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Cardiovascular assessment in middle-aged male long distance runners

by

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“Mitleidend bleibt das ewige Herz doch fest”

Hölderlin

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ABSTRACT

Endurance events such as long distance running races are increasing in popularity and convey multiple health benefits. However, such exercise forms also represent a major challenge to human cardiovascular physiology and are associated with a momentarily increased risk for adverse cardiac events. Using the world's largest cross-country running race *Lidingöloppet* as a model of endurance events, this thesis aims to: 1) investigate male and female participation and performance trends 2) detail the cardiovascular findings of a comprehensive cardiovascular preparticipation evaluation in novice male race participants aged 45 years and older 3) study the impact of race participation on cardiac autonomic tone and 4) assess features of cardiovascular function and vectorcardiography (VCG), and their response to endurance exercise in individuals with early repolarisation (ER).

Study I

Participation and performance trends were investigated in >120,000 runners partaking in the *Lidingöloppet* between 1993 and 2007. In a subgroup of 249 middle-aged males, the association between the cardiac biomarker NT-proBNP and runtime was also studied. Participation increased over the study period, particularly in females and older males, while participants' fitness deteriorated, as measured by an average increase in runtime of 21 ± 31 min. Longer runtimes were independently associated with higher levels of NT-proBNP.

Study II

A preparticipation cardiovascular exam was performed in 153 middle-aged male first-time *Lidingöloppet* race participants. Runners were assessed by medical history and physical exam, 12-lead ECG, echocardiography, and blood tests. 9 % of runners required further diagnostic work-up and 2 % were discouraged from race participation due to cardiac abnormalities that could increase their risk of exercise-related cardiac events.

Study III

Heart rate (HR) and heart rate variability (HRV) was continuously measured from 48 hours before until 96 hours after a *Lidingöloppet* 30km race. Compared to pre-race values, HR was elevated during the night after the race while HRV remained depressed for 64 [51 - 96] hours after the race. A reduced HR recovery and a greater fall in HRV post race were associated with higher levels of high-sensitivity troponin T (hsTnT).

Study IV

The prevalence and associated cardiac features of ER, characterized by ST-segment elevation (STE) and/or J-waves, was investigated in 153 middle-aged males registered for first-time participation in the *Lidingöloppet* 10, 15 or 30km race. ER was present in 40 % and generally associated with features of better cardiovascular fitness. The cardiovascular effects of participating in the 30km race (n= 94) were also assessed after the race; runners with J-waves, but not with STE alone, showed changes of repolarisation parameters usually considered unfavourable (e.g. prolonged T peak-to-end (Tpe) and QTc).

Conclusion

This thesis demonstrated that increased participation in a long distance running event (*Lidingöloppet*) was paralleled by deteriorating runtimes. In middle-aged men, longer runtimes were associated with higher levels of NT-proBNP. These findings may raise concern regarding the fitness and cardiovascular health of some of today's race participants. A comprehensive preparticipation evaluation identified 9 % of first-time runners needing additional work-up and 2% who were ultimately discouraged from participating, suggesting that such a protocol is useful to identify individuals requiring further testing prior to vigorous exercise. After the race there was a prolonged depression of HRV. The magnitude and duration of HRV depression correlated with higher levels of hsTnT, suggesting that the degree of troponin (Tn) increase after strenuous exercise may reflect the level of exercise-induced cardiovascular stress. ER was generally associated with a benign cardiovascular profile, although subjects with J-waves showed post-race changes in some parameters of ventricular repolarisation that are usually associated with increased arrhythmia propensity. More research into the mechanisms and potential preventive measures of adverse exercise related effects on cardiac function is warranted.

Key words: early repolarisation, exercise, heart rate variability, middle-age, NT-proBNP, screening, troponin, vectorcardiography

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
AHA	American Heart Association
A_m	Late diastolic longitudinal lengthening velocity
AMI	Acute myocardial infarction
ANOVA	Analysis of variance
ARVC	Arrhythmogenic right ventricular cardiomyopathy
Bpm	Beats per minute
CAC-score	Coronary artery calcium score
CAD	Coronary artery disease
CO	Cardiac output
CT	Computer tomography
CV	Coefficient of variation
ECG	Electrocardiogram
E_m	Early diastolic longitudinal lengthening velocity
ER	Early repolarisation
ESC	European Society of Cardiology
h	Hours
HCM	Hypertrophic cardiac myopathy
HR	Heart rate
HRS	Heart Rhythm Society
HRV	Heart rate variability
hsCRP	High-sensitivity C-reactive protein
hsTnT	High-sensitivity Troponin T
NT-proBNP	N-terminal pro-brain natriuretic peptide
IOC	International Olympic committee
IQR	Interquartile range
LAFB	Left anterior fascicular block
LQTS	Long QT syndrome
LVM	Left ventricular mass
LVMi	Left ventricular mass index
METS	Metabolic equivalents
RWT	Relative wall thickness
SCD	Sudden cardiac death
SCORE	Systematic COronary Risk Evaluation
SDANN	Standard deviation of the mean of normal sinus intervals in all 5-minute segments during a 24-h period
S_m	Peak systolic longitudinal shortening velocity
SV	Stroke volume
STE	ST-segment elevation
T_{pe}	$T_{peak-to-T_{end}}$
USPTF	United States Preventative Task Force
VCG	Vectorcardiography
VO2-max	Maximal oxygen uptake
Ys	Years

LIST OF ORIGINAL PAPERS

This thesis is based on the following studies, which will be referred to by their Roman numerals.

I

Philip Aagaard, Anders Sahlén, Frieder Braunschweig
Performance trends and cardiac biomarkers in a 30km cross-country race 1993-2007.
Med Sci Sports Exerc. 2012; 44(5):894-9.

II

Philip Aagaard, Anders Sahlén, Lennart Bergfeldt, Frieder Braunschweig
Preparticipation evaluation of novice, middle-aged long-distance runners.
Med Sci Sports Exerc. 2012; e-pub ahead of print.

III

Philip Aagaard, Anders Sahlén, Lennart Bergfeldt, Frieder Braunschweig
Temporal changes of heart rate and its variability in response to long distance running - associations with cardiac troponin.
In manuscript.

IV

Philip Aagaard, Frieder Braunschweig, Liliane Wecke, Anders Sahlén, Lennart Bergfeldt
Early repolarization in middle-aged male long distance runners -cardiovascular and vectorcardiographic characteristics.
In manuscript.

INTRODUCTION

Modern sports evolved in the Anglo-Saxon nations. During the industrial revolution, upper-class sports fused with traditional village games and classic scholars added a final touch of Ancient Greek Olympia.¹ The history of long-distance running is no different.

According to legend, the Greek messenger Pheidippides ran from the battlefield at Marathon to Athens, delivered his message "νικώμεν" ("we have won"), after which he immediately collapsed and died from sudden cardiac death (**Figure 1**).² When Baron de Coubertin introduced the modern Olympic games in 1896, he included a race of similar distance as that supposedly covered by Pheidippides (40km). Called the Marathon, the race quickly caught on among the audiences, perhaps owing to a widespread perception that runners, just like Pheidippides, were risking their lives.

The perceived danger of Marathon running was much in contrast to the perception of other sports, which were generally viewed as health promoting.¹ For example, improved longevity in college oarsmen had been established as early as 1873.³ The perception of Marathon running, on the other hand, remained until the jogging boom of the 70's when, in a full swing of the pendulum, some researchers went so far as to declare participants immune to coronary artery disease (CAD).⁴ However, these claims were soon dismissed as "cardiomythology",⁵ following sobering case reports of Marathon runners succumbing to CAD.⁶



Figure 1. The death of Pheidippides in 490 BC. By anonymous artist.

The apparent contradiction between epidemiological evidence of increased longevity in exercising individuals,⁷ and the transiently increased risk of acute cardiac events during sports, particularly in men previously unaccustomed to such activity,^{8, 9} has continued to puzzle the scientific community and given rise to the term "the paradox of exercise".¹⁰

The popularity of long distance running, usually defined as a distance 3000m or longer,¹¹ has withstood any safety concerns, however, and today millions of people worldwide annually complete a Marathon.¹² In addition to rising participation, the last decade also witnessed a significant increase in mean age, as well as increasing finishing times.^{12, 13} Coinciding with these trends, SCD risk increased in male participants.¹⁴

Health benefits of physical activity

In 1953, Morris and co-workers compared the incidence of CAD in drivers and conductors in the London transport system.¹⁵ Cardiovascular disease was more common, presented earlier, and had a higher mortality rate in the more sedentary drivers, compared to conductors, even though the two groups were otherwise alike. Similar results were found in multiple other studies^{16 17} and it was concluded that physical activity during work offered protection from CAD.

As many workplaces have become more sedentary, the importance of leisure time physical activity has increased and today it may in fact be the only source of exercise for most people in the western world.¹⁸ Several meta-analyses of leisure time physical activity have demonstrated its health benefits, particularly in the prevention of cardiovascular disease.^{18, 19} Possible mechanisms include beneficial effects on conventional cardiovascular risk factors such as blood pressure,^{20, 21} cholesterol levels,²² and insulin sensitivity.^{23, 24} Furthermore, beneficial effects on endothelial function,²⁵ thrombosis risk,^{26, 27} heart rate variability,^{28, 29} and ischaemic preconditioning³⁰ may also play an important role.

Today, it is generally accepted that regular moderate exercise improves cardiovascular health. In fact, lack of physical activity may be a stronger cardiovascular risk factor than hypertension or hypercholesterolaemia.³¹

Exercise recommendations

The well-established health benefits of exercise have prompted several major national and international organizations to provide exercise recommendations for the general population.^{32, 33} Although the details of these recommendations differ slightly, there is general agreement that important health benefits can be achieved already with moderately intense exercise (3 - 6 metabolic equivalents, METS) such as brisk walking. Furthermore, it is increasingly recognized that shorter bouts of exercise, as short as 10 minutes at a time, are cumulative and adequate to achieve those benefits.^{32, 33} However, the usefulness of absolute exercise intensity level cut-offs is limited as they do not take the relative fitness of the individual into account. For example, activities requiring <6 METS may considerably stress the cardiovascular system in unfit or older individuals.³⁴

Vigorous exercise (>6 METS) also improves health, with the advantage of requiring less time to achieve results.^{32, 33} However, it should be recognized that the term "vigorous" may be misleading. For example, slow jogging generally suffices to achieve >6 METS of energy expenditure while the intensity achieved during long-distance running often far exceeds current recommendations.

This terminology becomes particularly important in the context of regular or sporadic participation in more intense forms of exercise (e.g. long-distance running events), as its impact on cardiovascular health is less well established. In fact, while most of the health benefits of exercise are derived already at moderate physical activity levels, further increases yield steeply diminishing returns. Several studies suggest an L-shaped,³⁵ or even U-shaped,^{36, 37} relationship between exercise level and health benefits. The suggestion of an U-shaped relationship between exercise and stroke risk³⁶ is particularly intriguing when also considering that veteran endurance athletes have a 5-fold increased risk of developing atrial fibrillation.³⁸ Furthermore, veteran endurance athletes also have a higher prevalence of sinus node disease³⁹ and emerging evidence suggest that extreme endurance exercise may even induce arrhythmogenic right ventricular cardiomyopathy, ARVC.⁴⁰ These findings are clearly at odds with the common perception of physical activity and health, and beg the question if less exercise may sometimes be more.

Sudden cardiac death during sports

SCD (and myocardial infarction) is generally considered "exercise-related" when it occurs during or up to one hour after physical activity.³⁴ It is thought that such events require both a substrate and a triggering factor to occur.³⁴

In young athletes (<35 ys of age), the most common underlying substrates of SCD are inherited cardiomyopathies (e.g. hypertrophic cardiomyopathy (HCM) and ARVC), congenital vascular malformations (e.g. an anomalous origin of the coronary arteries) and channelopathies (e.g. Long QT syndrome, LQTS). Because vigorous exercise can trigger malignant ventricular arrhythmias in these conditions, and because exercise has no beneficial effect on the underlying substrate - it may in fact contribute to adverse structural remodeling - individuals with these conditions are discouraged from competitive sports participation.^{41, 42} Although the abovementioned conditions may also be present in middle-aged and older athletes (>35 ys), the most common underlying SCD substrate in this age-category is CAD.³⁴ In the presence of CAD, exercise can trigger acute adverse cardiac events through several potential mechanisms including coronary artery plaque rupture secondary to more forceful bending of the coronary arteries, increased coronary arterial pressure and shear stress, and vasospasm in atherosclerotic coronary arteries.⁴³⁻⁴⁵ Myocardial oxygen demand and supply mismatch can also occur during exercise, and perhaps represents a previously under-recognised cause.¹⁴ Finally, ventricular arrhythmias may originate from myocardial scars in previously infarcted areas.⁴⁶ Importantly, however, and in contrast to the situation in young athletes, physical activity exerts a favourable effect on the substrate, and is in fact recommended both in primary and secondary CAD prevention.³⁴ This has prompted some researchers to dub exercise a "two-edged sword".¹⁰

Preparticipation evaluation

SCD during sports challenges our perception of athletes being the epitome of health and casts a shadow over the overwhelmingly positive effects of exercise. These tragic unexpected events, although uncommon, are highly broadcasted and have stimulated efforts to prevent such untimely deaths through preparticipation screening.^{41, 42}

The implementation of a mandatory national preparticipation screening program of young competitive athletes (<35 ys) in Italy, including medical history taking, a physical exam and a 12-lead electrocardiogram (ECG), has been associated with a reduced incidence of SCD during sports due to the detection and exclusion of high-risk individuals (**Figure 2**).⁴⁸

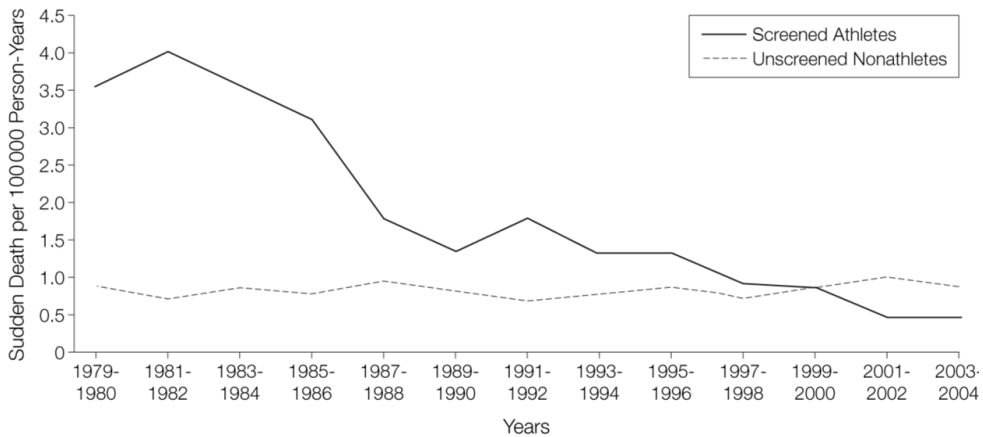


Figure 2. Mandatory preparticipation screening of young-competitive athletes in Italy has decreased the incidence of SCD in athletes, while the incidence of SCD in age matched non-screened non-athletes remained unchanged. Reproduced with permission from reference.⁴⁹

Such screening efforts are endorsed by the European Society of Cardiology (ESC) working group of sports cardiology⁴¹ as well as by several international sporting bodies, including the International Olympic Committee (IOC).⁵⁰ Preparticipation screening is also recommended in the United States, although without the 12-lead ECG as a first line test.⁴²

However, apart from cost-effectiveness issues and ethical concerns of preparticipation screening,⁴² the profound structural and electrophysiological adaptations in the hearts of exercising individuals, i.e. “athlete’s heart”,⁵¹ encumbers the differentiation of physiology from pathology. For example, physiological enlargement and electrocardiographic changes in athlete’s heart may be difficult to distinguish from pathological alterations commonly seen in patients with hypertrophic cardiomyopathy (HCM).⁵² This has raised concern that high false positive screening rates will lead to unnecessary diagnostic work-up and, in the worst case, exclude healthy individuals from enjoying the benefits of exercise.⁵³⁻⁵⁵ While guidelines to assist physicians in interpreting the athlete’s electrocardiogram^{56, 57} have shown promise in reducing the false positive rate,⁵⁸ the often heated debate over athletic preparticipation screening will likely continue.^{59, 60}

Although much of the focus in the news media and research community has been placed on adverse events in young competitive athletes, the risk of suffering from a cardiovascular event during exercise is actually much higher in middle-aged and older individuals. Incidence estimates of exercise-related SCD in young (<35 ys) athletes range from 1 in 33000 – 133000 person years^{61, 62} compared to 1 in 15000 – 18000 person years^{47, 63} in apparently healthy middle-aged men. During long-distance running race participation in particular, the risk of SCD is estimated at approximately 1 in 50,000 starting male runners¹⁴.

Importantly, the corresponding risks for women are generally 6 to 8 times lower regardless of age.^{47, 63, 64} In young athletes (<35 ys) this is probably due to a male predominance and earlier presentation of disorders predisposing to such events (e.g. HCM⁶⁵) whereas in older athletes (>35 ys) the difference is generally attributed to a delayed onset of CAD in women³⁴.

While many of the underlying pathological conditions in young athletes (eg. HCM, ARVD, LQTS) can be detected on a 12-lead ECG, CAD, the most common substrate in athletes >35 ys, may be difficult to detect even with an extensive diagnostic work-up including maximum exercise stress testing.^{34, 66} Nevertheless, both the American Heart Association (AHA)⁴² and

the ESC⁶⁷ recommend preparticipation screening (including questionnaires, a physician exam, and, in selected individuals, maximum exercise stress testing) also in middle-aged and older individuals who want to start, or increase their level of, exercise. However, these recommendations are largely based on expert group consensus and their implementation has not been evaluated, which was the purpose of study II of this thesis.

Exercise and biomarkers

Increased levels of the cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and Troponin (Tn) have been noted after endurance races, and has led to speculation that such exercise may cause cardiac harm.^{68, 69}

Increases in NT-proBNP, a polypeptide released in response to cardiomyocyte stretch,⁷⁰ after running is largely predicted by the baseline level.⁷¹ Because baseline levels of NT-proBNP well below the clinically used threshold for heart failure diagnostics still predict cardiovascular events, also in a normal population⁷², it has been speculated that small elevations in NT-proBNP may reflect mild degrees of cardiovascular dysfunction.⁷² Hypothetically, this could extend to a decreased ability to handle the cardiac stress of endurance running in individuals with higher NT-proBNP levels. In study I, we therefore assessed associations between NT-proBNP and running performance. Because NT-proBNP identified cases of severe cardiovascular disease in a previous study of self-reportedly healthy middle-aged endurance race participants⁷¹ it was also included in the preparticipation evaluation protocol in study II.

Tn is considered a specific marker for cardiac injury and constitutes a cornerstone in modern diagnosis of AMI.⁷³ Tn may however also be elevated in a range of other pathologic conditions including heart failure, pulmonary embolism, renal failure, and sepsis.⁷⁴

Furthermore, Tn levels after strenuous exercise often exceed threshold levels used clinically to diagnose myocardial infarction.⁷⁵ The mechanism behind this increase remains unknown. Several theories have been proposed, including transmembrane leakage of cytosolic Tn,⁷⁶ a stretch-related mechanism mediated by integrins,^{77, 78} and decreased renal clearance⁷⁹. Cross-reactivity with skeletal muscle Tn is unlikely, however, as the new generation of cardiac Tn assays are specific for cardiac Tn even in the presence of severe skeletal muscle damage.^{80, 81}

The clinical significance of elevated Tn after exercise is contested. While one report demonstrated Tn increases in all subjects during exercise and attributed this phenomenon to physiological remodelling,⁸² others have shown that older age and less previous exposure to endurance sports are independently associated with higher post-exertional levels.^{69, 71} Furthermore, higher Tn levels after exercise correlate with right (but not left) ventricular systolic dysfunction,^{69, 83} and with bi-ventricular diastolic dysfunction.⁸³ Finally, one recent study demonstrated that higher Tn levels following transient stress test-induced myocardial ischemia predicted the presence of CAD⁸⁴ and one author even suggested that high post-exertional Tn may represent unmasking of occult CAD.⁷⁴ Taken together, these findings suggest an association between higher post-exertional Tn levels and lower cardiovascular capacity. In study III we assessed associations between post-exertional Tn levels and parameters reflecting cardiac autonomic nervous regulation, including HRV.

Heart rate variability and exercise

Cardiac output (CO) is determined by stroke volume (SV) and heart rate (HR). SV only increases until approximately 60% of maximum exercise capacity is reached, whereafter further increases in CO will mostly depend on increases in HR.⁸⁵ Cardiac autonomic tone plays an important role in HR regulation during physical activity. In early stages of exercise,

HR increases primarily due to parasympathetic withdrawal, while an increase in sympathetic tone becomes necessary for further HR elevation during later stages of exercise.⁸⁶ Changes in cardiac autonomic activity during exercise and at rest can be measured by heart rate variability (HRV), which represents the sum of parasympathetic and sympathetic input to the sinus node, causing a beat-to-beat variation in HR.⁸⁷ Regular endurance training is associated with lower resting HR and increased HRV²⁹ whereas a bout of prolonged vigorous exercise acutely decreases HRV.⁸⁸ A low HRV reflects increased sympathetic tone and or vagal withdrawal,⁸⁷ and increases the propensity for malignant cardiac arrhythmias. Consequently, a low HRV portends a negative prognosis in several conditions including the time-period after a myocardial infarction,⁸⁹ in heart failure,⁹⁰ but also in the general population.⁹¹ It remains to be determined whether increased HRV with regular exercise is cardioprotective,⁹² and, conversely, whether lowered HRV after exercise plays a contributing role in exercise-related adverse cardiac events. Support for the former hypothesis can be extrapolated from secondary prevention studies in which exercise interventions reduce SCD, but not non-fatal re-infarction, suggesting that exercise primarily conveys cardiovascular benefit by increasing cardiac electrical stability.⁹³ Support for the latter hypothesis comes from animal studies in which dogs with a low HRV had an increased risk of ventricular fibrillation during exercise and ischemia that was attenuated with exercise-training induced increases in HRV.³⁰ In this context, it is noteworthy that women have more parasympathetic predominance⁹⁴ and a later onset of age-related decline in HRV⁹⁵ compared to men, which may contribute to a higher level of protection from malignant arrhythmias during exercise in women.^{94, 95} In study III, we studied the effects of endurance race participation on HR and HRV in first-time middle-aged and older male endurance race participants.

Early Repolarisation

In 1953, Osborn described hypothermia induced slurring of the terminal portion of the QRS complex originating from an elevated J-point that was associated with ventricular fibrillation.⁹⁶ This ECG-pattern became known as J-waves, “camel-hump sign”, or Osborn waves. Concurrently, others noted similar ECG patterns in healthy young individuals.^{97, 98} These latter changes, often called early repolarisation (ER)⁹⁹ were, despite their morphological similarities with Osborn’s findings, considered benign. However, this view was recently challenged by two case-control studies describing an increased prevalence of ER, particularly in the infero-lateral leads, in patients with idiopathic ventricular fibrillation.^{100, 101} Furthermore, a large population study showed that infero-lateral ER with a horizontal/descending ST segment was associated with reduced overall survival and increased risk for arrhythmic death.¹⁰² A high amplitude of J-point elevation (>2mm) further increased risk.¹⁰² Of note, a recent study found that these ECG patterns were also more common in athletes surviving SCD compared to in control athletes.¹⁰³

The most accepted mechanistic explanation for ER involves a transmural voltage gradient caused by differences of the epicardial and endocardial action potential during early ventricular repolarization phases 1 and 2 manifesting as a J-wave or J-point elevation on the ECG.¹⁰⁴ This voltage gradient is hypothesised to predispose to arrhythmias through phase 2 reentry.¹⁰⁵

However, as such ECG changes are present in 1-13 % of the general population,^{102, 106, 107} their implication for SCD risk stratification, particularly in subgroups with a high prevalence of ER, e.g. in athletes, is not clear^{108, 109}. In study IV we investigated the prevalence and associated cardiac features of ER patterns in middle-aged male long distance runners using vectorcardiography, as recently suggested by Surawitz and Macfarlane.¹¹⁰

AIMS

The general aim of this study was:

- To assess the cardiovascular health and investigate effects of long distance running on cardiac function in middle-aged and older male participants in a cross-country race (*Lidingöloppet*).

The specific aims of the study were:

- To analyse changes in race participation and runtimes in the *Lidingöloppet* 30km cross-country race 1993-2007.
- To study possible associations between runtime and cardiac biomarkers.
- To assess the cardiovascular health of male, middle aged and older first-time participants in the *Lidingöloppet* cross-country race.
- To characterize the cardiac autonomic response to long-distance running and possible associations with troponin T levels and other cardiac parameters.
- To establish the prevalence and morphological pattern of early repolarisation reflected by STE and/or J-waves in middle-aged male long distance runners.
- To investigate possible associations between early repolarisation patterns and other cardiovascular parameters.

MATERIAL AND METHODS

Study subjects

An overview of the recruitment of subjects is shown in **Figure 3**.

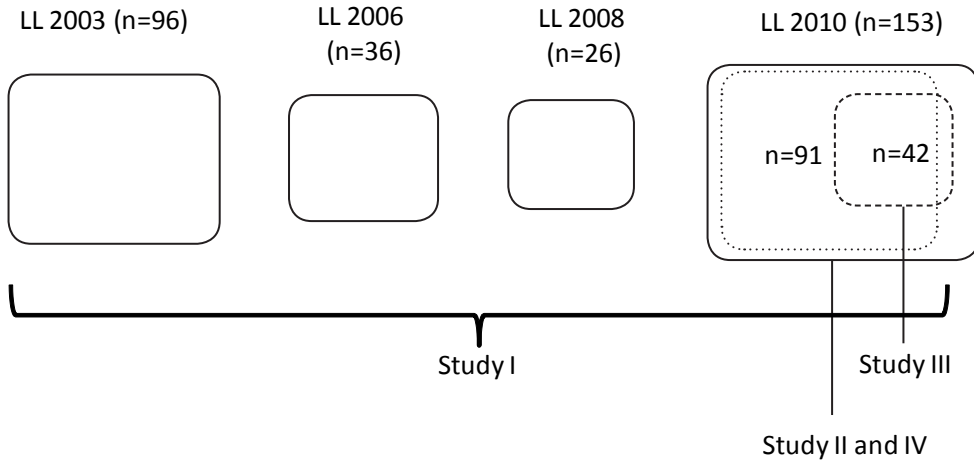


Figure 3. Overview of recruitment of study subjects.

Study I

The first part of study I analysed trends in participation and performance characteristics among all subjects who completed the *Lidingöloppet* 30km race between 1993-2007.

The second part of Study I is a pooled analysis of studies from our group on cardiac biomarkers (see below) and race performance in the *Lidingöloppet* 30-km race. Male subjects ≥ 45 ys from the 2003, 2006, 2008 and 2010 races were included in the analysis. The 2003 and 2006 studies included self-reportedly (by a medical questionnaire) healthy subjects ≥ 55 ys. The 2008 study included male subjects ≥ 55 ys registered for first-time participation and an age-matched group with ≥ 8 previous race participations. The 2010 study included subjects from study II of this thesis (male subjects ≥ 45 registered for first time participation in the 30km race, see below). Runners who were competing in multiple races (e.g. also ran the 10 or 15 km event) were excluded if their event was held before the 30 km race.

Study II

Study II included all males aged ≥ 45 ys registered for first-time participation in the 2010 *Lidingöloppet* (10 km, 15 km, or 30 km races) and who, for logistical reasons, were living in the greater Stockholm area. Subjects were invited by mail and email, non-responders to the initial invitation received up to three additional reminders via email and/or phone. Because the study focused on novice runners, subjects were asked about participation in other similar endurance events. Individuals with a history of ≥ 2 participations in any endurance race ≥ 10 km in the last 2 ys were excluded.

Study III

Subjects in study III were randomly selected (based on a limited amount of heart rate monitors) from 30 km race participants in Study II who had been deemed fit to participate following the thorough preparticipation evaluation.

Study IV

The first part of study IV included all subjects from study II (except two individuals with complete bundle branch blocks at the preparticipation evaluation who were excluded because of inherent difficulties to interpret the ST-segment in this setting). The second part of study IV included all 30 km race participants from study II who completed the race and who also participated in the post-race exam (see below).

Database analysis

The database (www.lidingoloppet.se) analysed in study I contained: an individual race identification number, date of birth, gender, and runtime of all race finishers between 1993-2007. For 2003-2007, the database also provided the number of previously completed races in the *Lidingöloppet* for any given runner (since 1965). Runtime was automatically measured using a radio frequency identification chip system (Neptron AB, Danderyd, Sweden).

Runners were separated into male (M) and female (F) age groups. M20 was used for male runners age 20–29 yr; M30: age 30–39 yr and so on. M60 was used for runners aged 60 ys and above.

Medical history and physical exam

A standardized medical history and physical evaluation, as per the 12-element AHA recommendations,¹¹ were performed in study II, III and IV. Runners were also interviewed about their training and smoking habits, the latter categorized as current, past, or never-smokers, and quantified in pack years. Cuff blood pressure was recorded as the mean of measurements from both arms after 5 minutes of rest in the supine position. Body weight and height were also measured to calculate the body mass index (BMI; kg*/m⁻²). Age, blood pressure, lipid levels and smoking status were incorporated into the Swedish adaptation of the Systematic COronary Risk Evaluation (SCORE) chart developed by the ESC to estimate the 10-year risk of fatal cardiovascular events both at current age and when extrapolated to age 60 ys.¹⁰

12-lead ECG

Standard 12-lead ECGs were recorded at 50 mm/s paper speed after 5 minutes of rest in the supine position (GE Medical Systems, Milwaukee, WI, USA) and checked by a physician on acquisition (study II, III and IV). All ECG tracings were later reassessed and changes classified as “common and training-related” or “uncommon and training-unrelated” as per recent ESC recommendations for 12-lead ECG interpretation in athletes,¹² based on the consensus of 2 electrophysiologists (FB, LB). The PQ, QRS, QT intervals and electrical axis were measured automatically by the ECG recorder and verified or modified using callipers. QT intervals were corrected according to Bazett’s formula: $QTc = QT * RR^{-1/2}$ (RR in s).

Definition of early repolarisation

In study II, ER was defined as >1mm ST elevation in 2 adjacent leads according to recent European recommendations.⁵⁶ In study IV, we separately investigated the STE and J-waves.

To increase specificity, STE in this study was defined according to AHA/ American College of Cardiology (ACC)/ Heart Rhythm Society (HRS)¹⁸ recommendations for the standardization and interpretation of the electrocardiogram¹¹¹ as ST-elevation ≥ 2 mm in lead V2 and/or V3, or >1 mm in any other lead with or without a preceding terminal QRS slurring or notching (see below), sometimes referred to as a J or Osborn wave¹¹⁰. ER was considered anterior in leads V1-4, lateral in V5-V6, aVL and I, and inferior in leads II, aVF and III. A J-wave was defined as “notched” when a positive “humplike” deflection immediately followed a positive QRS complex at the onset of the ST segment,²³ or as “slurred” when slurring of the terminal part of the QRS complex was present. J-wave patterns were classified according to the pattern in the lead with highest J-wave amplitude.

The ST-segment morphology was categorized as “up-sloping/rapidly ascending” when there was >0.1 mV elevation of the ST segment within 100 ms after the J point and the ST segment merged gradually with the T wave, or as “horizontal/descending /slowly ascending” when the ST-segment elevation was ≤ 0.1 mV within 100 ms after the J point and continued as a flat or down-sloping ST segment until the onset of the T wave. Whenever the ST segment was “up-sloping/ascending” in some leads and “horizontal/ descending” in others (looking only at leads with J-waves), it was categorized as “horizontal/descending”.^{103, 112} The isoelectric line was defined as the level between 2 adjacent T-P intervals. Morphologies, categorized as STE or J-waves had to be present in at least 2 inferior or lateral leads for positive grading. Examples of recordings and classifications of ER are shown in **Figure 4, panel A-C**.

Vectorcardiography

In study IV, VCG was recorded before and after the race using 8 electrodes positioned according to the Frank orthogonal lead system (X, Y and Z) as shown in (**Figure 5**) and using the CoroNet II system (Ortivus Medical AB, Danderyd, Sweden).

The recording time was 5 minutes. The VCG recordings were analyzed off-line with

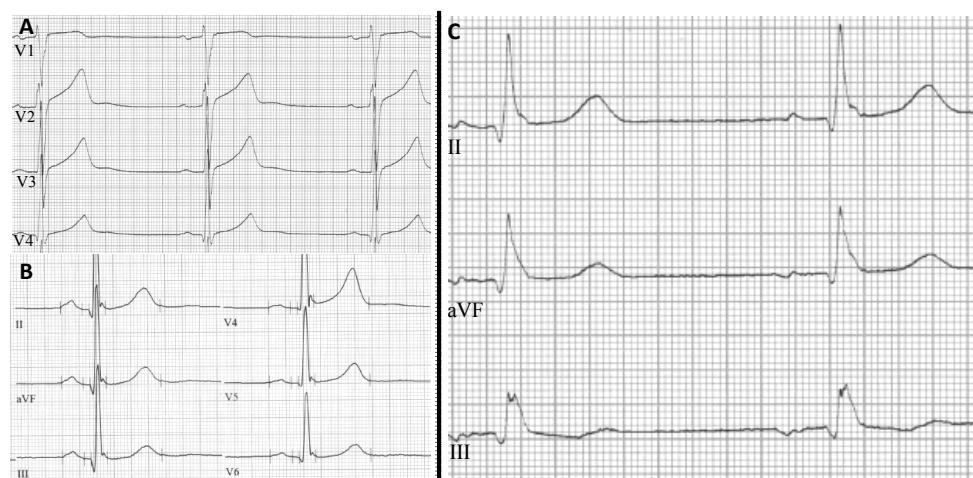


Figure 4, panel A-C. ECG examples of ER manifested as anterior ST-elevation (STE) without a distinct J-wave (Panel A), global notched J-waves with ascending ST-segments (Panel B), inferior slurred J-waves followed by a horizontal / downsloping ST-segment (Panel C).

specialized software that has been described previously¹¹³. An averaged three-dimensional QRST complex was constructed, as well as QRS and T vector loops in space. QRS, QT and Tpeak-end (Tp-e) intervals were obtained from the QRST complex. The QT interval was heart rate corrected according to both Bazett and Fridericia; $QTcB = QT \cdot (RR)^{-1/2}$ and $QTcF = QT \cdot (RR)^{-1/3}$, RR in seconds). In addition, the ventricular gradient (VG, QRSTarea), QRSarea and Tarea ($\mu V s$), which are the spatial areas under the curve formed by the moving heart vector during the QT, QJ and JT intervals, respectively, were computed from the QRST

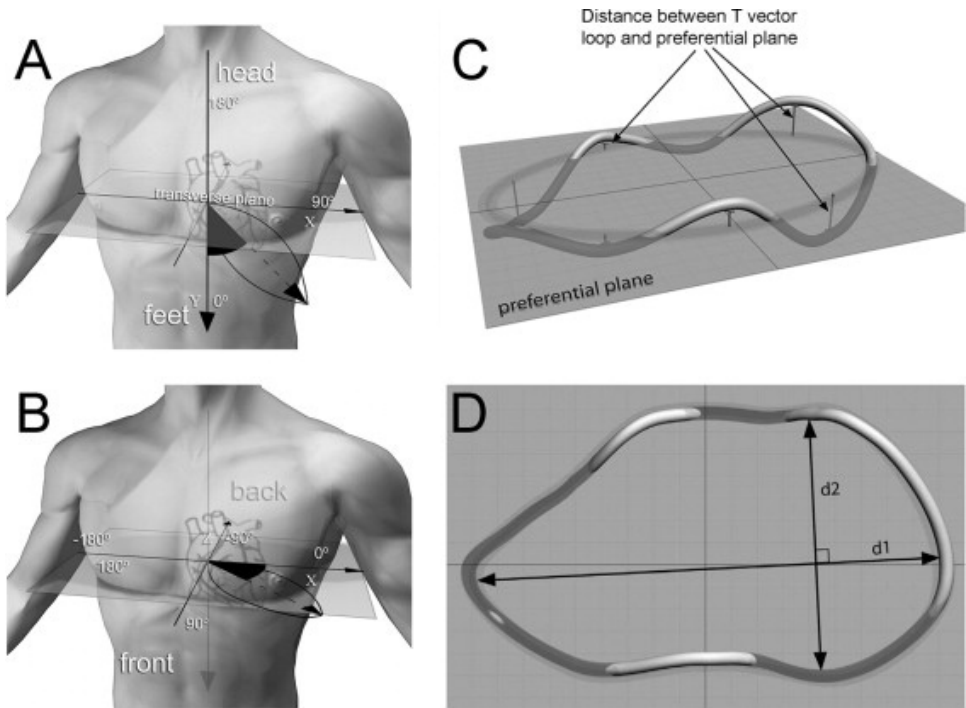


Figure 5, panel A-D. Vectorcardiographic parameters:

Panel A: *Tavplan* describes the angle between the maximum T vector and a cranio-caudal axis perpendicular to the transverse (horizontal) plane, which is depicted by the rectangle (also in panel B). At 0° the vector points downward (caudally), and at 180° it points upward (cranially).

Panel B: *Tazimuth* describes the angle between the maximum T vector projected on the transverse plane and the left extreme of the X-axis. At 0° the vector points to the left. Forward motions of the vector (left-front-right) are defined as 0° to 180° , and backward motions of the vector (left-back-right) are defined as 0° to -180° .

Panel C: *Tavplan* (in μV) expresses the distortion (bulginess) of the T loop or its deviation from the preferential plane and is measured as the mean distance between the periphery of the loop and this plane. A “healthy” loop deviates little and therefore has a small *Tavplan*.

Panel D: *Teigenv* (dimensionless) expresses the shape and geometry of the T loop and is calculated as the ratio between the two highest diameters ($d1/d2$); $d1 > d2$. A “healthy” loop is elongated and has a high *Teigenv*. Reproduced with permission from reference.¹²⁷

complex in the 3 orthogonal planes: for the QRSTarea between the QRS onset to the end of the T-wave, $QRSTarea = (QRSTx^2 + QRSTy^2 + QRSTz^2)^{1/2}$. Similarly, the QRSarea (QRS onset to the J-point) and Tarea (J point to the T end) were computed as $(QRSx^2 + QRSy^2 + QRSz^2)^{1/2}$ and $(Tx^2 + Ty^2 + Tz^2)^{1/2}$, respectively.

The magnitude and direction of the maximum QRS and T vectors in space were obtained from the individual 3-D loops and expressed as *amplitude (mV)*, *azimuth (degrees)* and *elevation (degrees)*. *Amplitude* is defined as the length of the maximum vector in space (mV), *azimuth* is the angle of the vector in the transverse plane (X-Z plane; 0° left, +90° front, -90° back, 180° right), and *elevation* is the angle in the cranio-caudal direction defined from 0° (caudal direction) to 180° (cranial direction). The QRS-T angle is the angle in space between the maximum QRS and T vectors, and the QRS-Tarea angle is the angle between the QRSarea-vector and the Tarea-vector. In healthy subjects, the latter angle is wider than the former.^{114, 115} The T-vector loop is normally elliptical and oriented in one individual preferential plane and its configuration or morphology was expressed as *Tavplan (μV)* and *Teigenvalue (Teigenv) (unitless)*. *Tavplan* is the mean distance between the T-vector loop periphery and its preferential plane and thus describes the “aplanarity” or distortion or bulginess of the T-vector loop. *Teigenv* is the quotient of the two highest eigenvalues (d1 & d2; ~diameters or axes) of the T-vector loop and describes the morphology (elliptical to circular).

Blood tests

In study I, the 2003, 2006 and 2008 pre-race blood samples were taken at a designated blood testing area in close proximity to the starting line of the race. The 2010 pre-race samples (study I-IV) were taken at the time of preparticipation evaluation 5 (IQR: 0-10) days before the race. Post-race blood samples in study I, III and IV were taken as soon as possible after race completion at a designated blood testing area in close proximity to the finishing line of the race. All blood samples were drawn from the antecubital vein. Haematological tests such as haemoglobin, haematocrit and white cell count were run on whole blood using standard laboratory methodology. For all biochemical analysis, EDTA containing tubes were used which were kept on ice and centrifuged within 4 hours. The supernatant plasma was analysed without prior freezing in all studies. To ensure that analyses were performed within the above time frame also for the post-race laboratory tests, a shuttle service between the designated blood testing area and the laboratory at Karolinska University Hospital was established on the race day. Although study I contained specimens from different yrs, all analyses were performed using the same methodology and reagents (except for troponin, see below). Normal ranges were determined by local laboratory standards (except for NT-proBNP and hsTnT, see below). In study II, direct-LDL testing was chosen over a conventional lipoprotein profile because overnight fasting could not be ensured within the protocol. To approximate the risk-SCORE we substituted total cholesterol values of 4, 5, 6, 7 and 8 with direct-LDL levels of <2.6, 2.7 - 3.3, 3.4 - 4.1, 4.2 - 4.9 and >5 respectively, corresponding to the Adult Treatment Panel III (ATP III) classification of LDL as optimal, near optimal, borderline high, high, and very high.¹⁶

NT-proBNP

In studies I and II we analysed NT-proBNP using an assay with a coefficient of variation (CV) of <6% (Roche Diagnostics, Bromma, Sweden). As per the manufacturers advice, <84 and <192 ng/L were considered normal in age <50 and ≥50 yrs respectively.

Troponin T

In study I, a 3rd generation Tn T assay with a CV of <7% (Roche Diagnostics, Bromma, Sweden) was used in subjects recruited in 2003, 2006 and 2008 and a high-sensitive assay with a CV of <10% (Roche Diagnostics, Bromma, Sweden) was used in subjects recruited in 2010. The latter assay was also used in study II, III and IV. The 3rd generation assay has a detection limit of 0.01 µg/L, making the data non-continuous. When pooling with data from 2010, when the high-sensitive assay was used, all hsTnT values <0.01 µg/L were coded as <0.01 µg/L. Tn values are presented as median (interquartile range) in all studies, because they were non-continuous and had a skewed distribution. According to the manufacturers' advice, the upper normal limits were 0.03 µg/L and 0.14 ng/L for the 3rd generation and high-sensitive Troponin assays, respectively.

Echocardiography

Pre-race echocardiography in studies II, III and IV was performed using VIVID E9 or VIVID 7 (GE-Vingmed Ultrasound AS, Horten, Norway). Post race echocardiography in studies III and IV were performed using a portable VIVIDi (GE-Vingmed Ultrasound AS, Horten, Norway), and a VIVID 7. A dedicated EchoPAC (version 7.0, GE-Vingmed Ultrasound AS, Horten, Norway) workstation was used for post-acquisition analyses.

Conventional echocardiography

All subjects were examined by transthoracic echocardiography using views and measurements recommended by the American Society of Echocardiography (ASE).¹³ Left ventricular mass (LVM) and other left ventricular dimensions were indexed for body surface area. Relative wall thickness (RWT) and left ventricular hypertrophy was defined according to ASE guidelines.¹³

Tissue Doppler imaging

Tissue velocities were recorded as peak systolic longitudinal shortening velocity (S_m), early diastolic longitudinal lengthening velocity (E_m), and late diastolic lengthening velocity (A_m) by colour-coded tissue Doppler measurements in the basal septum. The E/A ratio was calculated from the mitral inflow E and A wave velocities. Three beats were measured and averaged for all Doppler measurements.

Interobserver (PA, AS) and intraobserver (PA) reproducibility was tested in a random sample (n=26) and expressed as coefficients of variation (CV). Interobserver variability was 9.4 % (95% confidence interval (CI): 7.7 – 11.1), and 10.4 % (95% CI: 6.5 – 14.3) for cardiac dimensions and tissue velocity imaging, respectively. Intraobserver variability was 7.2 % (95% CI: 4.7 – 11.1) and 8.1 % (95% CI: 5.1 – 11.1) for cardiac dimensions and tissue velocities respectively.

Heart Rate Monitoring

All subjects in study III were equipped with a wireless cardiovascular monitor (AVIVO™ Mobile Patient Management System, Corventis Inc) 2 days prior to the race (**Figure 6**).

This device has been described in detail elsewhere.¹¹⁶ In summary, the monitor is lightweight (20g), cordless and water-resistant and therefore suitable for use in conjunction with physical activity. HR was continuously monitored 48 h prior to, during, and 96 h following the race. Any missing data was replaced by the mean of the preceding and following 5-minute median HR values. To control for the effects of daily living activity and sports¹¹⁷ we compared HR values during night-time (02-04 am), when participants were assumed to be in a similar state of rest.

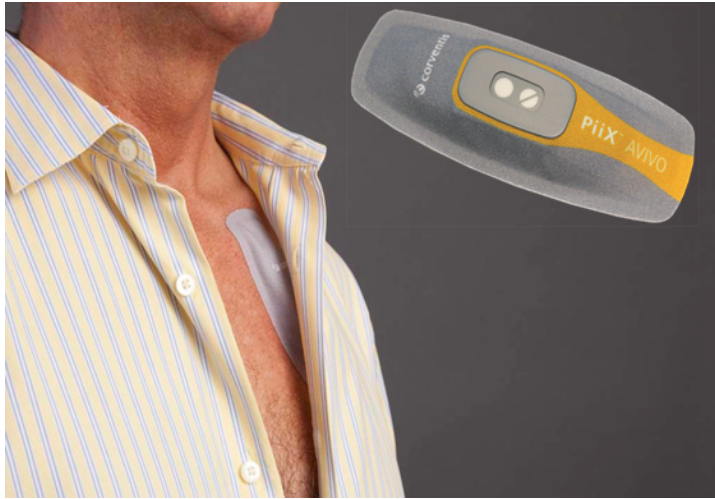


Figure 6. The AVIVO TM Mobile Patient Management System”, reproduced with permission from Corventis Inc.

HRV was calculated as the standard deviation of the mean of normal sinus intervals in all 5-minute segments during a 24-h period (SDANN) and is presented either as daily mean values (00:00 to 00:00) or as a moving average over the 12 hours before and after each time-point. Local SDANN¹¹⁸ was calculated by replacing each 5-min mean value with the 24-h heart period mean and then recalculating the standard deviation of the altered 24-h sequence. The difference between the standard deviation of the altered 24-h sequence and total SDANN is the local SDANN, i.e., the contribution made by that particular 5-min interval toward total SDANN. Local SDANN values were normalized¹¹⁸ such that the sum of all 5-min local SDANN values equalled the total SDANN for that 24h period.

The HRV recording during the day (00:00 to 00:00) prior to the race is referred to as *baseline*. The time to return of HRV to baseline levels was determined in each individual as the time between the end of race until the 95% CI of the post-race HRV moving average overlapped with the 95% CI of the baseline HRV. Subjects in whom HRV did not return to baseline during the monitoring period were assigned the end of their recording period as a return to baseline HRV.

Individual HR reserve (HRR) ($HRR = \text{maximum HR} - \text{resting HR}$) was calculated in all subjects. Maximum HR was determined according to the formula: $\text{maximum HR} = 220 - \text{age}$, or as the highest achieved HR during the monitoring period (whichever was highest). Resting HR was taken at the pre-race examination after 10 minutes of supine rest. Running intensity was measured both as the maximum and the mean % of HRR used during the race. Post-race heart rate recovery was measured as the % of HRR utilized 30 minutes after the race.

The monitor also recorded atrial and ventricular arrhythmia episodes. Episodes of atrial fibrillation were manually excluded from HR and HRV analyses.

Statistical analysis

Data are presented as mean \pm SD or median [interquartile range] as appropriate. For baseline characteristics in study II, the data range is also presented. Data distribution was analysed by Kolmogorov-Smirnov test. Correlations were tested using Pearson's r or Spearmans Rho.

The Student's t-test, Mann-Whitney U test or the Kruskal-Wallis tests (study III) were applied to compare means of groups as appropriate. Within group differences were compared using a paired samples t-test (study III). Multiple linear regression analysis (forced-entry method) was used to analyse predictors of runtime (study I), and to analyse predictors of HRV and hsTnT (study III). The coefficients are presented as standardised β -weight to allow for comparison between independent variables. Data from repeated measures were analysed using Friedmans analysis of variance (ANOVA). In study IV, proportions were compared using chi-square analysis or Fisher's exact test. All statistical analyses were performed using PASW Statistics, version 18 - 20 (IBM Corporation, Armonk NY, USA). A two-tailed p-value of <0.05 was considered statistically significant in all studies.

RESULTS

Study I

Total participation in the *Lidingöloppet* 30 km cross-country race increased 56% between 1993 and 2007, with larger gains in women (+1076 %) compared to men (29 %). As a result, the proportion of women increased from 2.7 to 19.8 % ($p<0.001$). The largest participation increases were observed in young women (<30 ys), whereas participation decreased in the corresponding male age group. Among male participants the largest increases were observed in those aged >60 ys (+271%). Consequently, mean age decreased from 37.4 ± 10.3 to 36.0 ± 9.5 ys in women and increased from 36.4 ± 9.9 to 38.2 ± 9.9 ys in men (both $p<0.001$).

Mean runtimes gradually deteriorated in both men (from 164 ± 27 to 184 ± 33 min, $p<0.001$) and women (from 179 ± 26 to 203 ± 32 min, $p<0.001$), following a strong linear relationship (men: $r=0.98$, women: $r=0.93$). Increased runtimes were seen in the mean (**Figure 7**), top and bottom quartile as well as in the top and bottom 5% of all analysed age- and gender groups. Considering only the top 50 men in each age group, runtimes increased in M20 to M50 but decreased in M60, while in women, runtimes increased in all analysed age-groups (p for trend <0.01 for all). In a pooled analysis of all runners from 1993-2007 (only one participation per individual, $n=64\,456$, 54 311 males and 10 145 females), runtimes in both genders remained stable from age 20 to age 47 (average annual increase 0.1% in men vs. 0.0% in women). After age 47, runtimes increased with age in both genders but at an attenuated rate in women (**Figure 8**).

Predictors of runtime were examined in a subgroup of 249 men ≥ 45 ys using multiple linear regression that included significant variables from univariate analysis (BMI, age, NT-proBNP and previous number of races). BMI ($\beta = 0.406$) was the strongest independent predictor of run time followed by age ($\beta = 0.400$) previous race participation ($\beta = -0.199$) and the pre-race level of NT-proBNP ($\beta = 0.105$).

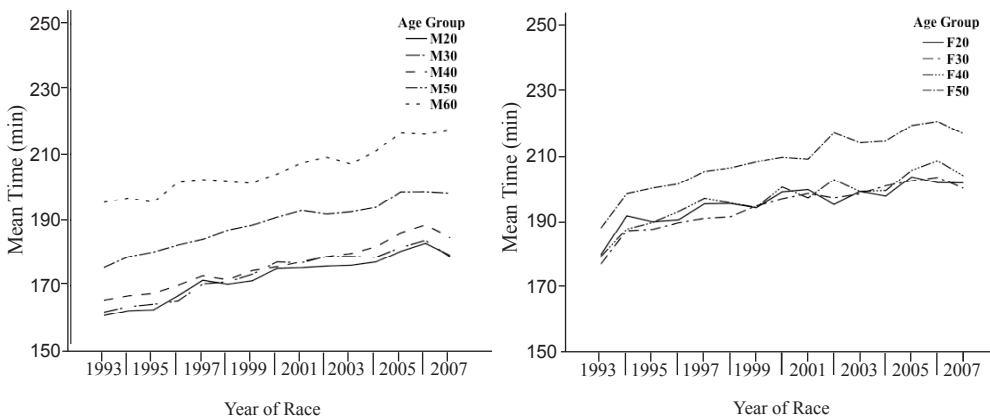


Figure 7. Runtimes increased over the study period in all age- and gender groups.

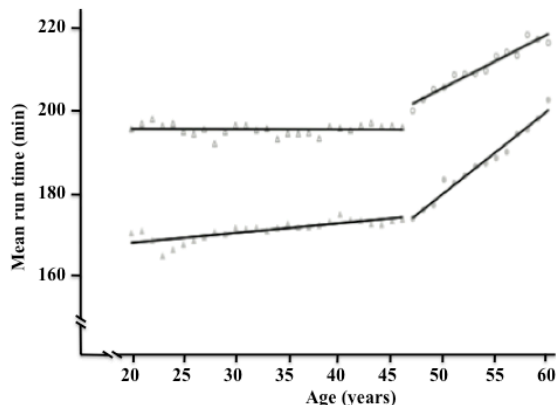


Figure 8. Changes in mean run time in relation to age in males and females participating in the *Lidingöloppet* 30 km cross country race 1993-2007. Solid triangles = men, hollow triangles = women.

Study II

Of 265 eligible individuals registered to make a first-time entry into the *Lidingöloppet* cross-country race, 153 (58%, age 51 ± 5 y) completed the study. **Figure 9** summarises the selection of participants. While the 10-year fatal cardiovascular event risk was low (SCORE: 1% (IQR: 0 - 1%)), mild abnormalities were common, e.g. elevated blood-pressure (19%), left ventricular hypertrophy (6%), elevated LDL cholesterol (5%). Physical inactivity (less than 30 minutes of physical activity at least 3 times per week) was reported by 12%, former and current smoking status by 23 and 1% respectively, and BMI exceeded 25 and 30 kg/m² in 34 and 6% respectively.

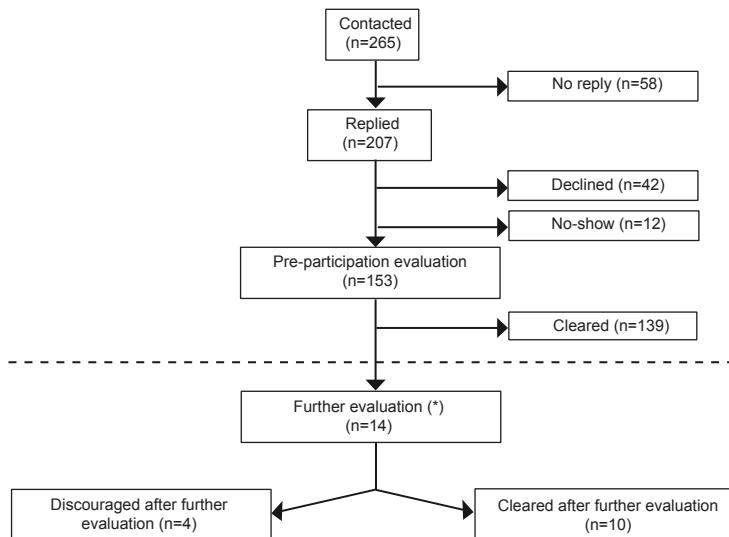


Figure 9. Flow-chart outlining the preparticipation evaluation process in study II.

ECG changes compatible with “athlete’s heart” were present in 82%, e.g. sinus bradycardia (61%) and/or early repolarisation (32%). ECG changes considered training-unrelated were found in 24%, e.g. prolonged QTc: 13%; left axis deviation: 5.3%; left atrial enlargement: 4%).

In 14 runners (9%) additional diagnostic work-up was clinically motivated (**Table 1**), and 4 (2%) were ultimately discouraged from race participation (and vigorous exercise) due to QTc intervals ≥ 500 ms ($n=2$), symptomatic atrioventricular block ($n=1$), and a cardiac tumour ($n=1$). The physician exam and the 12-lead ECG identified 12 of the 14 subjects requiring further evaluation. In addition, paroxysmal lone atrial fibrillation was discovered in 3 runners.

Table 1. Individual work-up of 14 runners with abnormal findings.

No.	Age	Test modality (finding)	Further testing	Diagnosis
1.	47	Medical history (syncope, risk-SCORE $\geq 5\%$)	ET, Holter	AV block III*
2.	48	Medical history (palpitations)	ET, Holter	A-Fib
3.	48	Medical history (palpitations)	ET, Holter	A-Fib
4.	55	Medical history (AMI, DM)	ET, Holter	-
5.	55	Medical history (exertional CP)	ET, Holter	A-Fib
6.	45	Physical exam (BP 180/110 mmHg risk-SCORE $\geq 5\%$)	ET, 24h BP	HTN
7.	46	ECG (QTc > 500ms)	ET, Holter	LQTS*
8.	48	ECG (QTc > 500ms)	ET, Holter	LQTS*
9.	48	ECG (ST-depression)	ET, Holter	-
10.	49	ECG (TWI beyond V3)	ET, Holter, SAECG, CMR	-
11.	51	ECG (QTc = 464 + MVP)	ET, Holter, Exercise echo	-
12.	56	ECG (QTc = 484ms)	ET, Holter	-
13.	45	Echo (cardiac tumor)	CT, Surgery	Cardiac lipoma*
14.	67	Echo (AR grade 1+)	ET, Exercise echo	AR grade 1+

Table 1. The individual work-up of 14 subjects with abnormal findings during the preparticipation evaluation. Abbreviations: 24-h BP, 24 hour blood pressure monitoring; A-Fib, atrial fibrillation; AMI, acute myocardial infarction; AR, aortic regurgitation; AV, atrioventricular; BP, blood pressure; CMR, cardiac magnetic resonance imaging; CP, chest pain; DM, diabetes mellitus; ET, symptom limited maximum exercise test; exercise echo; exercise echocardiography; Holter, 48-h Holter monitoring; LQTS, suspected long-QT syndrome; MVP, mitral valve prolapse; risk-SCORE $>5\%$, a 10 year risk for cardiovascular events $> 5\%$.¹¹⁹ SAECG, signal averaged ECG; TWI, T-wave inversions. * Denotes runner discouraged from race participation after complete work-up.

Study III

All 42 subjects who were registered for a first-time entry into the *Lidingöloppet* 30 km race were in sinus rhythm at the pre-race exam. No sustained ventricular arrhythmias occurred during the monitoring period but atrial fibrillation developed after the race in two runners.

The night-time HR (recorded 02 - 04 am) was 54 ± 8 bpm during the two pre-race nights, increased to 64 ± 9 bpm ($p = 0.002$) during the first night post-race and then returned to pre-race levels. HRV had a more protracted time-course before returning to pre-race levels than HR with a median time to return to pre-race HRV of 64 [51 - 96] hours (**Figure 10**).

Runners achieved a mean and maximum HR of 127 ± 14 and 166 ± 15 bpm, corresponding to a median and maximum relative running intensity of 102 ± 11 and 133 ± 12 % respectively, during the race. Mean HR recovered to 104 ± 18 bpm, corresponding to a mean HR recovery of $84 \pm 17\%$, 30 minutes after the race. While all subjects had normal hsTnT pre-race, levels exceeded the diagnostic threshold for myocardial damage in all but one post-race (97%).

A greater reduction in HRV on day 1 after the race was observed in runners with higher resting HR ($r = -0.66$, $p < 0.001$), higher post-race hsTnT ($r = -0.49$, $p = 0.003$), lower amount of training hours per week ($r = 0.35$, $p = 0.02$) and a higher relative mean running intensity during the race ($r = -0.33$, $p = 0.04$). In a multivariate model including these variables, only post-race hsTnT remained significantly associated with the degree of post-race HRV reduction ($\beta = -0.49$, $p = 0.01$). The relationship between quartiles of change in HRV on Day 1 and post exertional hsTnT levels is shown in **Figure 11**.

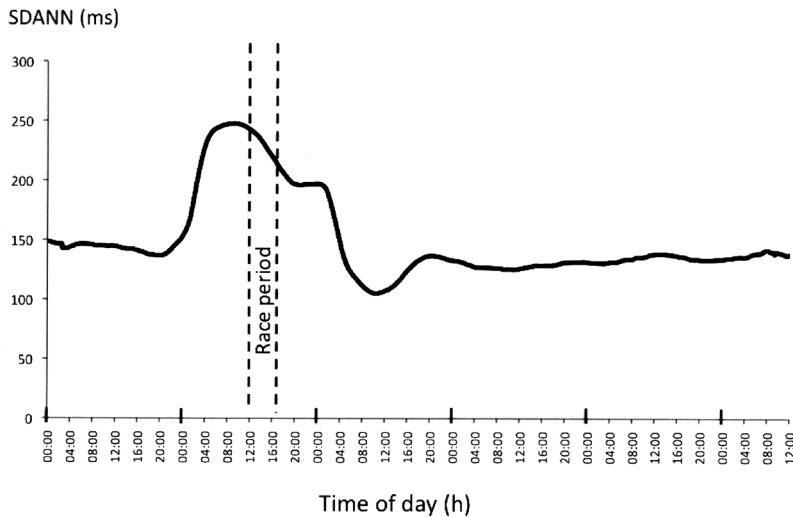


Figure 10. The moving average of heart rate variability (HRV) during the study period. HRV was calculated as the moving average of the standard deviation of the mean of normal sinus intervals in all 5-minute segments during a 24-h period.

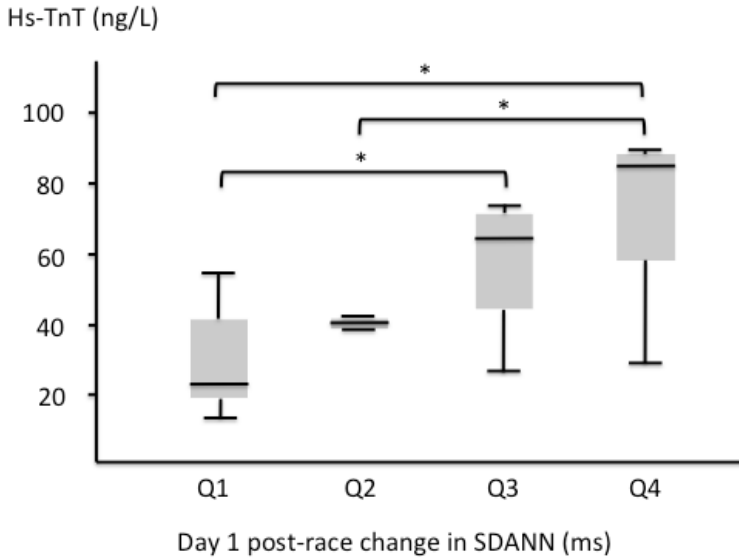


Figure 11. Quartiles of subjects according to change from baseline in Day 1 heart rate variability (HRV). Q1 ≥ 5 ms; $5\text{ms} < \text{Q2} \leq -13$ ms; $-14\text{ ms} < \text{Q3} \leq -40$ ms; $\text{Q4} < -40$ ms. * $p < 0.05$ between quartiles. Kruskal- Wallis One-way p-ANOVA = 0.02.

Local SDANN peaked during the race with plateaus between midnight and the early morning hours, except for a significant drop the night/morning after the race. Local SDANN also showed a large increase the night before the race.

Higher post-race hsTnT correlated with a higher mean running intensity ($r = 0.44$, $p = 0.006$), less HR recovery at 30 min post-race ($r = 0.48$, $p = 0.005$), and a longer time to return to baseline HRV ($r = 0.36$, $p = 0.03$). In a multivariate model, including the aforementioned factors as well as age and post-race creatinine, a greater post-race HRV reduction was the only parameter significantly associated with higher post-race hsTnT ($\beta = -0.52$, $p = 0.01$).

Study IV

STE was present in 37 (24%) out of 151 subjects with a mean age of 51 ± 5 . The location was anterior in 26 (17%), lateral in 7 (5%) and inferior in 4 (3%); 3 had “global STE”, i.e. in all locations, and in 5 (2 %) STE exceeded 2 mm.

A J-wave was present in altogether 45 (28%) subjects. The localization was anterior in 16 (11%), lateral in 15 (10%), and inferior in 19 (12%); 14 (9%) had global J-waves. The J-wave morphology was predominantly notched in 32 (21%) and slurred in 13 (8%). In 28 (18%) of the 45 subjects, the J-wave was followed by a horizontal/downsloping ST-segment, whereas 17 (11%) had J-waves followed by an up-sloping ST-segment. In 5 (2%) the J-wave amplitude exceeded 2mm (all with up-sloping ST-segments). ECG examples of subjects with ER and J-waves are shown in **Figure 4, Panel A - C**.

Both STE and J-waves were generally associated with features of good physical fitness (e.g. lower cholesterol, lower BMI, lower BP, faster runtimes). In subjects with J-waves, associated findings were similar regardless of J-wave location, amplitude, morphology (notched vs. slurred) or ST-segment morphology (ascending vs. horizontal).

In the vectorcardiographic exam post-race, subjects with pre-race J-waves had significantly more prolongation of both QTc (28 ± 16 vs. 16 ± 19 , $p=0.03$) and Tp-e/QT (0.023 ± 0.019 vs. 0.008 ± 0.019 , $p=0.01$). The magnitude of change did not differ significantly between groups for other VCG parameters.

GENERAL DISCUSSION

This thesis examined various aspects of cardiovascular health and function in long distance runners using the 30km cross-country race *Lidingöloppet* as a model. Participation, particularly among women and older male runners, increased over the 15-year observation period investigated in study I. Concurrently, fitness, measured as runtime, deteriorated and, in middle-aged men, slower runtimes were associated with higher levels of the cardiac biomarker NT-proBNP. The application of a preparticipation evaluation protocol identified 9 % of runners requiring further diagnostic evaluation and 2 % were ultimately discouraged from race participation. HRV, a marker of cardiac autonomic activity, showed a prolonged depression following race participation and both the degree and duration of HRV depression correlated with post-race levels of the myocardial damage marker Tn. Finally, a large proportion of middle-aged and older novice male endurance race participants had ER characterized by STE and or J-waves. ER was associated with overall benign cardiovascular exam findings, including VCG, and with several markers of better physical fitness. However, subjects with J-waves (but not subjects with STE only) showed possibly adverse changes in some cardiac arrhythmia propensity markers following race completion.

Participation and performance

Participation

Analysing a database of >120,000 participants in the *Lidingöloppet 30 km*, study I of this thesis describes a marked increase in race participation during the 15-year observation period, particularly in the minority groups of older runners and women. A similar trend has been observed in another study¹²⁰ and also in a large US endurance race database.¹²¹ This may reflect a generally increased awareness of the multiple health benefits of exercise¹⁸ and is also consistent with the increasing numbers of individuals enjoying a good state of health at an older age, enabling them to participate in more extreme forms of exercise. The dispelling of the stereotype that older people cannot complete long distance races may also have contributed.¹²⁰ The large increases in female participants may simply result from a reversal of previous attempts to ban this group from participating.¹²² In fact, up until the 1982 games in Los Angeles, the IOC considered the Marathon too dangerous to allow female participation, which may appear ironic today considering the much higher adverse cardiac event rate in men.³⁴

Performance

Concomitant with the increased participation, average runtimes prolonged. This increase was observed in all analysed percentiles, including the top 5 % in all age and gender groups. When analysing runtimes in the top 50 runners (of all age and gender groups), improved runtimes were only seen in men 60 ys or older, likely reflecting the previously unexplored potential and growing competition in this group. Therefore, the improvements in some older top runners in this and other studies¹²⁰ should not be viewed as representative for the growing population of middle-aged and older endurance runners as a whole.

As runtime correlates well with other markers of performance, such as VO₂-max and speed at lactate threshold and is a good predictor of fitness level,¹²³ increasing runtimes suggest that

today's participants are less well prepared to handle the physiological stress of endurance running than those starting 2 decades ago. This is concerning from a cardiovascular standpoint, as cardiorespiratory fitness is a strong predictor of cardiac events and survival in healthy individuals¹²⁴ and because the risk of adverse cardiac events during exercise is higher in individuals previously unaccustomed to such activity.^{9, 47} Although not documented in this study, lifestyle changes (sedentary behaviour, increasing body weight) may also have contributed to increasing runtimes. In fact, in our sub-analysis of 249 male runners, BMI was the strongest independent predictor of runtime. Another possibility is that today's runners have a less competitive attitude towards participation. However, in view of the correlation between runtimes and NT-proBNP discussed below the latter explanation appears less likely. The above findings suggest that increasing endurance race participation reflects a lowered threshold to come to the starting line, rather than a society becoming healthier, which is consistent with the increased SCD rate in male marathon runners over the last decade.¹⁴

Many people may desire to complete a Marathon although lack of time may constitute a barrier to regular exercise.¹²⁵ Such individuals are sometimes referred to as "weekend warriors", meaning that they do no or limited amounts of exercise during the week, and then do extreme exercise (e.g. Marathons) on the weekends. The outcome of this particular exercise pattern was examined in one study, which confirmed the health benefits of regular exercise, while "weekend warriors" with one or more cardiac risk factors had a trend to increased mortality.¹²⁶

As older male athletes are of particular interest in the context of exercise related cardiovascular risk³⁴, we performed a biochemical substudy in 249 male runners age 45 or above. Multivariate analysis in paper I showed that longer runtimes were independently associated with higher levels of the cardiac biomarker NT-proBNP. Our group has previously shown that the level of NT-proBNP before the race strongly predicts its increase during the race,⁷¹ suggesting that differences in baseline values reflect how well the heart is able to cope with the stress of endurance running. Furthermore, baseline NT-proBNP correlates with post-race echocardiographic findings of cardiac fatigue and exercise-related electrophysiological changes of ventricular repolarisation¹²⁷ and in one study identified older runners with severe underlying cardiac pathology.⁷¹ Although changes in NT-proBNP levels were not examined longitudinally, higher levels in slower runners contribute to the concern over the cardiovascular health status of some of today's older male participants.

Ageing and performance

Average run time was preserved in both genders until age 47, followed by an accelerated decline. As running economy is generally preserved with ageing,^{128, 129} this may largely reflect that oxygen uptake at the anaerobic threshold and VO₂-max can be held at top levels only up to the age of 45–49 ys.^{13, 130}

Interestingly, gender differences in race time decreased with increasing age, pointing toward a smaller age-related decline in VO₂-max in females compared with males,¹³¹ but may also indicate that older women still have a higher threshold to participate and only register for the race if they are well prepared. Such a gender bias, although not found in another study of performance, training and lifestyle parameters of Marathon runners,¹³² could potentially contribute to the higher, and increasing, prevalence of exercise related cardiovascular events in men.

Taken together, the above findings may strengthen the case for the appropriateness of a pre-participation cardiovascular evaluation, at least in higher-risk subgroups, to ensure adequate fitness in all participants.

Preparticipation sports evaluation in middle- and older age

Preparticipation evaluation of middle-aged and older individuals before starting (or increasing) exercise has been recommended both by the ESC⁶⁷ and the AHA.⁴² Few studies have been conducted in this field, however, and these recommendations are therefore largely based on expert group consensus (Class IIb, level of evidence C).⁵⁵

In study II, a preparticipation evaluation protocol, largely conforming to the ESC recommendations,⁶⁷ and, in addition, echocardiography and measurement of the cardiac biomarker NT-proBNP was applied in a presumed “high-risk group”³⁴ of middle-aged and older male runners registered to participate for their first time in the *Lidingölopet* cross-country race.

Using this protocol in study II, further medical workup was deemed necessary in 9%, while 2% were ultimately discouraged from vigorous exercise following a complete diagnostic work-up. These proportions are identical to a large Italian screening program of young competitive athletes,⁴⁹ which was associated with a reduced incidence of exercise-related SCD in the screened population. This analogy may be viewed as supportive of the usefulness of cardiovascular evaluation in the studied target group. Furthermore, our findings confirm the value of a thorough physician exam and a 12-lead ECG as first line tests in preparticipation evaluation. Combined, these tests identified 12 of the 14 runners requiring further diagnostic evaluation, while the SCORE, routine echocardiography and NT-proBNP did not add substantially to the diagnostic yield.

Calculating the modified SCORE¹³³ did not contribute significantly to the evaluation process. Because of its inherently low risk estimates in younger age-categories, particularly among non-smokers, it is hard to see a major role for this risk stratification tool in the studied population.

The absence of echocardiographic findings relevant in the context of exercise (e.g. HCM, which is present in approximately 1/500 in the general population¹³⁴) may relate to limited study size, while the unexpected finding of a cardiac lipoma in one participant illustrates that any widely applied test can lead to incidental findings requiring additional testing and/or treatment. Echocardiography, which was included in the screening protocol primarily to allow better validation of findings from other testing modalities (e.g. the 12-lead ECG), has been suggested as a first line test in the screening of young athletes,¹³⁵ and may be more appropriate in this population due to aetiological differences of exercise-related SCD (more structural heart disease underlying SCD in young athletes).

In keeping with the absence of structural echocardiographic abnormalities, NT-proBNP was within the normal range in all runners. These results contrast with findings from a previous study, where NT-proBNP was elevated in 15 runners of whom 4 had severe cardiovascular abnormalities.⁷¹ The discrepancy between these studies may be largely explained by older age and thus a higher prevalence of cardiac dysfunction in the former study.

Findings on the 12-lead ECG

According to recent recommendations for interpretation of the 12-lead ECG in the athlete,⁵⁶ we divided ECG findings into common and training-related and uncommon and training-unrelated. Training related ECG changes were present in 82 % on the baseline recording. In particular, 61 % had bradycardia and 12 % had 1st degree AV-block, which are both considered benign and common features of athlete’s heart.⁵¹ No subjects had higher degrees

of AV-block during their baseline recordings. In contrast, transient episodes of Mobitz type I AV-block, mostly at night, were commonly observed in those athletes undergoing Holter monitoring, demonstrating that the prevalence of rhythm disturbances will inevitably vary according to the length of the recording period and that "normal values" should be interpreted with caution. One subject with first-degree AV block at baseline who reported syncope with cardiogenic features had third-degree AV block on Holter monitoring and was discouraged from vigorous exercise pending pacemaker implantation.

Such changes in chronotropy (e.g. slowed AV-conduction) in athletes are often attributed to an exercise-induced increase in parasympathetic tone.⁵¹ However, this theory fails to explain why HR remains low many years after cessation of sports and it has instead been suggested that long-term vigorous exercise may permanently alter the intrinsic cardiac pacemaker function.³⁹ This is supported by findings of a higher prevalence of pathological conduction disorders, e.g. complete heart block, in veteran endurance athletes compared to age-matched controls, possibly due to increased fibrosis of the cardiac conduction system.³⁹

Training-unrelated ECG abnormalities, on the other hand, were found in 24% of subjects, a proportion markedly greater than previously reported in young competitive athletes (<5%). This difference was largely driven by a large proportion (13%) of QTc intervals exceeding the upper normal limit (440 ms) for men.

Notably, QTc intervals in our cohort were longer compared both to the general population¹³⁶ and to a group of young (mean age 20 ys) competitive athletes.¹³⁷ Because QTc intervals prolong secondary to endurance training¹³⁸ and older age¹³⁹ it is possible that more liberal cut-off values for prolonged QTc are appropriate in middle-aged and older endurance athletes, at least in asymptomatic individuals with no pertinent medical history. Nevertheless, in accordance with current recommendations,¹⁴⁰ the 2 individuals with QTc > 500 ms were discouraged from vigorous exercise. Both individuals ignored our advice to cease vigorous sports, which is in accordance with non-compliance reported in other studies.^{141, 142} As the main intervention to reduce SCD risk is to cease vigorous sports participation, such non-compliance with physician advice obviously defeats the purpose of screening. Furthermore, it should also be recognized that cessation of vigorous sports does not offer complete protection from arrhythmic events.¹⁴¹ Both these findings ought to be considered prior to implementing large-scale preparticipation evaluation efforts.

The prevalence of left anterior fascicular block (LAFB) was also higher in our cohort compared to in young athletes.⁵⁶ This may be expected as the prevalence of LAFB increases rapidly after age 30.¹⁴³ In contrast to in young individuals, where LAFB may be associated with congenital heart disease,¹⁴⁴ it is considered to portend a benign prognosis in middle and older age when present in isolation.¹⁴³ Importantly, subjects with uncommon and training-unrelated ECG changes, such as electrical axis deviation and left atrial hypertrophy could be reassured by echocardiography. If strictly adhering to the European guidelines however, i.e. not using echocardiography as a first-line test, more subjects with abnormal ECG's possibly would have required further work-up, which could constitute a potential barrier to implementing preparticipation sports evaluation in clinical practice due to high cost

However, some experts are beginning to question the need for further evaluation of these ECG alterations, when present in isolation.^{57, 145}

Coronary artery disease

Of note, no subject in Study II was diagnosed with coronary artery disease (CAD). Because CAD is the most common underlying cause of SCD in middle-aged and older individuals,¹⁴⁶ it appears tempting to try to identify and possibly exclude individuals with CAD from vigorous exercise. This strategy is however complicated by several problems.

Firstly, various forms of exercise tests, which are considered the screening test of choice for detecting occult CAD, have poor sensitivity and specificity in asymptomatic patients with a low pre-test likelihood of disease.⁴² Secondly, a positive exercise test requires a flow limiting lesion, while most exercise related events are secondary to the rupture of previously non-flow limiting vulnerable plaques.^{43, 44} For this reason, even if an individual has a positive exercise test, this result is much more predictive of future angina than of future SCD or MI.¹⁴⁷

Thirdly, most SCD will occur in individuals with relatively low risk.¹⁴⁸ This concept was elaborated on in a paper by Epstein and Maron,¹⁴⁹ which concluded that screening of 10,000 individuals with risk factor analysis and exercise testing would prevent 1 SCD in the test positive "high-risk" group, while 4 SCDs would still occur in the test negative "low-risk" group.

For the reasons stated above, and in accordance with recommendations by the EACPR and the United States Preventative Task Force (USPSTF),⁶⁶ exercise testing was not included in the initial evaluation.

Other potential CAD screening tests include CT-scanning to determine the coronary artery calcium score (CAC-score). Because the CAC-score reflects total coronary artery plaque burden, it may be a better predictor of future plaque rupture than an exercise test although cost, availability, and radiation exposure currently limits its wide application.¹⁵⁰ Interestingly, one study reported higher than expected CAC-scores in endurance runners compared to cardiovascular risk factor and age-matched controls. Levels were particularly high in runners who later had events.¹⁵¹ Although the authors speculate that marathon running may play a causative role in accelerating the atherosclerotic process, possibly through oxidative stress, other explanations are also possible. For example, the study has been heavily criticized for self-selection bias with a large proportion of former smokers (50%) in the athlete group and, as was suggested in the accompanying editorial, some participants were perhaps pondering about running as a means to reverse previously unhealthy living habits.¹⁵² If true, the latter explanation falls in line with the trend of endurance events attracting less fit individuals.

In the current era of advanced medical technology, the value of a thorough medical history taking, which was included in study II, should not be underestimated. In fact, one case-control study of 57 individuals hospitalised for acute exercise-related cardiac events identified a previous coronary event, smoking, and flu-like illness or unusual fatigue in the month leading up to the event, as major risk factors. Although some of these complaints may appear vague, several studies have shown that athletes suffering SCD commonly seek medical attention shortly before their event^{153, 154} and it is important to raise awareness of such potential warning signs among both physicians and athletes.

Finally, as many individuals today commence exercise late in life it is possible that they harbour previously undetected cardiac conditions typically associated with adverse events in young competitive athletes, such as cardiomyopathies and channelopathies. Therefore, preparticipation evaluation in middle- and older age should not exclusively focus on identifying subjects with CAD.

Ethical- and sex aspects of preparticipation sports evaluation

Selectively screening certain sub-groups of the population, e.g. athletes, is controversial.^{60, 155} The argument that such screening discriminates against groups that do not participate in organised sports but who may still be exposed to an increased risk of exertion-related SCD, for example during gym-class or leisure-time sports, is often raised in the United States¹⁵⁵ but is largely lacking in the European debate.

In Sweden, for example, The National Board of Health, with regards to young competitive athletes, recommends screening of elite (competing on at least a national level) athletes only.¹⁵⁶ This approach comes not only with obvious ethical concerns, but arguably also lacks scientific rationale. For example, it has been suggested that subtle cardiac dysfunction in HCM, the most common cause of SCD in young athletes,¹⁵⁷ naturally select out most afflicted individuals from participation in the highest-intensity sports^{158, 159} and consequently the screening-yield may be lower in elite-athlete sub-groups than in the general athletic population as a whole.

With regard to preparticipation evaluation in middle- and older age, some countries (e.g. France¹⁶⁰) mandate endurance race participants to provide a doctors note stating sufficient health in order to participate. However, most countries, including Sweden, do not. The implementation of such a mandatory preparticipation exam is not uncomplicated from an ethical point of view, regardless of whether the economic burden for the evaluation is placed on the individual or on the society. In the former case, cost may impose a barrier to endurance race participation in financially challenged individuals. In the latter case, it may be questioned, particularly given the relatively low event rate, whether resources spent on screening members of a group often considered to be the fittest in society could be used more efficiently elsewhere.

Adverse cardiac events during sports are known to be more common in males than in females, regardless of age.³⁴ However, with regard to middle- and older age sports participants, it should be kept in mind that much of the epidemiological data in support of a higher male than female incidence rate are from the 1970's and 1980's, when female participation was still rare.^{47, 63} Also, the steady decline in CAD in the general population over the last decades has been largely driven by a decline in males, adding further uncertainty to assumptions based on previously collected data.¹⁶¹ Importantly, however, a large recent study on 10 million marathon runners conducted from 2000-2010 also reported higher SCD rates in men and, in contrast to the situation in female runners, the event rate in males increased over the study period.¹⁴

Thus, although the dramatic change in participation patterns and CAD epidemiology over the last decades may warrant further studies to avoid underestimating female risk of exercise-related SCD, it appears reasonable to focus current screening efforts on apparent high-risk groups (the approach evaluated in study II). While this is not unproblematic, as outlined above, universal screening on the other hand would be logistically very challenging for the health care system and would likely decrease the cost-effectiveness of this intervention given the much lower female event rate.

Troponin and heart rate variability

TnT

In paper I, III, and IV the cardiac marker Tn was measured before and after participation in the 30 km cross-country running race *Lidingöloppet*. While all subjects had normal levels of Tn before the race, a large proportion of subjects had levels exceeding the clinically used cut-off to diagnose myocardial ischemia¹⁶² after the race. A meta-analysis of 26 studies (n=1120 participants) showed that elevated Tn was present in 47% (95% CI: 39–56) following exercise with wide interstudy variation.⁷⁵ As exercise induced troponin elevation is characterized by rapid peaking and a quick return to baseline, in contrast to the prolonged elevation usually observed during AMI, the interstudy variation has been partly attributed to the timing of post-race blood sampling.⁸²

One widely cited report on 9 “well-trained men”, all with elevated Tn *during* exercise, even attributed this phenomenon to physiological remodelling.⁸² In fact, however, none of the subjects in that study had elevated Tn *after* exercise (except for a second peak 24-hours post-exercise). It is likely that these well-trained men would have been Tn-negative in studies with a different protocol, which, given their reported training status, is consistent with finding that more previous exercise experience correlates with lower post-exertional Tn levels.^{69, 71, 163} Regardless of its potential pathological implications, it is important for physicians to be aware of the possibility of Tn elevation after exercise to avoid unnecessary invasive work-up.¹⁶⁴

HR and HRV

In study III, monitoring of HR and HRV in middle-aged male first time endurance race participants deemed fit to participate following a thorough preparticipation cardiovascular examination showed an extended period of altered autonomic activity. This period was longer compared with a previous study in which cardiac vagal outflow was restored within hours of race completion, followed by enhanced vagal regulation the day after the race.⁸⁸ However, the latter study included younger athletes (mean age 36 ys) who may have been better accustomed to the challenge of endurance exercise than the older and novice runners in our study. In fact, although our inclusion criteria (novice middle-aged runners) attempted to limit the effect of age¹⁶⁵ and previous endurance experience²⁹ on autonomic regulation, some heterogeneity with regards to fitness level remained. As expected, better fitness (e.g. lower resting HR, less utilization of cardiac reserve to complete the race), predicted runners with a less pronounced HR elevation during the night following the race as well as runners with a less pronounced post-race decrease in HRV.

Since prolonged endurance exercise is associated with decreased intravascular volume and decreased cardiac systolic function (“cardiac fatigue”)⁶⁹ it is conceivable, as speculated by Hautala and co-workers,⁸⁸ that increased sympathetic drive, reflected by increased HR and decreased HRV, is necessary to maintain cardiac output in this setting. Furthermore, exercise-induced hypotension may stimulate a counter regulatory increase in sympathetic activity possibly contributing to an increased incidence of adverse cardiac events following exercise.¹⁶⁶

Given the long-lasting cardiac alterations after prolonged strenuous exercise, an appropriate rest period appears prudent to allow for complete cardiac recovery, particularly in older and less fit runners as their autonomic changes may be more pronounced.¹⁶⁷

In order to study short-term components contributing to the changes in 24-hour SDANN, we applied the concept of local SDANN.¹¹⁸ The effect of physical activity on SDANN¹⁶⁸ may largely explain the prominent peak in local SDANN during the race and may also account for the plateaus in local SDANN observed around the transitions between sleep and awaking between midnight and early morning hours. In contrast, the significant drop in local SDANN the night/morning after the race may rather reflect true changes in autonomic modulation. Interestingly, local SDANN largely increased the night before the race. As our subjects all lived in the Stockholm area without a need for long distance travelling or changing accommodation, this pattern may reflect important psycho-emotional components of cardiac autonomic activity. In fact, other studies have shown that sympathetic tone increases in athletes prior to competitions¹⁶⁹ and it has been speculated that this may contribute to an increased risk during competitive events as compared to during training.¹⁷⁰

Finally, the episodes of atrial fibrillation registered in two subjects are compatible with the increased incidence of atrial fibrillation in endurance athletes.³⁸

Correlations with troponin levels

A novel finding was the significant relationship between changes in HRV and concentrations of hsTnT; hsTnT levels were higher in subjects with lower pre-race HRV, a larger HRV-fall post-race and a delayed return to baseline HRV. Furthermore, hsTnT elevation was more pronounced in runners performing at a higher relative running intensity and in those with a prolonged HR recovery period following the race. The latter association is concerning as poor HR recovery following exercise-testing is prognostically unfavourable and has in fact been linked to increased mortality,¹⁷¹ also in middle-aged men without known cardiac disorders.¹⁷²

The association between post-exertional HRV changes and hsTnT levels remained significant upon multivariate analysis that included independent predictors of Tn elevation in both the present study and in a previous study of participants in the same cross-country race.⁷¹ This suggests that similar factors predisposes both to the development of cardiac autonomic alterations and to elevated biomarker release after strenuous exercise. It also provokes questions whether these phenomena are entirely physiological and benign or whether the magnitude of change may carry clinically important information that could be used to identify individuals less suited for this type of exercise. The latter view is supported by findings of Sahlén et al that runners with post-race elevations of Tn are characterised by increased left-ventricular dyssynchrony¹⁷³ and a depressed ventriculo-arterial coupling, ratio¹⁷⁴ indicating suboptimal cardiac work efficiency during exercise. Though our study does not provide evidence for a direct impact of exercise related autonomic changes on Tn release, this hypothesis deserves to be addressed in future studies.

Early repolarisation

In study IV, we examined the prevalence and morphological pattern of ER, both in the form of STE and J-waves, in middle aged male first-time endurance race participants. We also investigated associations between these ECG features and other cardiovascular parameters, including vectorcardiography. Finally, we assessed the impact of endurance race participation on cardiovascular function in runners with and without these ECG patterns.

Our study showed a higher prevalence of J-waves with horizontal/down-sloping ST segments than previously reported by Rosso and co-workers in young healthy athletes.¹⁰⁹ This might be explained by a large variation in the prevalence of various ER patterns between different sporting disciplines, with a higher prevalence in endurance trained individuals,¹⁷⁵ and also by lower age (17-19 ys) in the latter study. Although J-waves have been associated with malignant ventricular arrhythmias in athletes,¹⁰³ their frequent occurrence (30% in this study), including variants considered to confer higher risk (e.g. J-waves of high amplitude (>2mm), infero-lateral localisation, and accompanying horizontal/ down-sloping ST-segments), and the association with benign cardiac features in this study cohort argues against its use for risk-stratification. This is also in line with the view emphasized by Viskin and co-workers.¹⁷⁶ Thus, the results of this study and others are consistent; J-waves should not be used for risk stratification in asymptomatic individuals. Rather, all asymptomatic subjects with STE and/or modest J-waves should currently be reassured that their risk of harmful arrhythmias is “too low to worry about”.¹⁷⁶

At the preparticipation evaluation, both STE and J-waves were associated with features compatible with better fitness including lower BMI, blood pressure, and faster runtimes. In the VCG analysis, subjects with STE had significantly larger QRS- and T- amplitudes and -areas and hence a greater vector gradient (QRST-area). The latter differences remained after

the race and may, at least partly, be related to lower resting and post-race HR in the STE group, since these parameters are heart rate dependent.¹⁷

Runners who had J-waves (but not runners with STE only) at baseline had changes in some parameters that are commonly associated with increased arrhythmia propensity (QTc, Tpe, Tpe/QT)^{177, 178} after completion of the 30km race. However, the clinical significance of this finding remains unclear.

While idiopathic VF predominately strikes in younger age (20-40 ys), ER may possibly predispose to SCD together with various other triggers.¹⁷⁹ In the age category evaluated in the present study, ischemia is presumably the most common trigger of VF¹⁰⁸ and ER has in fact been associated with more arrhythmic events during myocardial ischemia¹⁸⁰ as well as in ICD implanted CAD patients.¹⁸¹ Because middle-aged and older marathon runners may have a higher than expected CAD burden,¹⁵¹ future studies should address if ER may put such individuals at increased risk of exercise-related SCD.

CONCLUSIONS

- Participation in the *Lidingöloppet* 30 km cross-country race substantially increased between 1993 and 2007, particularly in women and older men, confirming the increasing popularity of this exercise form.
- Runtime gradually deteriorated over the study period, suggesting a decreasing fitness threshold to participation.
- Longer runtimes are independently associated with higher pre-race levels of NT-proBNP in middle-aged and older male race participants, raising concerns as to the cardiovascular health of participants with lower fitness.
- Preparticipation evaluation of middle-aged and older male first-time participants in a long distance running event appears useful to identify individuals requiring further testing prior to vigorous exercise.
- Heart rate variability is reduced for several days after completion of a long distance running race.
- This reduction is associated with increased hsTnT levels, suggesting that the magnitude of Tn increase after strenuous exercise may reflect the level of exercise-induced cardiovascular stress.
- Early repolarization is a common finding in middle-aged and older novice long-distance runners and generally associated with a benign cardiovascular profile.

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