

Prospective long-term follow-up analysis of the cardiovascular system in marathon runners: study design of the Pro-MagIC study

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ABSTRACT

Introduction Prolonged strenuous exercise training may result in structural, functional and electrical cardiac remodelling, as well as vascular and myocardial injuries. However, the extent to which high-volume, intense exercise is associated with arrhythmias, myocardial fibrosis, coronary heart disease and pathological alterations of the vasculature remains unknown. In addition, there is no clear consensus on the clinical significance of these exercise-induced changes. Previous studies typically used cross-sectional designs and examined exercise-induced cardiovascular changes in small cohorts of athletes for up to 3–7 days of recovery. Long-term longitudinal studies investigating cardiovascular changes induced by prolonged strenuous exercise in large cohorts of athletes are needed to improve scientific understanding in this area.

Methods and analysis In this prospective observational monocenter study, 277 participants of the Beer, Marathon, Genetics, Inflammation and the Cardiovascular System (Be-MaGIC) study (ClinicalTrials.gov: NCT00933218) will be invited to participate in this 10-year follow-up study. A minimum target sample size of 130 participants will be included in the study. Participating athletes will be examined via the following: anthropometry, resting electrocardiography and echocardiography, blood sampling, retinal vessel diameters, carotid sonography and cardiopulmonary exercise testing, including exercise electrocardiography.

Discussion This longitudinal study will provide comprehensive data on physiological changes in the cardiovascular system and the development of pathologies after a 10-year period of prolonged and strenuous endurance exercise. Since the participants will have engaged in a wide range of training loads and competitive race events, this study will provide useful risk factor determinants and training load cut-off values. The primary endpoint is the association between the exercise-induced increase in cardiac troponin during the Munich marathon 2009 and the decline in right ventricular ejection fraction over the next 10 years.

Trial registration number NCT04166903.

INTRODUCTION

In recent years, endurance races such as marathons have enjoyed growing participation rates worldwide. For example, in the USA, the number of marathon finishers increased from 299 018 in 2000 to 507 600 in 2016.¹ Similar developments have been observed in 160 km ultramarathons.^{1 2} Furthermore, there appears to be a shift towards older participants, with the majority of runners being 40 years of age and older.³

Regular moderate intense physical activity has positive effects on the cardiovascular system and improves the quality of life.^{4 5} In contrast, several studies indicate that prolonged and strenuous endurance exercise with high workload volumes over long periods of time may lead to structural, functional and electrical remodelling, as well as myocardial damage induced by an increased cardiac load.^{6 7} Furthermore, studies support that extreme endurance exercise may correlate with increased cardiovascular events in the form of a ‘J-shaped’ curve.^{8 9} However, these results have evoked considerable debate without a clear consensus.^{10 11}

The breakdown of cardiomyocytes by myocardial necrosis and increased cardiac wall stress can be determined using cardiac biomarkers like troponin (cTn) and N-terminal pro-B-type natriuretic peptide (NT-proBNP). An increase in these cardiac biomarkers, in the context of extreme exercise, suggests either pathological processes or physiological adaptations in the meaning of the athletes’ heart. Recent analyses showed an increase in cardiac biomarkers after ultraendurance runs that peaked immediately posttrace and then normalised within 24–72 hours postexercise.^{12–14} The underlying mechanisms of these exercise-induced



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changes in biomarkers of cardiac damage remain unclear.

There is a growing consensus that dysfunctional changes occur in left ventricular (LV) diastolic but not systolic function following heavy exertion.^{15–17} Using sensitive examination methods, some groups were able to detect slight but distinct changes in the diastolic filling, pulmonary pressure and left atrial function with a simultaneous increase in cardiac biomarkers (NT-proBNP and/or cTn).^{15 18} These results link an increased risk of cardiac dysfunction with prolonged and strenuous exercise.

There is an increased focus on right ventricular (RV) function because the end-systolic wall stress during peak exercise is 10 times higher in the RV compared with the LV.¹⁹ Thus, some individuals, especially those who may be predisposed due to unknown factors, may experience greater dysfunction, fatigue and tissue injury in the right ventricle versus the left ventricle.²⁰ Typically after one bout of cardiac strain, normalisation of RV function to baseline levels occurs within 1 week.²¹ In some athletes, however, prolonged RV dysfunction is experienced especially after repetitive bouts of strenuous exercise. This has been termed ‘exercise-induced arrhythmogenic RV cardiomyopathy’.²²

La Gerche *et al* suggested sustained excessive exercise might result in chronic myocardial fibrous remodelling with increased prevalence of delayed gadolinium enhancement during magnetic resonance testing in endurance athletes.²³ Underlying mechanisms for myocardial fibrosis and the linkage to clinical events in endurance athletes have not been clearly established, and some have argued that such changes are relatively rare and may even represent normal cardiac adaptations to exercise stress.²³ Interestingly, the acute rise in cTn and the decline in right ventricular ejection fraction (RVEF) after an ultraendurance race show similar kinetics.^{12 24} La Gerche *et al* demonstrated a strong correlation between those two parameters,²⁴ indicating myocardial damage leading to RV dysfunction. However, pathophysiology has not been proven so far, and temporal association of cTn and RVEF kinetic does not confirm causality.

The underlying factors which may influence the development of RV dysfunction and myocardial fibrosis in vulnerable individuals include age, genetic factors, pre-existing or coexisting diseases such as recurrent infections, exercise intensity, ethnicity, anthropometric data and others. However, the prevalence and clinical significance of these potential risk factors are still unknown.²³ The hypothesis for our proposed study is based on data indicating an association between a decline in RVEF and cardiac biomarkers of myocardial damage (cTn).²⁴ These findings, however, are based on cross-sectional data, indicating the need for long-term cohort trials to detect long-term adaptations.

Intense and prolonged exercise training may also impact on the vasculature. Potential changes can be investigated using measurements of carotid–intima thickness

with ultrasound and retinal microcirculation with a fundus camera. These are accessible, reliable and non-invasive methods for the early detection of subclinical vascular impairment (eg, atherosclerosis) and cardiovascular disease.^{25 26}

Some studies indicate that participants of strenuous and prolonged sports ultramarathon events had above-average coronary artery calcium scores, higher incidence of calcified coronary plaques and higher average plaque formation.²⁷ The underlying factors and clinical significance of these findings have been hotly debated.²⁸ Our research group conducted comprehensive vascular measurements in a cohort of 97 male marathon runners and reported that age but not participation in multiple marathon races was linked to premature subclinical vascular impairment.²⁹ Taken together, athletes may have a slight increase of coronary plaque burden. However, the risk of acute myocardial ischaemia due to infarction seems to be decreased due to the stable nature of these plaques.³⁰ Some individuals, however, can apparently tolerate extremely high exercise workloads without any discernable negative clinical effect on the cardiovascular system.

In conclusion, the clinical significance of structural cardiovascular remodelling processes and pathologies associated with prolonged and strenuous endurance exercise is unclear. There is a need for improved studies with stronger research designs, outcome measures and larger cohorts followed up for long time periods.

The Prospective Follow-up, Marathon, Long-Term, Inflammation, Cardiovascular System (Pro-MagIC) study aimed to evaluate cardiovascular changes induced by prolonged and strenuous exercise and repetitive participation in (ultra-)endurance events over a period of 10 years. The primary endpoint is the association between the exercise-induced increase in cTn during the Munich marathon 2009 and the decline in RVEF over the next 10 years.

HYPOTHESIS OF THE STUDY

The primary hypothesis is an association between the exercise-induced increase in cTn during the Munich marathon 2009 (troponin_{post marathon}–troponin_{pre marathon}) and the decline in RVEF over the next 10 years (RVEF_{pre marathon}–RVEF_{10-year follow-up}).

METHODS AND ANALYSIS

Design and Participants

Pro-MagIC study is a prospective observational mono-center study. The participants will be recruited from the Beer, Marathon, Genetics, Inflammation and the Cardiovascular System (Be-MaGIC) study in 2009 (details published previously).³¹ A total of n=277 male Be-MaGIC participants aged 30–70 years will be invited for this 10-year follow-up study. All participants will voluntarily provide written informed consent and procedures will be in accordance to the 2008 Declaration of Helsinki. The study protocol has been approved by the local ethics

Table 1 Overview of outcome parameters of the Prospective Follow-up, Marathon, Long-Term, Inflammation, Cardiovascular System study

Examinations	Outcome parameters
Anthropometry	Height, weight, body fat percentage, BMI, blood pressure and RPP
Blood samples	Calcium, potassium, sodium, magnesium iron, glucose, HDL, LDL, cholesterol, triglycerides, IL-6, cardiac troponin, NT-proBNP
Resting and exercise ECG	Resting and exercise heart rate, PR interval, QRS duration, QT interval, QTc interval, ST-segment alterations, T-wave inversion, early repolarisation pattern
Echocardiography	Root and ascending aortic diameters, LVEDD, IVSd, LVPWd, LVESD, IVSs, LVPWs, LVEF, LAVI, HV ^{Dickhut} markers of diastolic function (E/A, E/e' septal und lateral), valve regurgitations, RVEF, TAPSE, strain analytics
Carotid sonography	Plaques, IMT
Retinal vessel analysis	CRAE, CRVE and AVR
Cardiopulmonary exercise testing	Maximal workload (W/kg), VO _{2peak} , VT1, VT2 lactate, blood pressure, Borg Scale 6–20
Questionnaire	Prevalence of diseases and sports history

BMI, body mass index; HDL, high-density lipoprotein; HV, heart volume; IL, interleukin; IMT, intima-media thickness; IVSd, interventricular septum thickness at end diastole; IVSs, interventricular septum thickness at end systole; LAVI, left atrial volume index; LDL, low-density lipoprotein; LV, Left ventricle; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVPWd, left ventricular posterior wall thickness at end diastole; LVPWs, left ventricular posterior wall thickness at end systole; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RPP, rate pressure product; RVEF, right ventricular ejection fraction; TAPSE, tricuspid annular plane systolic excursion.

committee of the University Hospital Klinikum rechts der Isar, Munich, Germany (approval reference number 306/19S-SR) and registered at ClinicalTrials.gov.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Recruiting

All former Be-MaGIC participants will be contacted and recruited via email, telephone and mail. In the absence of response, the cross-national death registers will be checked for potentially cardiovascular events or death.

Clinical measurements and setting

Clinical measurements and detailed outcome parameters are presented in table 1. The participants will be examined with the same measurements and settings as in 2009. Procedures will be conducted in the outpatient clinic of the Department of Prevention, Rehabilitation and Sports Medicine, University hospital 'Klinikum rechts der Isar', Technical University of Munich. The measurements will take place in a comparable season as in 2009.

Physical examination and anthropometry

Detailed medical and family history, as well as physical examination, will be performed by qualified medical personnel in accordance with international standards. Special attention is paid to cardiovascular risk factors and risk factors of sudden cardiac death, drugs, medications, nutrition and alcohol use over the last 10 years. Anthropometry will be conducted by qualified medical staff, including height, weight, blood pressure, rate pressure product (RPP) and body fat. Height (metre) and weight

(kg) will be measured by the Seca scale (Seca model 764, Seca GmbH & Co, Germany). Blood pressure will be measured according to standards after 5 min of rest, and body mass index will be calculated as weight divided by the square of height (kg/m^2) and RPP as heart rate \times systolic blood pressure/100. Body fat percentage will be calculated with the seven-site skinfold method using callipers according to the formula of Jackson *et al.*³²

Laboratory measurement

Blood samples will be extracted in the fasting state in supine position from the antecubital vein by qualified medical staff. Participants will not have consumed any other food or drink than water 8 hours before the extraction the blood. All blood samples will be prepared according to the study protocol from the Be-MaGIC study,³¹ centrifuged and finally stored at -80°C .

Standard blood parameters of clinical blood counts, electrolyte state, blood sugar and fatty acid status will be measured. Additionally, renal, inflammatory, cytokine, muscle and cardiac parameters will be collected (table 1).

Electrocardiography

Standard 12-lead electrocardiography will be performed using Custo Cardio 200 with Custo diagnostics 3.8, customized GmbH, Ottobrunn, Germany, in supine position. After 5 min of rest, the resting electrocardiography examinations will be digitally recorded for a duration of 1 min, with a speed of 50 mm/s and a voltage scale equivalent of 10 mm/mV. The exercise electrocardiography will be recorded in upright position for the duration of the cardiopulmonary exercise test. Normal electrocardiography characteristics for both electrocardiography recordings were calculated using automated

measurement (eg, resting and exercise heart rate (HR), PR interval, QRS duration and QT interval) as previously described.⁷ QTc interval will be calculated by formula of Bazett³³ and—in case of very low HRs—by the Sagie-Framingham method.³⁴

Additionally, abnormal repolarisation (eg, ST-segment alterations, T-wave inversion and early repolarisation pattern) and depolarisation disorder will be analysed manually by experienced medical investigators according to Sharma *et al.*³⁵ and Reinhard *et al.*³⁶

Echocardiography

Transthoracic echocardiographic examinations (ie, 33, Philips, Amsterdam, The Netherlands) by standard two-dimensional (2D) parasternal, apical and subcostal views (1–5 MHz frequency range 2D phased-array transducer) and three-dimensional (3D) apical views (1–3 MHz frequency range 3D matrix array transducer) will be conducted to achieve best image quality. Image acquisition will take part at suspended respiration, usually at complete expiration, and in left lateral decubitus position by experienced echocardiographers in accordance to current recommendations.^{37–39} Ventricular and atrial dimensions and function will be assessed by real-time 3D echocardiography (RT3DE) as previously described.⁴⁰

Static retinal vessel analyser

Ocular fundus retinal vessels microcirculation will be analysed using a noninvasive fundus camera Static Retinal Vessel Analyzer (SVA-T, Imedos Systems UG, Jena, Germany). Two valid images per eye with a centred papilla will be recorded, in a darkened room. The analysis of the images will be conducted offline using analysis software Vesselmap 2 (Visualis, Imedos Systems UG, Jena, Germany). Image capture and analysis will be performed by two independent investigators experienced within this method. Both will be blinded to prior examinations. Detailed description of image capture and analysis are described previously.⁴¹ However, not only seven vessels will be assessed but all in the relevant area. Parameters for central retinal arteriolar equivalent (CRAE) and central retinal arteriolar venular equivalent (CRVE) and arteriolar-to-venular ratio (AVR) will be calculated.⁴² The AVR is calculated from the quotients of CRAE and CRVE. According to the Atherosclerosis Risk in Communities study (ARIC study), the AVR limit for our age group is ≥ 0.82 . An AVR value below this limit will be classified as reduced.⁴²

Carotid sonography (intima-media measurement)

The intima-media thickness (IMT) will be measured at common carotid arteries by B-mode Doppler ultrasound using iE33 Philips with a linear 11 MHz transducer (Philips, Healthcare, Amsterdam, Netherlands) ultrasound machine. In detail, the far wall of the distal 1 cm of the common carotid arteries bilaterally in the anterior and lateral views (multiple angles) will be analysed. The interpretation will be conducted with an automated

edge-tracking software (Philips QLAB IMT plug-in, Philips Healthcare, Hamburg, Germany). The examinations will be performed on both side carotid arteries and calculated as the mean of both. Parameters of the IMT will be measured from end diastolic. Plaques will be defined for presence of focal thickening (>1.5 mm) within the vascular lumen present in two orthogonal planes.⁴³

Cardiopulmonary exercise test

A cardiopulmonary exercise test will be performed on an electronically braked cycle ergometer by ramp protocol after a resting period, including a phase of unloaded pedalling for 3 min. A 12-lead electrocardiography will be measured continuously with special focus on arrhythmias, T-wave inversion and ST-segment alterations. Blood pressure and lactate will be measured before and at maximum exercise, as well as 1, 3 and 5 min after the test. Maximal workload (W/kg), VO_{2peak} , ventilatory threshold (VT1, VT2) and lactate levels will be measured. Additionally, the rate of perceived exertion will be determined by Borg scale 6–20 (as previously described⁴⁴).

Questionnaire

All study participants will complete a training and disease history non-validated questionnaire. The questionnaire will include the following items: training history (sport types), running history (number of events and results etc. of marathons, half-marathons and ultramarathons) training kilometres/year, training hours/week, cardiovascular diseases, for example, myocardial infarction, myocarditis, coronary heart disease, cardiac death, cardiomyopathy, medication history, family history of cardiovascular diseases and sudden cardiac death, symptoms, palpitations and/or chest pain in rest or during exercise, risk factors for underlying cardiovascular diseases which are related to sudden cardiac death/arrest over the last 10 years.

OUTCOMES

The primary goal of this study was to assess the rise in cardiac troponin after the Munich marathon and the association with the decline of RVEF in participants of the Be-MaGIC-study. Furthermore, secondary goals are associations between clinical (eg, completed ultraendurance races, age and training history) and cardiac parameters (eg, acute changes of RVEF). A detailed overview of the further outcome parameters is shown in [table 1](#).

Sample size calculation

The primary objective will be to evaluate the association between acute rise in cardiac troponin immediately after the Munich marathon and the decline of RVEF within the next ten years. Therefore, the null hypothesis will be tested that the correlation between the acute rise in cardiac troponin after the Munich marathon in 2009 and the RVEF changes (follow-up after 10 years) equals 0.2, which can be considered as very weak to weak correlation. Under the assumptions of a true correlation of 0.5,

about 100 individuals have to be assessed to reject the null hypothesis with a probability (power) of 90% (significance level of 5%, two-sided test). Due to expected missing values, a minimum number of about 130 individuals are planned to be included into the study (from former 277 participants of the Be-MaGIC study 2009).

Statistical analyses

All statistical analyses will be performed using software SPSS and R.

For the primary analysis assessing the changes in RV and their association to the troponin rise, Pearson's correlation coefficient will be estimated with a corresponding 95% CI. A statistical tests for the null hypothesis that the true correlation coefficient equals 0.2 will be performed (two-sided test, significance level of 5%). A scatterplot will be drawn to visualise the association between within marathon troponin rise and RVEF decline over follow-up time.

To assess mean changes over time for continuous secondary outcome measures, t-tests for paired samples will be conducted. For binary measures (eg, frequency of pathological assessments), Mc Nemar's test will be performed to test for systematic changes in proportions. Correlation coefficients will be estimated to evaluate associations between continuous variables as changes in RVEF and numbers of marathon races between the two assessments, total training history and changes of baseline values of relevant blood parameters. CIs will be calculated and presented for relevant measures and effect sizes. Significance will be defined as a p value of <0.05 throughout.

DISCUSSION

To our knowledge, the Pro-MagIC study is the first trial to investigate cardiovascular changes caused by prolonged and strenuous exercise and repetitive participation in (ultra-)endurance events over a period of 10 years.

Previous studies indicated that repetitive participation in prolonged and strenuous exercise might be associated with arrhythmias, myocardial fibrosis or premature arteriosclerosis with the potential for elevated risk of coronary heart disease.^{30 45 46} This relationship may be more apparent in predisposed, older athletes with underlying risk factors and may result in an increased risk of sports-related sudden cardiac death. This study is designed to provide insights into predicting which marathon runners are at higher risk of developing cardiovascular impairment and disease.

Regular moderate physical activity decreases cardiovascular mortality and morbidity. In contrast, as emphasised in this paper, prolonged and strenuous exercise over a certain individual threshold may result in an increased cardiovascular risk. This relationship can be represented with a 'J-shaped curve', but much remains to be discovered regarding the subset of athletes vulnerable to cardiovascular harm from high exercise workloads.^{9 47} Data collected in the Pro-MagIC study will provide important

information on the underlying risk factors associated with RV dysfunction and related cardiovascular complications in athletes who chose to exercise at the high end of the exercise workload continuum.

There are several strengths of the ProMagIC-study compared with prior studies. First of all, this is the first study to follow a relatively large cohort of marathon runners using a longitudinal study design over a 10-year period. Most other studies evaluating RV function have used cross-sectional designs or followed small cohorts for short periods of time.²³ Additionally, and in contrast to prior studies, we will use novel diagnostic approaches, especially with regard to the right ventricle. Given the complex shape of the right ventricle, RT3DE avoids plane position errors and unverified geometric assumptions, which are typical problems in two-dimensional echocardiography. Previous evaluations of RT3DE showed excellent accuracy and reproducibility when compared with cardiac magnetic resonance.⁴⁸

Our longitudinal study design will elucidate cardiovascular changes caused by prolonged and strenuous exercise and repeated participation in (ultra-)endurance events over a period of 10 years, and will provide strong evidence of causality.

Despite the many strengths of the proposed study, some limitations must be acknowledged. First, this study is based on the Be-MaGIC study of 2009, in which only male participants were included. Therefore, the results may not be generalisable to the whole population. Second, the-10year follow-up may result in a loss of follow-up and missing data points, which could lead to a smaller sample size and thus to a reduced significance of the study results. To overcome this obstacle efforts to minimise loss of follow-ups include various communication channels (networking through the many years of conducting Marathon studies), several contact persons, registration channels, and external registries for unresponsive participants. Third, imaging techniques (eg, cardiac magnetic resonance imaging (cMRI)) or Holter monitoring to define fibrotic remodelling of the myocardium, stenosis, hypertension or arrhythmias are not performed in all participants. This is due to the fact that these examination modalities were not carried out in the initial Be-MaGIC study in 2009 and that no classic pre-post comparisons could be made here. However, in cases with suspect findings in the 2019 examination, further investigations are carried out according to the guidelines (eg, also cMRI, coronary CT or Holter monitoring). These results will be described separately.

As described in the editorial by Sharma and Zaidi⁴⁹ our prospective study aims to address the 'elephant in the room' by a detailed and longitudinal assessment of a large cohort of endurance athletes, with regard to both left and right cardiac chambers and vasculature. Furthermore, from a practical point of view, our results should be relevant to clinicians for risk stratification in athletes to detect cardiovascular risk factors for an underlying diseases and discover athletes who are at particular risk.

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