1.5	3.8 ± 1.4	3.8 ± 2.6	2.0 ± 1.1	< .001
Physical parameters						
	Weight change (kg)	- 1.02 ± 0.88	- 0.68 ± 0.74	- 0.38 ± 0.68	0.08 ± 0.58	< .001
	Plasma volume change (%)	- 2.17 ± 10.10	1.36 ± 7.41	4.07 ± 7.06	7.82 ± 8.16	< .001
	Mean heart rate (bpm)	108.1 ± 15.4				
	Max heart rate (bpm)	122.6 ± 17.5				
	Exercise intensity (%HRmax)	75.7 ± 10.9				

Values are mean values for the 4 walking days. Asymp. Sign P values refer to a repeated measures ANOVA for the effect of days. Weight difference is calculated as post-exercise - pre-exercise, a negative value means weight loss. Plasma volume change is calculated as day # - baseline, plasma volume is calculated with Dill and Costill calculation 1974 (Dill & Costill 1974).

Table 4
Participants below reference values

	Baseline	Day 1	Day 2	Day 3	Day 4
tMg	(0) 0%	(2) 3%	(11) 16%	(3) 4%	(4) 6%
iMg	(23) 34%	(60) 88%	(18) 26%	(15) 22%	(17) 25%

Amount of participants below reference values of tMg and iMg, presented as (n) %.

compared to the third day of exercise (p = 1.00).

A significant lower iMg was measured after the first walking day compared to baseline (- 0.10 ± 0.09 mmol/L, p < .001). This decline was measured in 78% of the participants. Furthermore, a significant higher iMg concentration was measured at day 2 compared to day 1 (+ 0.11 ± 0.07 mmol/L, p < .001). iMg was stable between day 2 and day 3 (p = 1.00), and declined again at day 4 (– 0.01 ± 0.02 mmol/L, p < .001). The average ratio between ionized and total magnesium was lowest after the first day of exercise: 0.44. Correcting tMg and iMg levels for plasma volume changes did not affect the observed significant findings during the four exercise days.

After the first day of walking, only 2 participants (3%) had tMg levels below the reference value, while 60 participants

(88%) had iMg levels below the reference value. The number of participants below the reference value at walking day 2 recovered for iMg, while it increased for tMg (table 4).

Variables contributing to iMg decrease after first day of exercise

Mean heart rate during exercise predicted significantly whether iMg decreased after the first day of exercise or not ($F(1, 46) = 7.18$, $p = .010$, $R2 = .135$). Participants who showed a decrease in iMg after the first day of exercise had a significantly higher mean heart rate (111 ± 15 bpm) compared to the participants who showed no decrease in iMg (97 ± 14 bpm). Independent variables such as sex, age, height, weight, resting heart rate, walking duration and speed, weight and plasma change from baseline till day 1, dietary magnesium intake and total magnesium levels at baseline did not contribute significantly to the decrease in iMg.

Discussion

Although lower Mg blood concentrations and (or) clinically relevant hypomagnesemia have been reported in elderly, our study population of 80+ vital years old showed average tMg and iMg levels that were within the normal range. Remarkably, their blood level patterns of iMg during and after exercise showed similarities with those found earlier in much younger adults undergoing an acute physical exercise protocol (15). The decrease in iMg after the first exercise day which restored to baseline levels during consecutive exercise days suggests a rapid adaptation and points towards redistribution between different Mg body pools.

Total and ionized magnesium at baseline

Older adults are suggested to be more prone to magnesium deficiencies due to the age related reduction in bone mass (8), a decreased magnesium absorption (9), and the frequent use of drugs by this group (10), but studies on Mg levels in older adults are scarce. For the assessment of magnesium status, the measurement of total serum or plasma magnesium (tMg) is most commonly used (11), but its reliability is subject of debate. It is suggested that iMg should be the preferable parameter to evaluate Mg status (14, 21), as iMg is the free active form, involved in cellular processes. Reference values for iMg are lacking, however, suggested is that iMg comprises 60% of the total magnesium amount (17). Therefore, we used a minimum reference value of 0.46 mmol/L for iMg.

Our finding that tMg plasma levels were in the range considered as normal may be due to the fact that our participants are very vital for their age-group and regularly exercising, also because finishing this walking event requires frequent training (22). Average iMg levels were generally within normal range as well, although they were below the assumed reference value in one third of the participants. This led to a ratio (tMg : iMg) of 0.55, while 0.60 – 0.65 is provisionally proposed (16, 17). Whether these reference values for iMg are meaningful for this age group is questionable though. Based on our ratio (0.55) the reference value might be 0.39 mmol/L. Literature about iMg levels in older adults is lacking. Therefore, we are not sure whether this reference value is applicable in this population. More research in older adults is needed to assess what a healthy iMg level is for this age group.

Exercise response

We found a clear decrease in iMg after the first day of exercise for almost all participants, while we did not find this decrease for tMg. This is in contrast to most studies in athletes, where decreases in both tMg and iMg were reported after one bout of exercise (12-15).

An explanation for the decrease in iMg levels following exercise is an increased uptake in muscle cells and adipose tissue. Catecholamines, like epinephrine and norepinephrine, are produced during exercise and induce iMg uptake into muscle cells and regulate the magnesium dependent Na/K ATPase pumps in skeletal muscle (23). In addition, increased rates of lipolysis, which probably occurs during this type of prolonged moderate intense exercise, increases the uptake of magnesium into adipocytes (24, 25). On consecutive days, catecholamine levels might be lower, explaining the observed recovery in iMg at the second, third and final day of exercise. Another explanation for the recovery in iMg might be resilience and/or fast adaptation to the demanded exercise.

We expected plasma volume changes to cause the different patterns we observed between tMg and iMg. Bound magnesium is not able to migrate passively across the membrane and is therefore influenced by plasma volume changes, while iMg can passively diffuse and is therefore not influenced by plasma volume changes. We indeed found a decrease in calculated plasma volume (from blood haematocrit and haemoglobin concentrations) after the first day of walking and an increase after subsequent days of walking. This is in line with literature, showing that one bout of exercise causes haemoconcentration (26) and repeated endurance exercise causes long term expansion of plasma volume (27). Our data suggest that correcting tMg and iMg values for changes in plasma volume did not alter the observed difference between tMg and iMg. Therefore, something else might have influenced tMg levels as well, which causes it to react differently in this study compared to previous studies. Previous studies used shorter exercise bouts (varying from ~20 minutes to 4 hours) (12-15) compared to our ~8 hour exercise bouts. Whether this explains the decrease in tMg in those studies and the unchanged tMg in our study is questionable though. Nevertheless, a shift between bound and unbound magnesium clearly influenced the levels of tMg and iMg in this study, as ratios at baseline (0.55) decrease after one day of exercise (0.44). Possibly, changed conditions due to prolonged exercise (e.g. blood pH) might have a more profound effect on the equilibrium between bound and unbound magnesium in older adults.

The exercise induced decrease in iMg resulted in levels below the reference value (0.46 mmol/L) in as much as 88% of our participants. tMg levels were lowest at the second walking day, resulting in levels below the reference value in 16% of our participants. It is suggested that symptoms of magnesium deficit may not be manifested until plasma total magnesium levels decrease below 0.50 mmol/L (28). This would translate to iMg levels below 0.3 mmol/L (60% of tMg). We only had 2 participants on the second walking day with tMg levels below 0.50 mmol/L and they reported no health problems. A total of 88% of our participants had iMg levels below reference value and even 6 of them had iMg levels below 0.30 mmol/L, none of them reported any health problems and/or magnesium deficiency symptoms.

Variables contributing to iMg decrease after first day of exercise

An association between mean heart rate during exercise and the decrease in iMg was found. Previous studies reporting an exercise-induced decrease in magnesium did not investigate which variables contributed to that decrease (12-15). It may be expected that a higher heart rate relates to a higher production of catecholamines, resulting in increased magnesium transport to muscle (23). It would be interesting to study the effects of different exercise intensities on magnesium levels. Unfortunately, studies comparing different exercise intensities and magnesium changes are lacking. However, studies with high intensity exercise, like a progressive treadmill ergometer test until exhaustion (14) and a heavy 90 minutes bicycle ergometer test at 70% VO2max (15) show almost comparable results with iMg decreases of 0.05 mmol/L and 0.06 mmol/L, respectively.

Limitations

A strength of the present study was the inclusion of a large group of participants. This large population enabled to establish rapid adaptation occurring to this type of exercise. Furthermore, our study population, characterised as generally healthy, regularly exercising older-aged persons is very unique and apparently underrepresented in the field of exercise physiology.

The present study had some practical limitations. First, baseline blood samples were not collected at the same time of day across participants, which might introduce some variability in the measurement, caused by a possible circadian rhythm of both ionized and total magnesium (29, 30). However, the within-day variation is much smaller than the decreases we observed between days, suggesting that timing did not affect our results. Secondly, we did not assess magnesium excretion via urine, which could have given us information about magnesium handling of the kidneys during this type of exercise.

In conclusion, these results indicate that in an older adult population, prolonged walking exercise causes an acute decrease in ionized magnesium levels while levels restore after consecutive days of exercise, suggesting rapid adaptation or resilience in this population. Furthermore, iMg and tMg show different responses to (repeated) exercise.

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Statement: Results of the present study do not constitute endorsement by ACSM.

Authorships: The study was designed by R. Terink, M.G.J. Balvers, C.C.W.G. Bongers, M.T. Hopman, T.M.H. Eijsvogels and J.M.T. Klein Gunnewiek; data were collected and analyzed by R. Terink, M.G.J. Balvers, and C.C.W.G. Bongers; data interpretation and manuscript preparation were undertaken by R. Terink, M.G. Balvers, C.C.W.G. Bongers, T.M.H. Eijsvogels, R.F. Witkamp, M. Mensink, M.T. Hopman, and J.M.T. Klein Gunnewiek. All authors approved the final version of the paper.

Declaration: We declare that the results of this study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Conflict of Interest: We have no conflict of interest to share.

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