Factors influencing post-exercise proteinuria after marathon and ultramarathon races

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ABSTRACT: Post-exercise proteinuria is one of the most common findings observed after short and intensive physical activity, but is observed also after long runs with low intensity. The aim of this study was to analyze factors influencing proteinuria after marathon runs. Two groups of male amateur runners were studied. The results of 20 marathon finishers (42.195 m), with a mean age of 49.3 ± 6.85 years; and 17 finishers of a 100-km ultramarathon with a mean age of 40.18±4.57 years were studied. Urine albumin to creatinine ratio (ACR) was calculated before and after both races. The relationship between ACR and run pace, metabolites (lactate, beta hydroxybutyrate), markers of inflammation (CRP, IL-6) and insulin was studied. The significant increase in ACR was observed after both marathon races. ACR increased from 6.41 to 21.96 mg/g after the marathon and from 5.37 to 49.64 mg/g after the ultramarathon (p<0.05). The increase in ACR was higher after the ultramarathon that after the marathon. There was no correlation between run pace and proteinuria. There was no correlation between ACR and glucose, free fatty acids, lactate, beta-hydroxybutyrate and insulin levels. There was significant negative correlation between ACR and interleukin 6 (IL-6) (r = -0.59, p< 0.05) after ultramarathon. Proteinuria is a common finding after physical exercise. After very long exercises it is related to duration but not to intensity. There is no association between metabolic and hormonal changes and ACR after marathon runs. The role on inflammatory cytokines in albuminuria is unclear.

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INTRODUCTION

Post-exercise proteinuria (PEP) is a typical finding after exercise [1,2,3,4,5,6,7] and has been described after various activities in many studies. PEP is an intriguing issue but the precise mechanism leading to protein loss in urine is still unknown [1,6]. Albumin is the main protein lost during exercise and albuminuria after exercise can reach a 10–25-fold increase in healthy subjects after running [8,9], cycling [10] and swimming [4]. It means that after intensive physical activity, laboratory abnormalities typical for serious nephropathies are observed in healthy young athletes. The accepted hypothesis is that PEP is a result of two processes: increased glomerular permeability and decreased renal tubule reabsorption [4,5,6]. Yet, it is unclear what factors influence glomerular membrane and tubular cells in the kidneys during exercise. Several possible factors have been proposed and studied: local vascular changes, local hypoxia, lactate accumulation, oxidant stress, hormonal changes, and a general septic reaction [1,6]. Many previous studies have focused on PEP after short exercises. It has been proved that albuminuria reaches the highest level during the most intensive exercises. The most important factors that are proposed to lead to PEP after short, intensive exercise are acute vascular changes caused by catecholamines, local hypoxia and lactate accumulation [1,4,5,6], but not duration of exercise [2,4,5]. Nevertheless, PEP is also observed after very long physical activities, and this phenomenon could not be explained purely by local vasconstriction and hypoxia. Prolonged hypoxia would cause acute kidney injury due to acute tubular necrosis, which is an extremely rare complication of exercise [11]. Probably some other factors, such as transient metabolic and hormonal changes or inflammation, are more important in very long exercises.
It is possible that mechanisms leading to proteinuria are different in short and intensive exercise than in long and exhausting activity. Additional factors such as weather conditions, body position (horizontal or supine) and mechanical stress may additionally influence the range of PEP.

The aim of this study was to investigate PEP after long exercises – marathon and ultramarathon races. The first hypothesis was that PEP is related to intensity of the run and the second hypothesis was that during long exercise the metabolic, hormonal and inflammatory markers correlate with PEP.

### MATERIALS AND METHODS

Two groups of subjects were studied. The first group finished a marathon (distance 42 km 195 m) and the second group finished an ultramarathon (distance 100 km). All studied subjects were invited to participate in the study via a letter sent by email by the race organizer informing them about the study purpose and design. The subjects were experienced amateur runners, but none had a previous history of a professional sports career. They had no contraindications against active sport exercise.

Two experiments were performed. In the ultramarathon study, the changes in PEP were examined four times during the run to establish the relationship between PEP and the intensity of exercise. In the marathon study, the relationship between PEP and metabolites was analyzed. In both studies inflammatory and muscle injury markers were evaluated.

### Table 1. The training experiences and anthropometric features of finishers.

|            | Marathon                  | Ultramarathon             |
|------------|---------------------------|---------------------------|
| Distance (km) | 42.195                    | 100                       |
| Number of subjects | 20                        | 17                        |
| Mean age (years) | 49.3 ± 6.85               | 40.18 ± 4.57              |
| Mean time of regular running (years) | 9.35 ± 5.32               | 6.31 ± 7.57               |
| Average training distance in the 3 months preceding the study (km/month) | 170.5 ± 87.37            | 228.4 ± 105.22            |
| Mean number of marathons completed | 17.03 ± 16.19            | 48.38 ± 116.39            |
| Mean marathon personal best time (h:min) | 3.24 ± 0.26              | 3.23 ± 0.23               |
| Mean number of ultramarathons completed | 4.05 ± 4.36              | 15.75 ± 13.99             |
| Mean height (cm) | 179.27 ± 5.22             | 178.59 ± 6.21             |
| Mean weight (kg) | 80.22 ± 7.25              | 77.47 ± 8.8               |
| Mean BMI kg/m² | 24.96 ± 2                 | 24.26 ± 2.28              |
| Mean PBF (%) | 15.44 ± 4.89              | 13.56 ± 5.8               |
| Mean WHR | 0.84 ± 0.06               | 0.81 ± 0.06               |
| Mean pre-race systolic blood pressure (mmHg) | 139.5 ± 14.94            | 136.12 ± 10.62            |
| Mean pre-race diastolic blood pressure (mmHg) | 90.69 ± 9.92             | 82.12 ± 7.92              |
| Mean pre-race heart rate (bpm) | 56.31 ± 7.55              | 66.41 ± 8.69              |

Abbreviations: BMI – body mass index, PBF – percentage body fat, WHR – waist-hip ratio, bpm – beats per minute. Data are presented as mean ± SD.
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Run routes
The routes of both races were located in the local university grounds, approximately 28 meters above sea level. The ultramarathon was held on the university stadium track, and the marathon was held in the alleys. The food and beverages such as water, caffeinated drinks, sports drinks, tea, soup, fruits, chocolate, energy bars and bread were provided by the organizer during the races. There were no diet restrictions.

Run pace
Run pace was measured in both races. The changes in run pace during the ultramarathon were correlated with changes in albuminuria.

Weather
Both races were organized in autumn and the weather conditions were similar (Table 2).

Laboratory tests
During both experiments, albuminuria (defined as albumin to creatinine ratio (ACR)) and selected biochemical, hormonal, metabolic and inflammatory markers were measured.

Schedule of sample collection during the marathon
Samples of blood and urine were taken immediately before and after the marathon.

Schedule of sample collection during the ultramarathon
Samples of blood were taken immediately before the start and then after every 25 km, four times during the run. Before the start, runners performed 12-h urine collection. During the event, runners urinated into special containers, and after every 25 km a sample of urine was taken for analysis.

Samples
All blood samples were drawn from the antecubital vein in a sitting position. Blood was collected into an SST gel separator tube (BD Vacutainer). Serum was separated by centrifuging at 1000G for 10 min. Urine and serum were stored at – 80°C until analysis.

Laboratory analysis
1. Blood morphology was assessed before the marathon and ultramarathon using the same method.
Haemoglobin was measured by spectrophotometry (Sysmex XN). Erythrocytes and platelets were measured by the DC sheath flow detection method (Sysmex XN). Leucocytes were measured by flow cytometry (Sysmex XN). All reagents used in the Sysmex XN analyzer were manufactured by Sysmex.

2. Urinalysis was performed before both races using a test strip for the semi-quantitative determination of specific gravity, pH, leucocytes, nitrite, protein, glucose, ketone bodies, urobilinogen, bilirubin and blood before marathon (iChem Velo analyser, Beckman Coulter Diagnostics) and ultramarathon (Combur 10 Test M, Roche Diagnostic GmbH, Mannheim).

3. Albuminuria Urine albumin was measured using immunoturbidimetric assay before and after the marathon (Architect c8000 Abbott Laboratories) and ultramarathon (ALBT2, Roche Diagnostics GmbH, Mannheim for USA).

4. Biochemical measurements before and after both races were performed using two different analyzers
Marathon. Creatinine, blood urea nitrogen and uric acid were measured in serum and urine; C-reactive protein (CRP) and creatine kinase in serum and glucose in plasma using an Architect c8000 analyzer (Abbott Laboratories).

Ultramarathon. Creatinine, urea and uric acid were measured in serum and urine; C-reactive protein (CRP) and creatine kinase in serum and glucose in plasma using a Cobas 8000 analyzer (Roche Diagnostic GmbH, Mannheim).

5. Metabolic indices were determined only before and after the marathon:
Lactate was measured by potentiometry (ABL800; Radiometer). Insulin was measured by immunoochemiluminescence (Architect i2000 Abbott Laboratories). Beta-hydroxybutyrate and free fatty acid serum concentrations were measured by the ELISA method using a MyBioSource kit (USA).

| Weather conditions | Marathon (28.10.2017) | Ultramarathon (05.11.2016) |
|--------------------|------------------------|---------------------------|
| Temperature        | From 9°C (10 am) to 10°C (2:30 pm) and drop to 9°C (3 pm) | From 1°C (7 am) to 4°C (1-4 pm) and drop to 3°C (4-7 pm) |
| Relative humidity  | From 82% (7 am) to 93% (3 pm) | From 100% (7 am) to 93% (10 am) and rise to 100% (4-7 pm) |
| Barometric pressure| 1000 hPa (10 am) to 993 hPa (3 pm) | 1009 hPa (7 am) to 1000 hPa (7 pm) |
Proteinuria was established from the calculation of albumin to creatinine ratio (ACR) from urine samples using the formula:

$$\text{ACR (mg/g)} = \frac{\text{urine albumin (mg/g)}}{\text{urine creatinine (mg/g)}}$$

Ethics
All participants gave their written informed consent.
The experiments reported in the manuscript were performed in accordance with the ethical standards of the Helsinki Declaration.
The marathon study was approved by the Bioethical Committee of the Local Medical Council in Gdansk (approval no. KB-27/17). The ultramarathon study was approved by the Local Medical Bioethical Committee of the Medical University of Gdańsk (approval no. NKBN 448/2016).

RESULTS

Runners
All runners were very experienced. Table 1 presents the results of questionnaire and anthropometric analysis of finishers of both races. The results of pre-race basic biochemical evaluation are presented in Table 3.

6. Interleukin-6 was measured only before and after the ultramarathon.
The interleukin-6 serum concentration was measured by the ELISA method using an R&D Systems kit (USA).

Statistical analysis
In all analyses a p-value < 0.05 was considered statistically significant. The authors used Statistica 12 software (StatSoft, Poland) for analysis. Descriptive statistics for continuous variables were reported as mean values and standard deviations. The Shapiro-Wilk test was applied to assess the homogeneity of dispersion from the normal distribution.

As the Shapiro-Wilk test showed that the distributions of examined parameters were significantly different from normal (p < 0.05), we used a nonparametric Mann-Whitney U test, a Wilcoxon signed-rank test and Spearman’s rank correlation test for the statistical analysis.

Calculations:
Urea was calculated using the formula:

$$\text{Urea [mg/dL]} = \text{blood urea nitrogen [mg/dL]} \times 2.14$$

(this calculation was used only for results from the marathon study)

Proteinuria was established from the calculation of albumin to creatinine ratio (ACR) from urine samples using the formula:

$$\text{ACR (mg/g)} = \frac{\text{urine albumin (mg/g)}}{\text{urine creatinine (mg/g)}}$$

TABLE 3. Pre-race basic biochemical evaluation of finishers.

|                      | Marathon          | Ultramarathon     |
|----------------------|-------------------|-------------------|
| Mean glucose (mg/dl) | 91.65 ± 9.52      | 87.67 ± 11.1      |
| Mean haemoglobin (g/dl) | 15.06 ± 0.85    | 15.46 ± 0.9       |
| Mean erythrocyte count (T/l) | 5.02 ± 0.33 | 5.22 ± 0.4       |
| Mean white blood count (G/l) | 5.33 ± 1.26 | 6.5 ± 1.16       |
| Mean platelet count (G/l) | 220.85 ± 49.88 | 250.58 ± 39.43   |

Urinalysis

|                      | Marathon          | Ultramarathon     |
|----------------------|-------------------|-------------------|
| Mean special gravity | 1.017 ± 0.006     | 1.015 ± 0.007     |
| Mean pH              | 5.7 ± 0.66        | 6.17 ± 1.03       |
| Glucosuria           | None              | None              |
| Proteinuria          | None              | None              |
| Haematuria           | None              | None              |

Data are presented as mean ± SD.

TABLE 4. Kidney function before and after marathon and ultramarathon

|                      | Before marathon | After marathon | p      | Before ultramarathon | After ultramarathon | p     |
|----------------------|-----------------|----------------|-------|----------------------|---------------------|-------|
| ACR (mg/g)           | 6.41 ± 5.53     | 21.96 ± 18.62  | <0.001| 5.37 ± 3.07          | 49.64 ± 50.38       | <0.01 |
| Serum creatinine (mg/dl) | 0.95 ± 0.11     | 1.19 ± 0.2     | <0.001| 0.88 ± 0.11          | 1.10 ± 0.20         | <0.001|
| Serum urea (mg/dl)   | 31.64 ± 6.88    | 47.68 ± 8.56   | <0.001| 34.29 ± 7.25         | 55.94 ± 15.34       | <0.001|
| Serum uric acid (mg/dl) | 5.22 ± 0.93     | 5.92 ± 0.95    | <0.001| 5.15 ± 0.87          | 5.94 ± 1.50         | <0.01 |

Abbreviations: ACR – albumin to creatinine ratio. Data are presented as mean ± SD.
Post-exercise proteinuria

The marathoners were older than ultramarathoners (p < 0.05), with longer time of regular running (p < 0.01) but with a lower number of ultramarathons (p < 0.01) and marathons (p = ns) completed.

There were no other statistically significant changes in training experience and anthropometric features between the two studied groups. The runners differ a lot in running experience and trainings methods. This heterogeneity is typical for a group of amateur runners.

Kidney function and proteinuria

Albuminuria and markers of kidney function were similar in both groups before the start. The typical biochemical changes, including increase in ACR, were observed after both races. ACR increased 3.85 times after the marathon and 9.54 times after the ultramarathon (p < 0.05). There was no correlation between albuminuria and other markers of kidney function. The changes in kidney function are shown in Table 4.

Significant increases in creatinine, urea and uric acid in serum were observed after both races. These changes were similar after both races.

Run pace

The run pace of both races was low, typical for such long exercises. The first marathon runner completed the race in 3 h 11 min, and the last runner in 4 h 29 min (mean time 3 h 50 min). The mean run pace was 5 min 26 s/km.

The first ultramarathon runner completed the race in 9 h 52 min, and the last in 13 h 34 min (mean time 10 h 47 min). The mean run pace of the ultramarathon was 6 min 28 s/km and decreased from 6 min 3 s/km (9.92 km/h) to 7 min 24 s/km (8.11 km/h). There was no correlation between run pace and ACR after the ultramarathon and the marathon.

ACR and run pace during the ultramarathon

During the ultramarathon ACR was analyzed 4 times and reached the highest value after 100 km. During the first 75 km the increase was rather slow with the peak in the last 25 km (Figure 1). This pattern was different than the run pace, which went down slightly. The highest values of ACR were observed at the end when the run pace was the lowest (Figure 1).

Changes in energy substrates, metabolites and insulin after the marathon

Significant increases in glucose, lactate, free fatty acids, beta-hydroxybutyrate (BHB) and insulin were observed after the marathon (Table 6). A positive correlation was found after the race between glucose and insulin (r = 0.80, p < 0.05) and between free fatty acids and BHB (r = 0.80, p < 0.05). There was no correlation between ACR and energy substrates, metabolites and insulin.

Inflammation and muscle damage

Significant increases in creatine kinase (CK) and C-reactive protein (CRP) were observed after both runs. The changes in CK and CRP levels were higher after the ultramarathon. Interleukin 6 (IL-6) was studied only after the ultramarathon and increased 25.64 times (p < 0.001) after this run (Table 5). Multiple increases in all studied markers of inflammation and muscle injury were observed. Similar changes in ACR were observed. Nevertheless, there was no strong positive correlation between albuminuria and studied markers of

### TABLE 5. Changes in CK, CRP and IL-6 levels after marathon and ultramarathon

|                      | Before Marathon | After Marathon | p    | Before Ultramarathon | After Ultramarathon | p    |
|----------------------|----------------|---------------|------|----------------------|---------------------|------|
| CRP (mg/l)           | 0.57 ± 0.42    | 0.63 ± 0.43   | <0.05| 0.55 ± 0.33          | 5.21 ± 3.92         | < 0.01|
| CK (U/l)             | 174.15 ± 70.35 | 605.7 ± 522.28| <0.001| 175.06 ± 103.7       | 9330.59 ± 10290.57  | <0.01|
| IL6 (pg/ml)          | n.d.           | n.d.          | –    | 0.98 ± 0.34          | 22.41 ± 1.95        | <0.001|

Abbreviations: CRP – C-reactive protein, CK – creatine kinase, IL 6 – interleukin 6, n.d. – not done. Data are presented as mean ± SD.

FIG. 1. Changes in run pace and ACR during ultramarathon.
inflammation and muscle injury. In the ultramarathon a significant negative correlation was found between post-race IL-6 and ACR 
\( r = -0.59, p < 0.05 \), although pre-race ACR was positively corre-
lated with IL-6 \( r = 0.49, p < 0.05 \). Post-marathon CK correlated 
positively with both pre- \( r = 0.80, p < 0.05 \) and post-race \( r = 0.64, 
p < 0.05 \) ACR. There was no correlation between CK and ACR measured upon the ultramarathon.

**DISCUSSION**

Post-exercise proteinuria is a transient, benign sequel of intensive physical activity. The haemodynamic, metabolic and hormonal changes, as well as hypoxia, oxidant stress and inflammation are possible factors contributing to PEP [1,6]. In previous papers, Poortmans et al. reported that PEP is related to intensity rather than duration of exercise [2,3,4,5]. They observed that PEP reached the highest values after the most intensive exercise [2,3,4,5].

The positive correlation between exercise intensity and proteinuria is an established fact after short exercises; nevertheless PEP is also observed after long exercises with relatively low intensity [7,12,13]. The long runs have some special aspects. First, the organism has to use a large amount of energy [14]. Second, the prolonged exercise leads to muscle damage and release of cytokines [15]. Both these changes are not typical for short exercises.

It is possible that factors contributing in PEP after very long exercises are different than after short ones. In the present study, the authors analyzed factors contributing to PEP in very long physical activities.

**Albuminuria, duration and intensity of run**

In previous studies, the highest values of PEP were observed after the most intensive exercises [2,3,4]. Therefore the hypothesis was proposed that PEP does not depend on the duration of the ultramarathon but would be stable or even decrease slightly during the race. To our knowledge albuminuria has never been studied sequentially several times during an ultramarathon.

In the present study the run pace decreased slowly during the ultramarathon, but a continuous increase in ACR was observed. In the final 25 km ACR rose sharply and reached the highest values at the end of the run. Both changes – the decrease in run pace and ACR elevation – were observed when runners were very exhausted.

During both races – marathon and ultramarathon – no correlation between albuminuria and run pace was observed. Albuminuria was higher after the ultramarathon, which was a longer and slower run than the marathon. These results show that during very long runs the PEP is related to the duration rather than the intensity of exercise.

**Energy**

Running a marathon is an exhausting effort for the whole organism [16]. During exercise the kidneys need a lot of energy to reabsorb water and salt. This process takes place in the very active metabolically proximal tubule and is essential to maintain homeostasis. It seems that reabsorption of albumin is not a priority during physical activity, because this kind of albuminuria is transient and does not lead to hypoalbuminemia.

Lactate, free fatty acids and hydroxybutyrate levels are increased after exercise due to enhanced metabolism [4,17,18]. Since both lactate increase and albuminuria are typical findings after intensive exercise, it was suggested that PEP is related to lactate (LA), a metabolite of carbohydrates [2,4]. The evidence that LA can directly or indirectly influence proteinuria is rather insufficient. A significant positive correlation between LA level and proteinuria (albuminuria and beta-2 microglobulinuria) was observed in a few studies after exercise [2,10,19,20] and in the early period after burn injury [21]. A strong significant correlation between blood LA levels and PEP was also found in diabetic patients after 20-min intensive exercise [22]. It is not known if LA influences albuminuria directly, or indirectly, due to the decrease in pH. It was suggested that low pH causes changes in the permeability of the glomerular membrane and configuration of albumin molecules [1,19, 20]. However, amateur runners had a low running pace and there is no significant acid-base imbalance or lactate acid accumulation after a long run in this group [17].

During long exercises the organism starts to use fat as a fuel. Therefore increases in free fatty acids and lipid metabolite beta-hydroxybutyrate (BHB) are observed after long exercise [18]. In our early observation we found that during a 50-km all-night country

**TABLE 6. Changes in energy substrates, metabolites and insulin levels after marathon.**

|                    | Before marathon | After marathon | P   |
|--------------------|-----------------|----------------|-----|
| Glucose (mg/dl)    | 91.65 ± 9.52    | 117 ± 27.58    | <0.05|
| Lactate (mmol/l)   | 1.35 ± 0.33     | 3.19 ± 0.74    | <0.0001|
| FFA (µM/L)         | 735.78 ± 246.19 | 1225.59 ± 178.8 | <0.001|
| BHB (µM/L)         | 448.21 ± 348.9  | 885.16 ± 188.63 | <0.001|
| Insulin (µU/ml)    | 5.35 ± 1.89     | 12.03 ± 8.1    | <0.01|

Abbreviations: FFA – free fatty acids, BHB – beta-hydroxybutyrate. Data are presented as mean ± SD.
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walk, albuminuria was found mainly in subjects with positive ketone bodies in urine [13].

In the present study all studied metabolic markers increased significantly after the marathon (Table 6). These changes were suspected and are typical for this type of exercise. In earlier studies concerning short exercises correlations between PEP and metabolic markers were found; therefore such a correlation was expected in the present study. Yet, there was no correlation between PEP and studied metabolic markers after marathon. There is no evidence that a direct relationship between albuminuria and energy substrates (glucose, free fatty acids or metabolites (lactate and beta-hydroxybutyrate) occurs after a marathon).

There was also no correlation between ACR and insulin, although insulin level was significantly increased. Hyperinsulinemia is known to increase perfusion of the glomerulus, which is a mechanism of proteinuria in diabetes. Insulin can promote proximal tubular absorption of sodium with decreased delivery to the distal tubule causing a feedback reflex that results in greater perfusion of glomerulus, which is a mechanism of proteinuria [23].

Muscle damage and general inflammation

The authors suspected that PEP was associated with inflammation and muscle injury after long runs. It seemed logical because PEP was increasing gradually during the ultramarathon, reaching the top values when markers of inflammation and muscle injury were very high.

Increases in CK, inflammatory markers, cytokines and myokines after long runs were observed in several earlier studies [24,25,26]. The cytokines are not only markers of inflammation but also act as muscle hormones – myokines [27,28].

In the present study increases in CRP, IL-6 and CK were observed. Although the changes in studied markers of inflammation and muscle injury were similar to changes in ACR, there was no strong positive correlation between these variables. The weak correlations which were found were difficult to interpret. The possible explanation of the negative correlation between IL-6 and ACR ($r$ =-0.59, $p< 0.05$) after the ultramarathon could be a difference in physical fitness. The better trained runners run an ultramarathon at a steady pace, but worse runners at the end of the ultramarathon are trotting at a very slow pace. These differences may influence release of IL-6 and ACR.

CONCLUSIONS

In clinical practice albuminuria is an important indicator of increased capillary leak resulting from endothelial damage and is observed in inflammation, ischemia-reperfusion injury, surgical stress, burn and sepsis [21]. Albuminuria after exercise is a benign and still unexplained condition.

In the present study, for the first time we showed that during the ultramarathon a continuous increase in ACR was observed, although the run pace decreased slowly. It suggests that during very long runs the PEP is related to duration but not intensity of exercise.

Nevertheless, the precise mechanism leading to PEP after marathon races is elusive and still unknown. No single factor (metabolic, inflammatory or related to muscle damage) is related to PEP. It is possible that PEP is caused by multiple causes. This explanation seems to be the most rational.

There are several methodological problems and limitations of this study. The relative changes in ACR differ a lot between runners; a very high standard deviation was observed. It suggests that some individual features, inherited or acquired, influence albuminuria. This high variability is probably the reason why there was no strong correlation between ACR and studied markers.

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Conflict of interest declaration

Authors declare no conflict of interest.

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