Paracelcus Reloaded: Searching for the Perfect Dose of Exercise?

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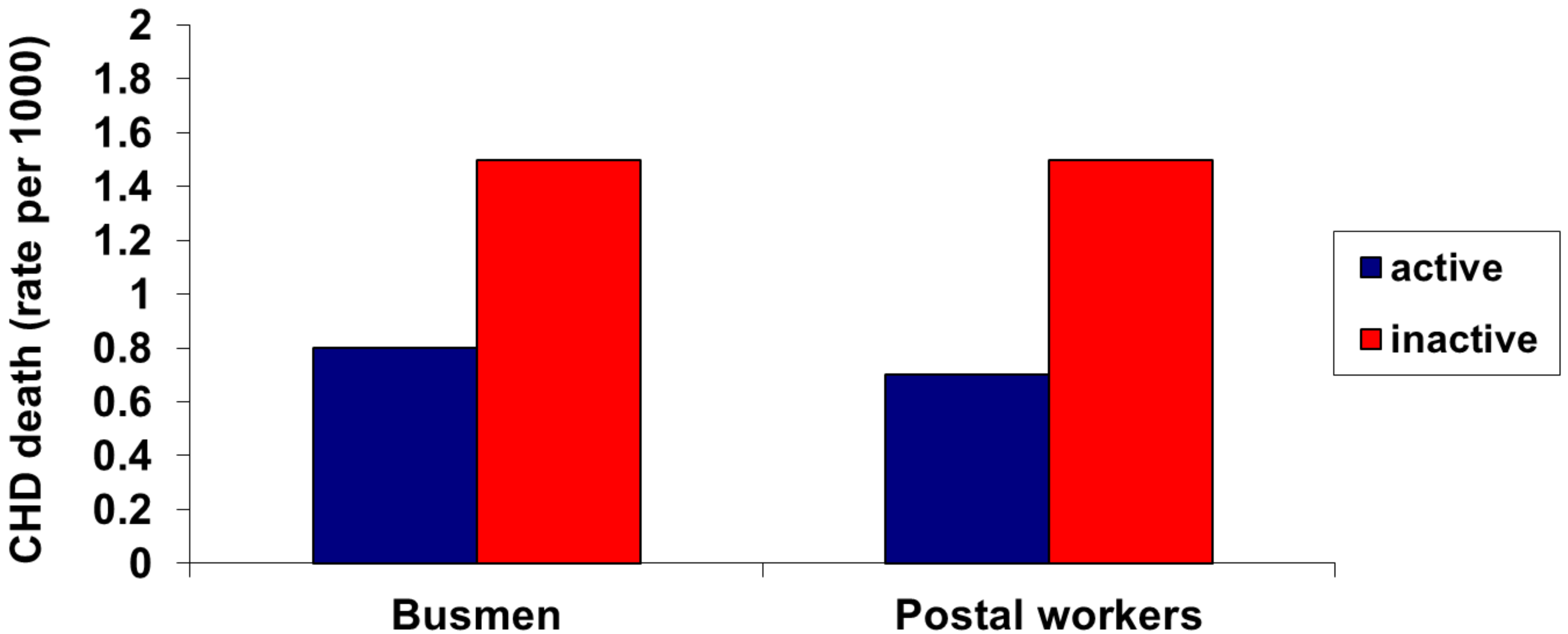
Conflicts/Disclosures: None

Objectives

- To provide a brief overview of the recognised benefits of physical activity on cardiovascular health.
- To discuss the currently recommended dose of physical activity for all individuals.
- To question whether too much exercise may have a deleterious impact on an otherwise normal heart.

Physical activity and CVD: Early Work

The first study to show an association between physical activity and risk of heart disease.



Morris et al. (1953) Lancet

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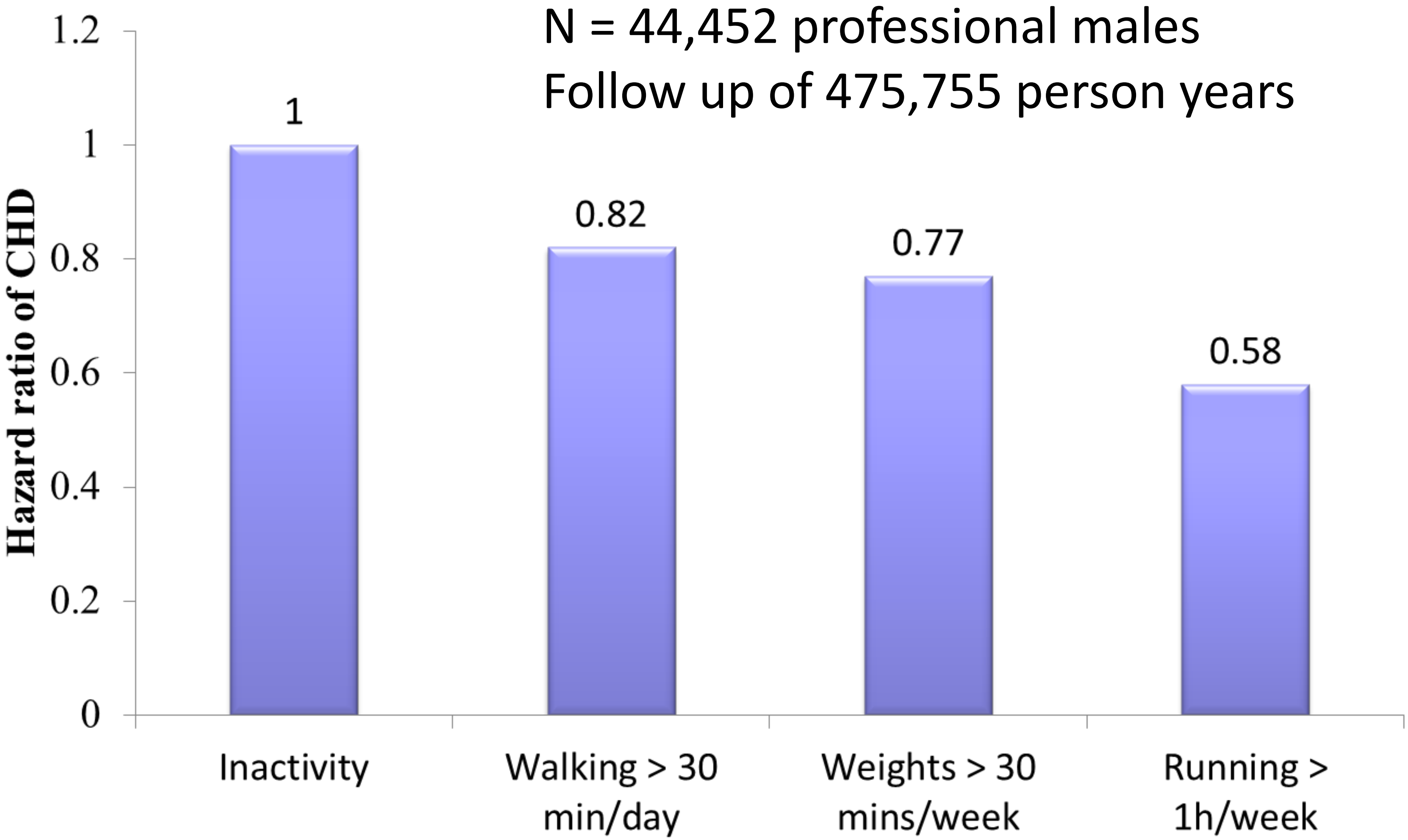
Centre for Sports Cardiology

Risk Hazard of CHD in Relation to Physical Activity



Tenesescue M et al JAMA 2002

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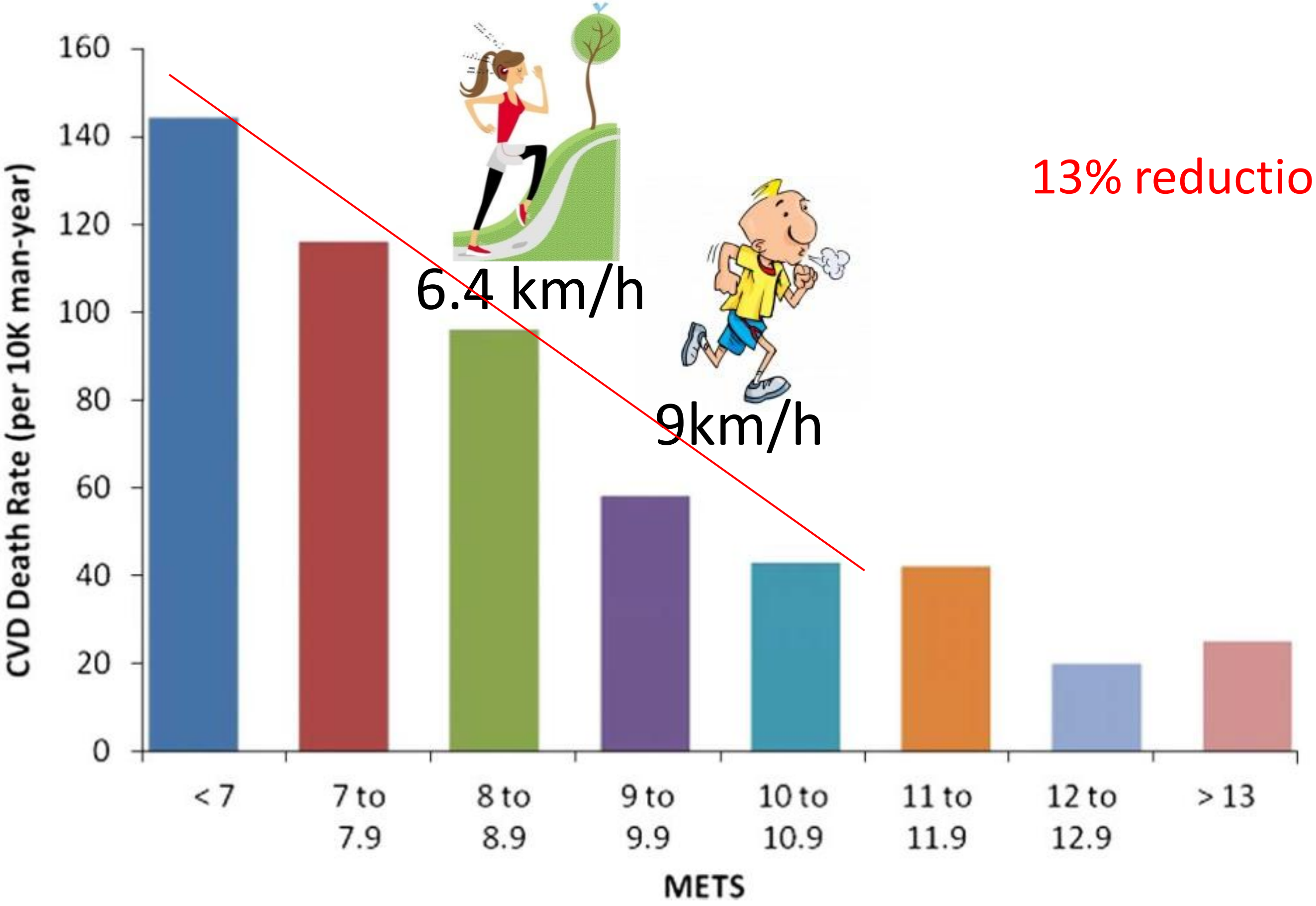
Death Rates as a Function of Cardiovascular Fitness



Church TS. Arch Int Med 2005

Kokkinos P et al Circulation 2008

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Leisure-Time Running Reduces All-Cause and Cardiovascular Mortality Risk

Duck-chul Lee, PhD,* Russell R. Pate, PhD,† Carl J. Lavie, MD,‡§ Xuemei Sui, MD, PhD,† Timothy S. Church, MD, PhD,§ Steven N. Blair, PED||

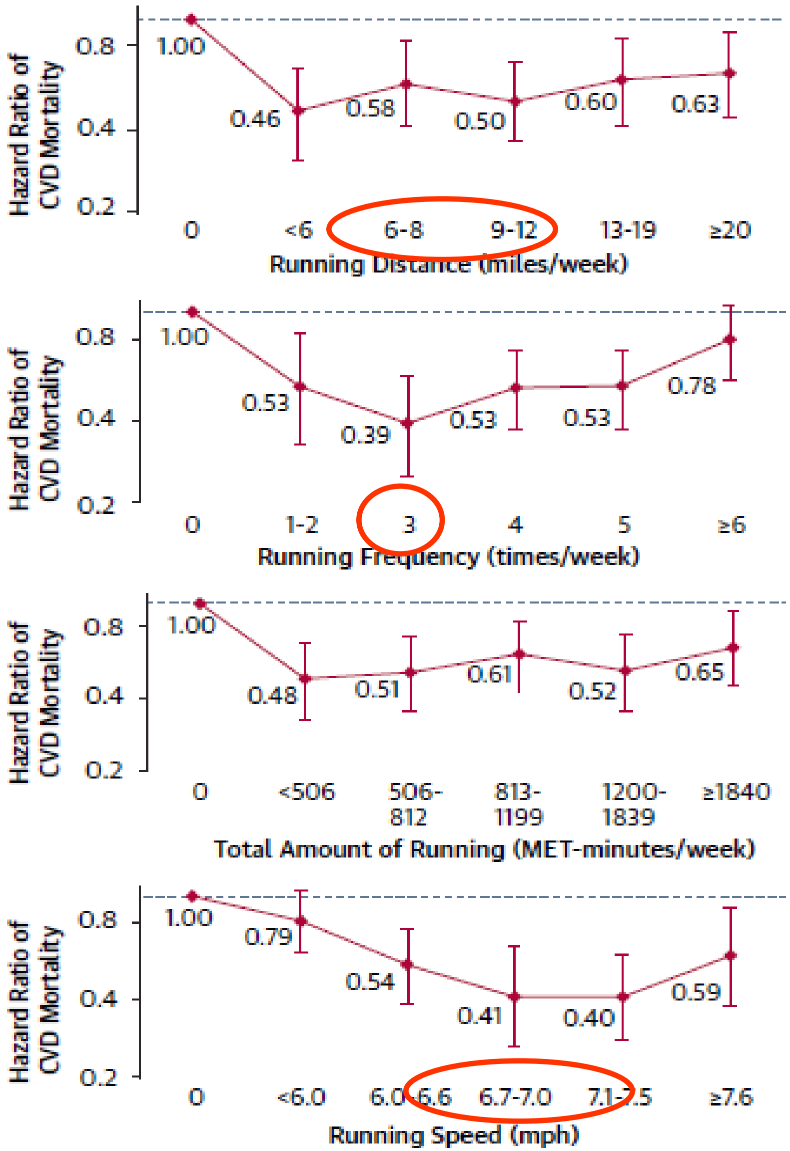
Duck Chul-Li et al. JACC 2014

15 year observational study.

55,137 individuals.

Mean age 44 years old.

Runners had a 30% all cause reduction in mortality and a 45% reduction in CVD events.



Dose of Jogging and Long-Term Mortality

The Copenhagen City Heart Study

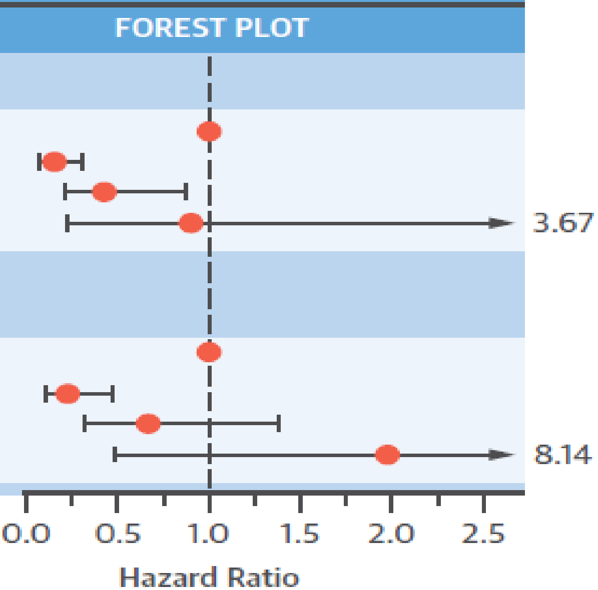
Schnohr et al. JACC 2015

Peter Schnohr, MD, DMSc,* James H. O'Keefe, MD,† Jacob L. Marott, MSc,* Peter Lange, MD, DMSc,*‡
Gorm B. Jensen, MD, DMSc*§

1098 joggers and 3,950 healthy non joggers.

Jogging 1-2.4 hours, over 2-3 times per week and a slow to moderate pace (6-10 MET equivalents) was associated with the best results for reduction in all cause mortality.

DOSE OF JOGGING	NO. OF PARTICIPANTS	ALL-CAUSE MORTALITY DEATHS
Adjusted for age and sex		
Sedentary nonjogger (reference)	413	128
Light jogger	576	7
Moderate jogger	262	8
Strenuous jogger	40	2
Adjusted for age, sex, smoking, alcohol intake, education, and diabetes		
Sedentary nonjogger (reference)	394	120
Light jogger	570	7
Moderate jogger	252	8
Strenuous jogger	36	2



Current Physical Activity Guidelines

- **Adults:**

  30 mins of moderate intensity physical activity at least days per week

  or 25 min vigorous activity 3 days per week

- **Children:** at least 60 minutes per day of moderate intensity physical activity.

(Chief Medical Officers Report 2004)

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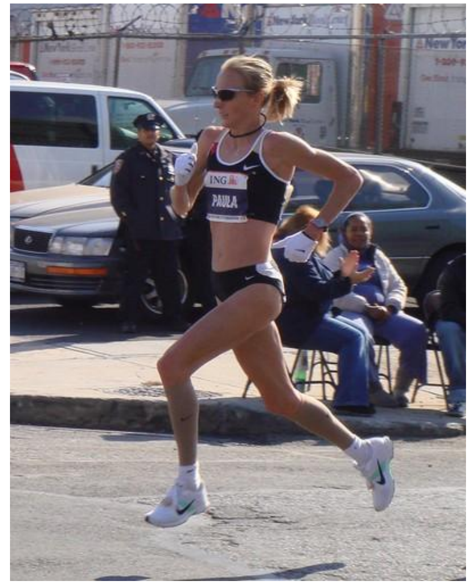
Endurance Athletes



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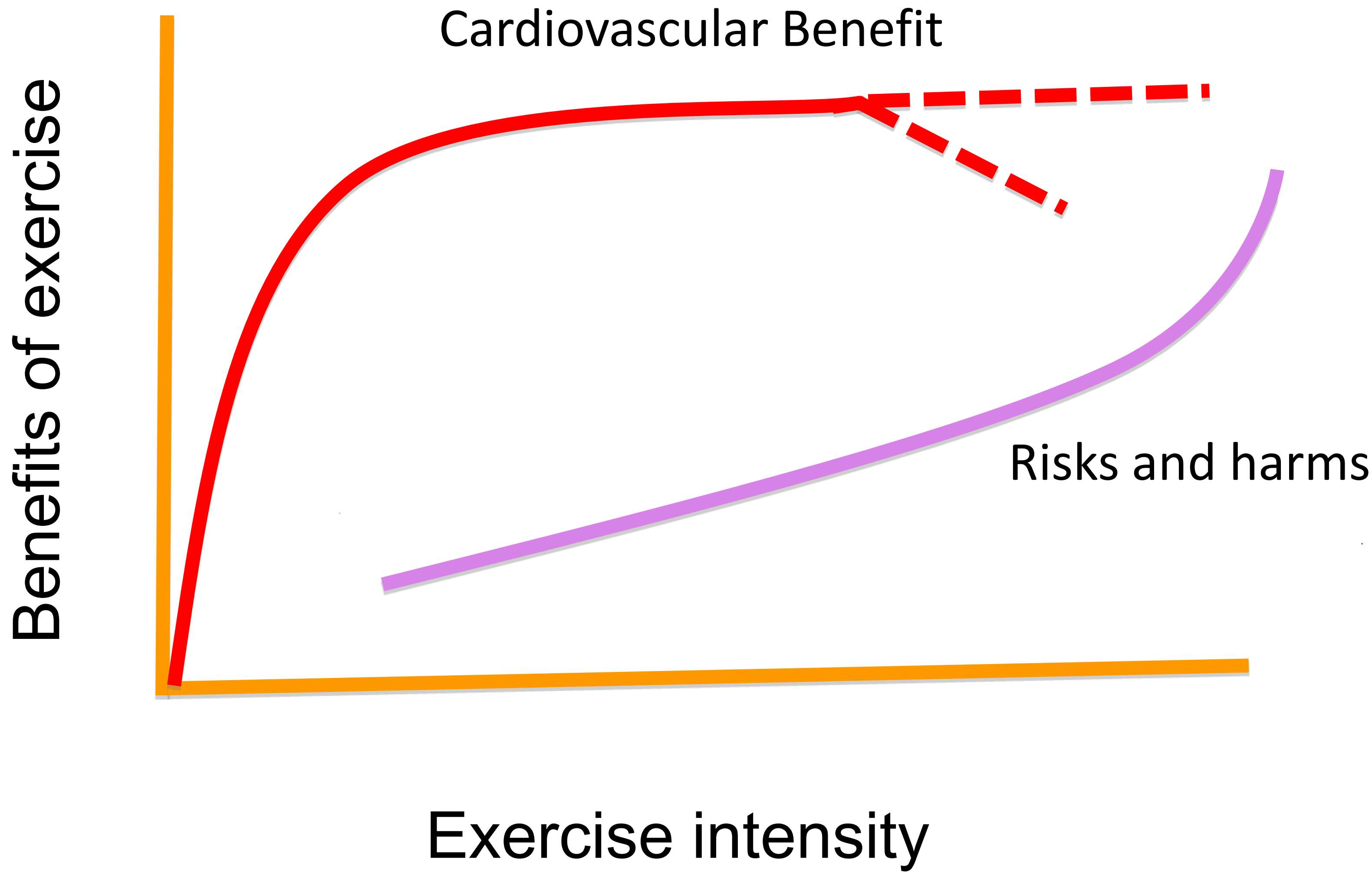
Dose-Benefit Relationship



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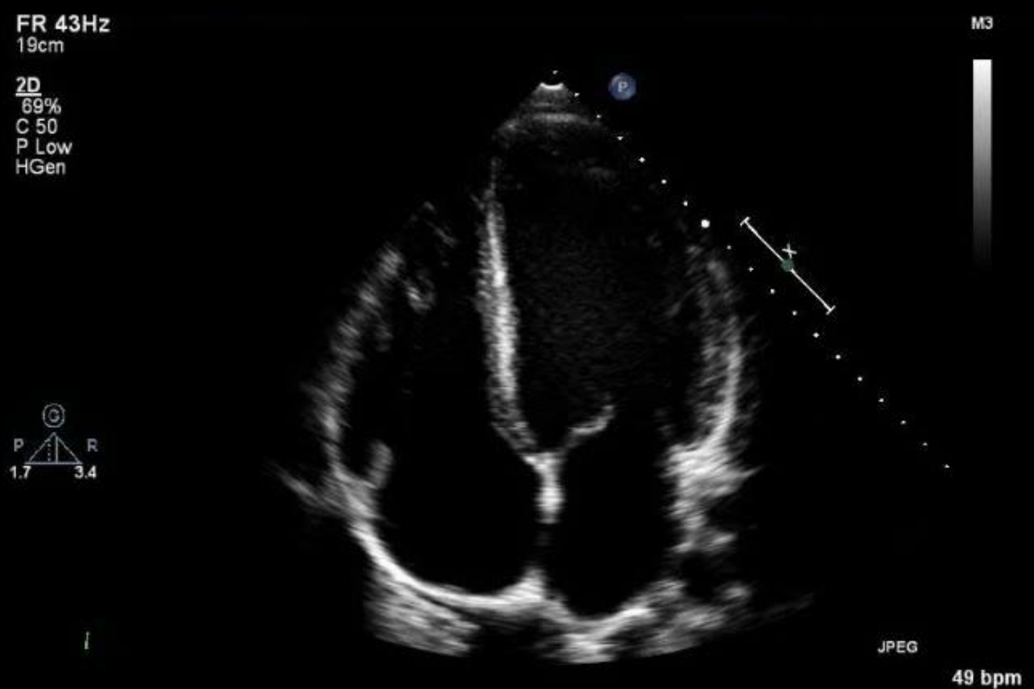
The Young Athlete's Heart



10% increase in LV and RV cavity.

10-20% increase in left ventricular wall thickness

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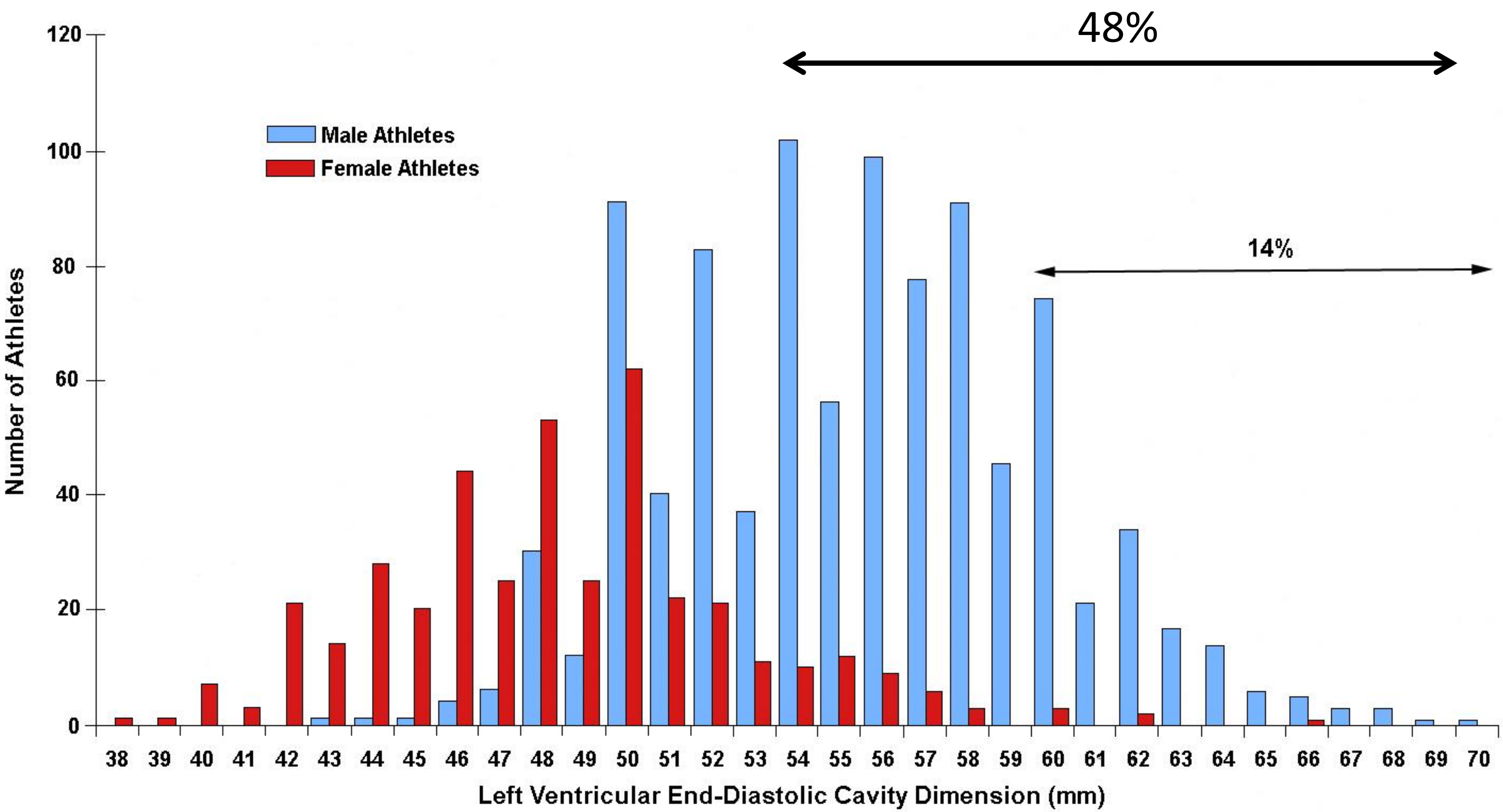
Left Ventricular Cavity Dimensions in Highly Trained Athletes



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Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION
American Heart Association. Learn and Live

Remodeling of Left Ventricular Hypertrophy in Elite Athletes After Long-Term Deconditioning

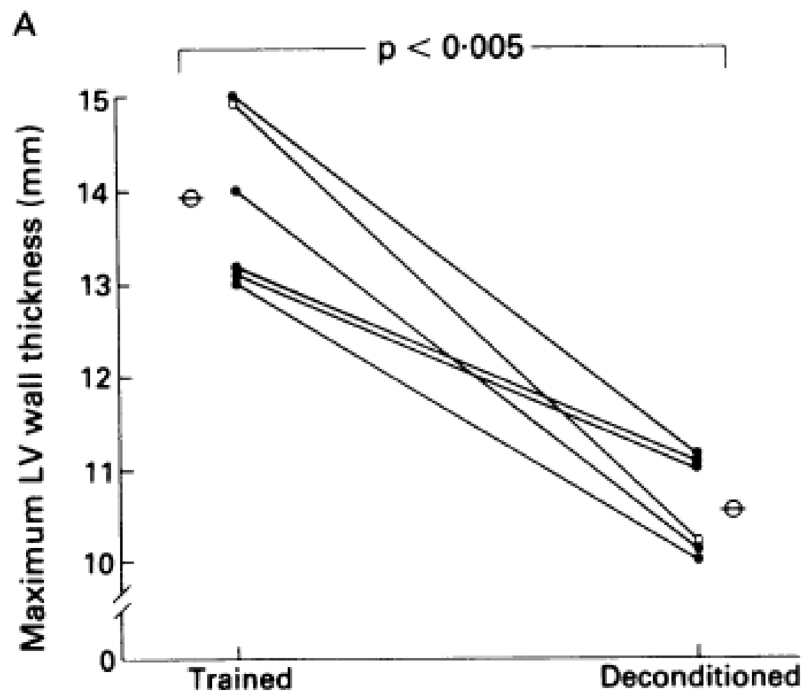
Antonio Pelliccia, Barry J. Maron, Rosanna De Luca, Fernando M. Di Paolo, Antonio Spataro and Franco Culasso

Circulation 2002;105;944-949; originally published online Feb 4, 2002;
DOI: 10.1161/hc0802.104534

44 Italian Olympian males with LVH (> 13 mm) and enlarged LV cavity (> 60 mm).

De-trained for a mean of 53 months.

LV wall thickness and LV mass normalised.



The Ugly Side of Exercise: Sudden Cardiac Death

90% during or just after exercise

90% in males

80% don’t have prodromal symptoms

40% in age < 18 years old

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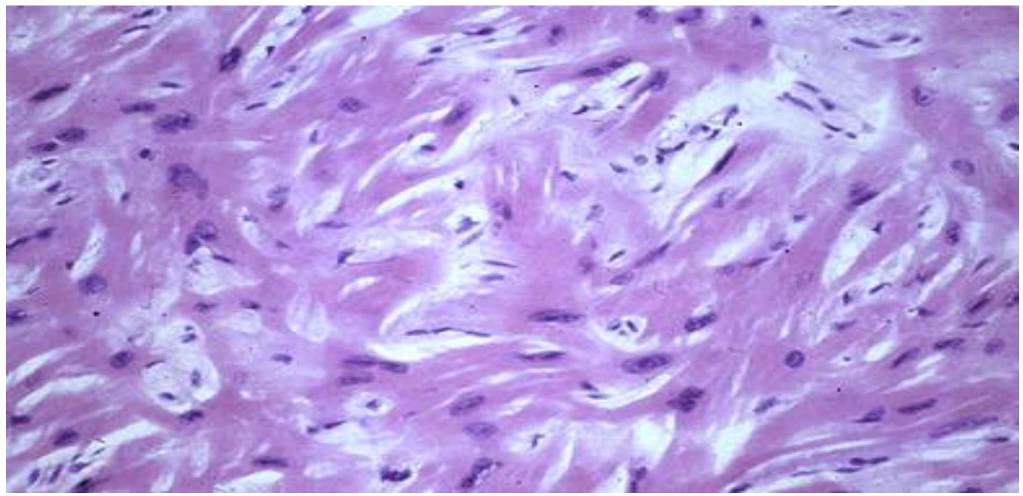
Triggers for Sudden Cardiac Death

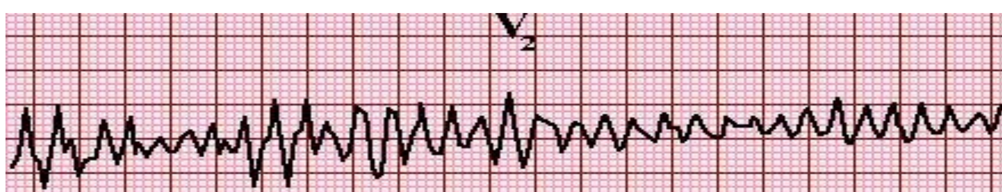
Dehydration

Adrenergic surges



Electrolyte imbalance

Acid/base disturbance



Can Exercise Induce Cardiomyopathy in a Normal Heart?

Endurance athletes exercise 10-15 x the daily recommended exercise.

2 million marathon participants each year.

Can you get too much of a good thing?

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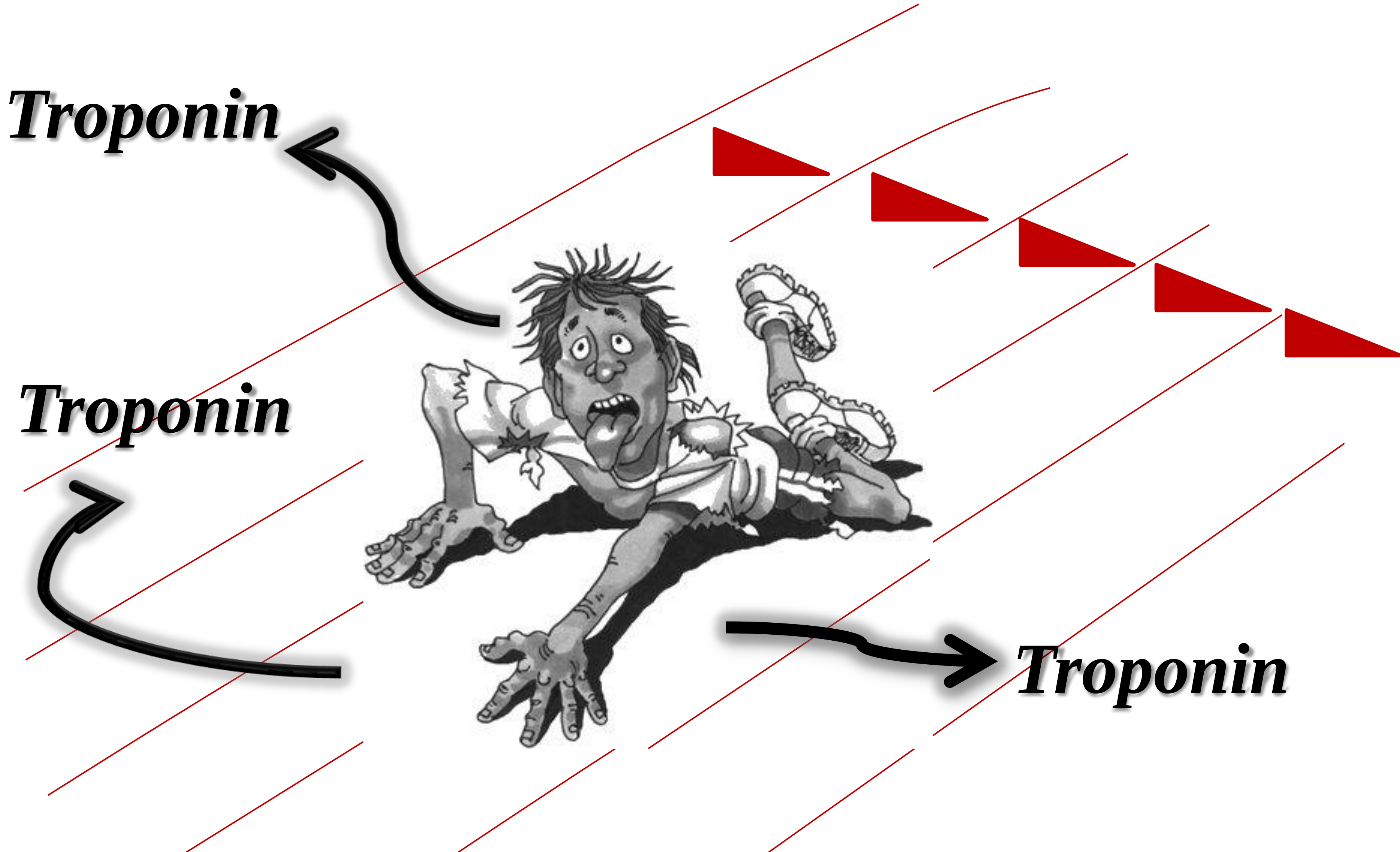
Evidence of Transient Cardiac Injury Post Marathon Running

- Raised cardiac troponin levels post race (EXERCISE INDUCED CARDIAC DAMAGE)

- Impaired left ventricular function
  (EXERCISE INDUCED CARDIAC FATIGUE)

Could Too Much Exercise Be Cardiotoxic?



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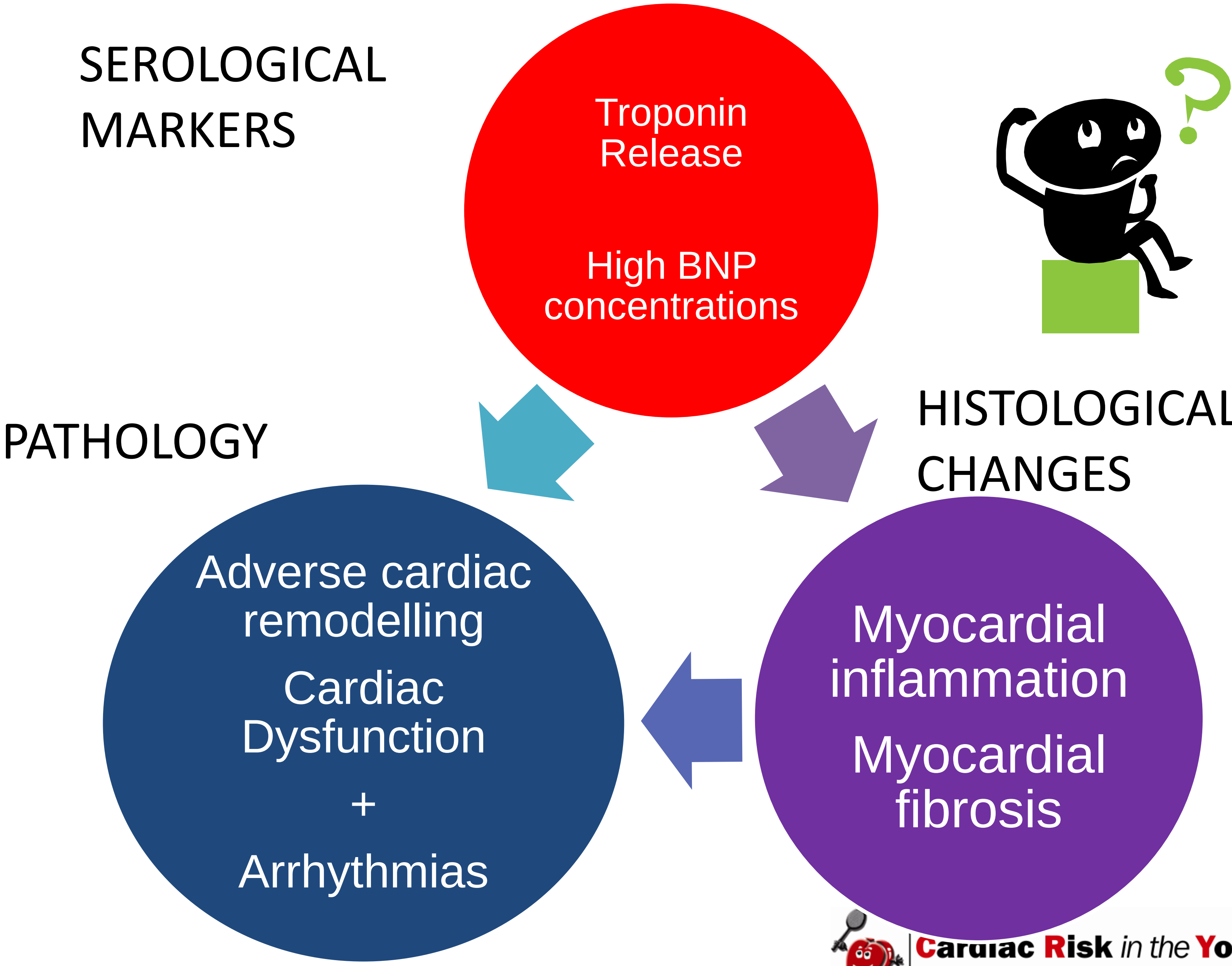

SEROLOGICAL MARKERS
Troponin Release
High BNP concentrations
HISTOLOGICAL CHANGES
Myocardial inflammation
Myocardial fibrosis
PATHOLOGY
Adverse cardiac remodelling
Cardiac Dysfunction
+
Arrhythmias

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association

Cardiac Arrhythmogenic Remodeling in a Rat Model of Long-Term Intensive Exercise Training

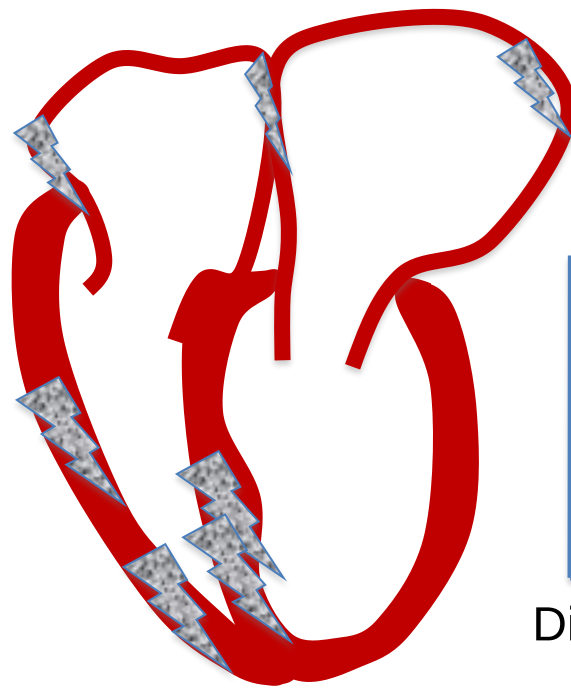
Begoña Benito, Gemma Gay-Jordi, Anna Serrano-Mollar, Eduard Guasch, Yanfen Shi, Jean-Claude Tardif, Josep Brugada, Stanley Nattel and Lluis Mont

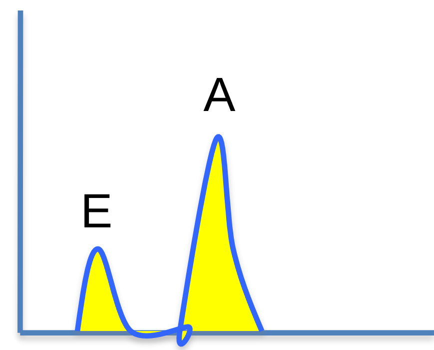
Circulation. 2011;123:13-22; originally published online December 20, 2010;
doi: 10.1161/CIRCULATIONAHA.110.938282
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

Animal model of Endurance Training

Enlarged Atria and RVH/LVH
Fibrosis

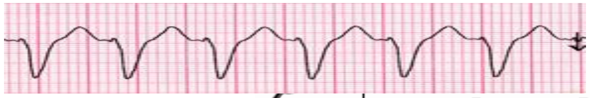




Diastolic dysfunction

Exercised for 60mins daily for 16 weeks

Compared with sedentary rats



VT in 42 %

Myocardial Late Gadolinium Enhancement: Prevalence, Pattern, and Prognostic Relevance in Marathon Runners[1]

Breuckmann. Radiology 2009

102 healthy males aged 50-72 years old.

Completed at least 5 marathons in the past 3 years.

12 had late gadolinuim enhancement which was 3-fold commoner than in age-matched controls.

5 had LGE with a coronary artery disease pattern.

7 had non specific patchy fibrosis.

Atrial Fibrillation in Athletes

Is the risk
than in
revie

Atrial fibrillation in at
literature-based conn
overtraining and subs
be a contributory mechanism

European Heart Journal (2002) 23, 477–482
doi:10.1053/euhj.2001.2802, available online at http://www.idealibrary.com on IDEAL

Long-lasting sport practice and lone atrial fibrillation

L. Mont[1], A. Sambola[1], J. Brugada[1], M. Vacca[1], J. Marrugat[2], R. Elosua[2], C. Paré[1], M. Azqueta[1] and G. Sanz[1]

[1]Institute of Cardiovascular Diseases, Hospital Clínic, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Villarroel 170, Barcelona 08036, Spain; [2]Lipids and Cardiovascular Epidemiology Research Unit, Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain

BJSM

Atrial fibrillation in endurance-trained athletes

A V Sorokin, C G S Araujo, S Zweibel, et al.

Br J Sports Med published online July 13, 2009
doi: 10.1136/bjsm.2009.057885

tes

Atrial Fibrillation in Sportsmen

Table I Summary of the published studies analyzing the relationship between atrial fibrillation and atrial flutter and endurance sport practice.

Studies	Type of study	Men (%)	Age	Type of sport(s)	Cases/ controls	Odds ratio (CI) for AF in athletes
Karjalainen *et al.*[5]	Longitudinal case/control	100	47 ± 5 runners, 49 ± 5 controls	Orienteers	262/373	5.5 (1.3–24.4)
Mont *et al.*[6]	Retrospective compared to general population	100	44 ± 13 athletes, 49 ± 11 non-athletes	Endurance sports >3 h per week	70 lone AF	61% in male athletes with lone AF
Elosua *et al.*[7]	Retrospective case/control	100	41 ± 13 AF pat, 44 ± 11 controls	Endurance sports: current practice and >1500 accumulated hours of practice	51/109	2.87 (1.39–7.05) adjusted for age and hypertension
Heidbuchel *et al.*[8]	Case/control in patients undergoing flutter ablation	83	53 ± 9 sports, 60 ± 10 controls	Cycling, running, or swimming >3 h per week	31/106	1.81 (1.10–2.98)
Molina *et al.*[9]	Longitudinal case/control	100	39 ± 9 runners, 50 ± 13 sedentary	Marathon runners	252/305	8.80 (1.26–61.29) adjusted for age and blood pressure
Baldesberger *et al.*[27]	Longitudinal case/control	100	67 ± 7 cyclist, 66 ± 6 golfers	Cyclists	134/62	10% AF in cyclists, 0% AF in controls
Mont *et al.*[10], GIRAFA study	Prospective case/control	69	48 ± 11	Endurance sports	107/107	7.31 (2.33–22.9), >550 h of accumulated heavy physical activity

Incidence

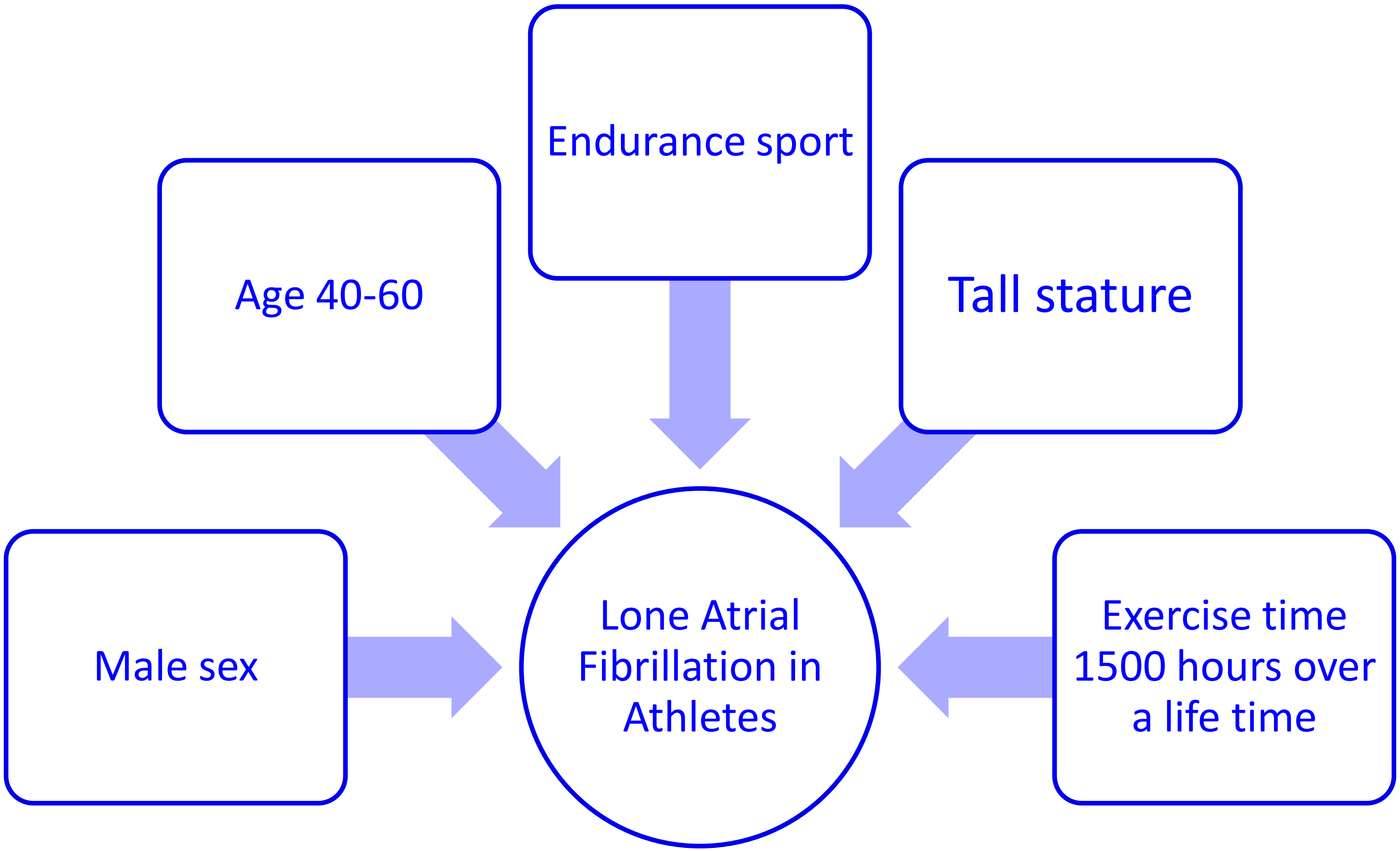
5-10% of middle aged endurance athletes

Risk of lone AF over 5-fold greater than in matched sedentary individuals.

Usually sportsmen who have been exercising since youth.

Almost all male.

Risk factors for Atrial Fibrillation in Athletes



AF in Athletes

Trigger

?Increased pulmonary vein ectopy

Modulators

Increased vagal tone:
Bradycardia
Shortening and dispersion of the atrial refractory period

Gastro-oesophageal reflux

Substrate

Pressure and volume overload:
Atrial stretch
Myocyte Hypertrophy
Atrial dilatation
Inflammatory response
Atrial fibrosis

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EUROPEAN SOCIETY OF CARDIOLOGY
European Heart Journal
doi:10.1093/eurheartj/ehm555

CLINICAL RESEARCH

Sinus node disease and arrhythmias in the long-term follow-up of former professional cyclists

Sylvette Baldesberger[1], Urs Bauersfeld[2], Reto Candinas[1], Burkhardt Seifert[3], Michel Zuber[4], Manfred Ritter[5], Rolf Jenni[6], Erwin Oechslin[6], Pia Luthi[1], Christop Scharf[1], Bernhard Marti[7], and Christine H. Attenhofer Jost[1]*

	Former professional cyclists (n=62)	Golfers (n=62)
Mean age	66 ± 6 yrs	66 ± 7 yrs
QRS	102 ± 20 msec	99 ± 13 msec
HR	66 ± 9 bpm	70 ± 8 bpm
SND	10%	2%
Pacemaker	3%	0%
Pauses > 2.5 s	6%	0%
Atrial flutter	6%	0%
NSVT	15%	3%

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Centre for Sports Cardiology

European Heart Journal
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CLINICAL RESEARCH

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European Heart Journal
doi:10.1093/eurheartj/eht188

CLINICAL RESEARCH

Risk of arrhythmias in 52 755 long-distance cross-country skiers: a cohort study

Kasper Andersen[1*], Bahman Farahmand[2,3], Anders Ahlbom[2], Claes Held[1], Sverker Ljunghall[1], Karl Michaëlsson[4], and Johan Sundström[1]

Studied participants in the Vasalopett (90k) cross country ski race between 1989-1998. 90% Male.

Followed by until December 2005.

959 had significant arrhythmias (AF, A flutter and bradyarrhythmias) which correlated with the number of races completed and faster finishing times; HR 1.30 each.

High prevalence of right ventricular involvement in endurance athletes with ventricular arrhythmias

Role of an electrophysiologic study in risk stratification

Hein Heidbüchel[a]*, Jan Hoogsteen[b,d], Robert Fagard[a], L. Vanhees[a], Hugo Ector[a], Rik Willems[a], Johan Van Lierde[c,d]

46 endurance athletes

Symptoms n = 36

Syncope 65%
Aborted SCD 2%
Palpitation 15%

Complex ventricular arrhythmias

Very abnormal ECG in 58%

VT or RV origin in 49%
Criteria for ARVC in 59%

9 died suddenly and 9 got ICD

European Heart Journal (2007) 28, 345–353
doi:10.1093/eurheartj/ehl468

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Clinical research
Arrhythmia/electrophysiology

Reduced right ventricular ejection fraction in endurance athletes presenting with ventricular arrhythmias: a quantitative angiographic assessment

Joris Ector, Javier Ganame, Nico van der Merwe, Bert Adriaenssens, Laurent Pison, Rik Willems, Marc Gewillig, and Hein Heidbüchel*

22 symptomatic athletes; cyclists (77%)

Arrhythmias of right ventricular origin

Right ventriculography revealed enlarged right ventricles with reduce ejection fraction

Possible explanations:

1. Increased RV work load may unmask heterozygotes for ARVC
2. Exercise causes adverse remodelling of the RV and increases risk of arrhythmias

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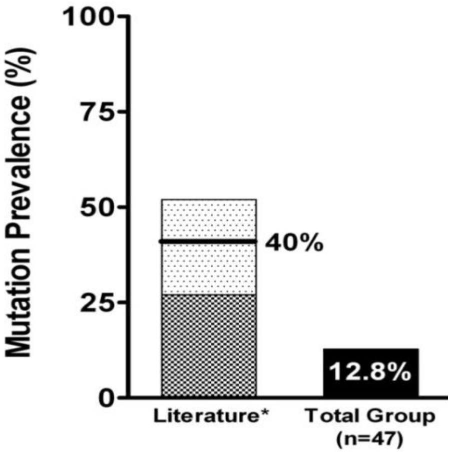
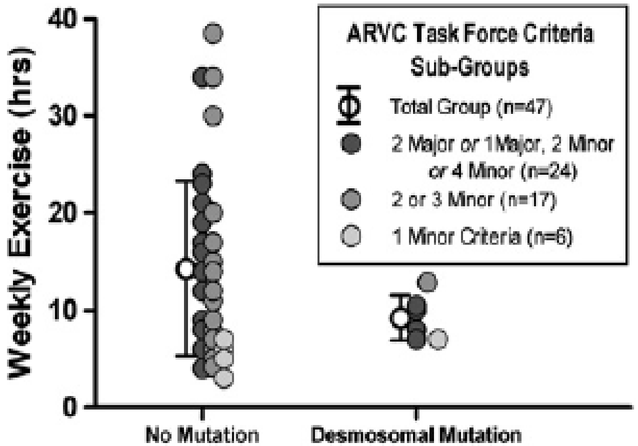
Lower than expected desmosomal gene mutation prevalence in endurance athletes with complex ventricular arrhythmias of right ventricular origin

A La Gerche, C Robberecht, C Kuiperi, et al.

Heart 2010 96: 1268-1274 originally published online June 4, 2010
doi: 10.1136/hrt.2009.189621

n = 47
51% 'Definite ARVC' by TFC
36% 'Suspected ARVC' by TFC





An ARVC-like phenotype may be acquired through intense exercise

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Exercise-induced right ventricular dysfunction and structural remodelling in endurance athletes

André La Gerche[1,2]*, Andrew T. Burns[3], Don J. Mooney[3], Warrick J. Inder[1], Andrew J. Taylor[4], Jan Bogaert[5], Andrew I. MacIsaac[3], Hein Heidbüchel[2], and David L. Prior[1,3]

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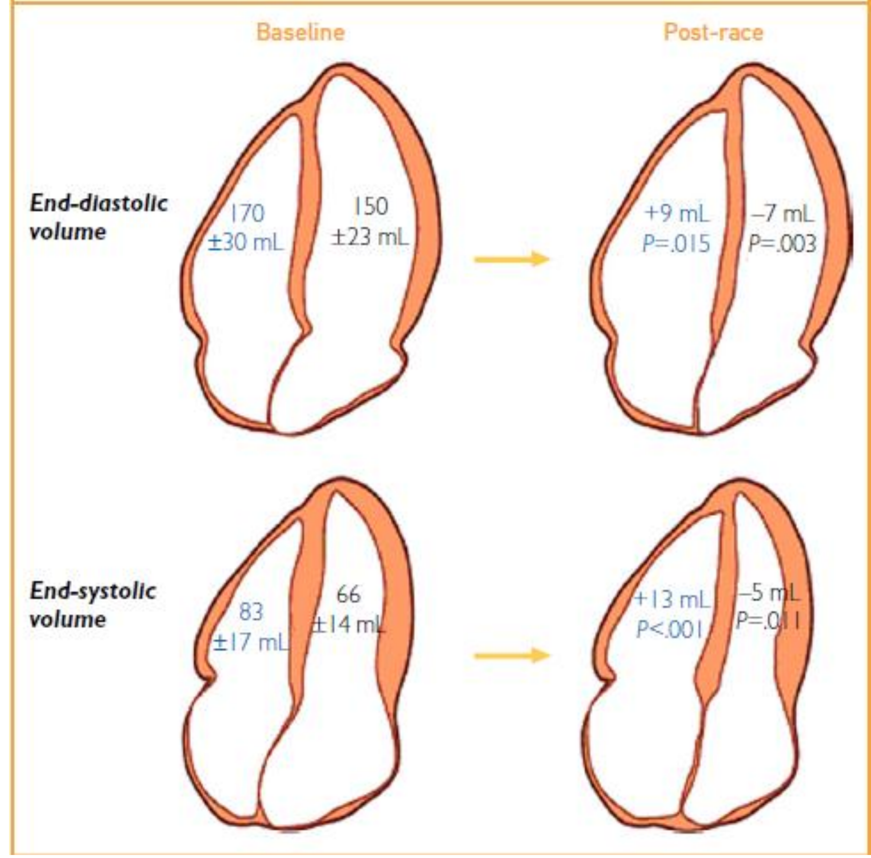
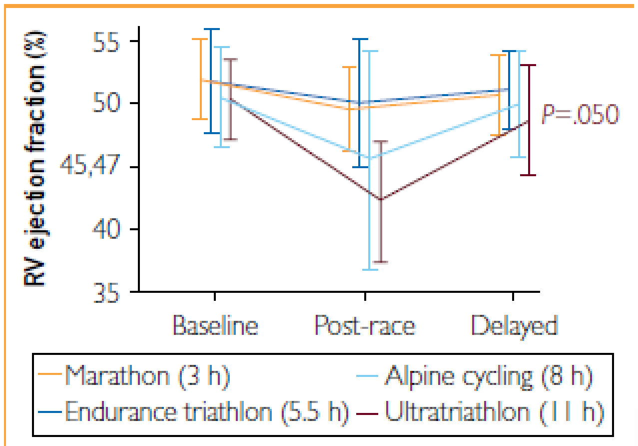


40 healthy endurance athletes

Assessed immediately before, after and 7 days after an ultra-endurance race.

Troponin levels correlated with magnitude of RV dysfunction



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Right Ventricular Exercise Physiology

REST	**Left Ventricle**	**Right**
Cardiac output (l/min)	5	5
Vascular resistance (dyne/sec/cm3)	1100	70
Load pressure (mm Hg)	130/75 (85)	25/9(15)
EXERCISE		
Cardiac output (l/min)	25	25
Vascular resistance (dyne/sec/cm3)	↓↓↓	↓
Load pressure (mm Hg)	↑	↑↑↑

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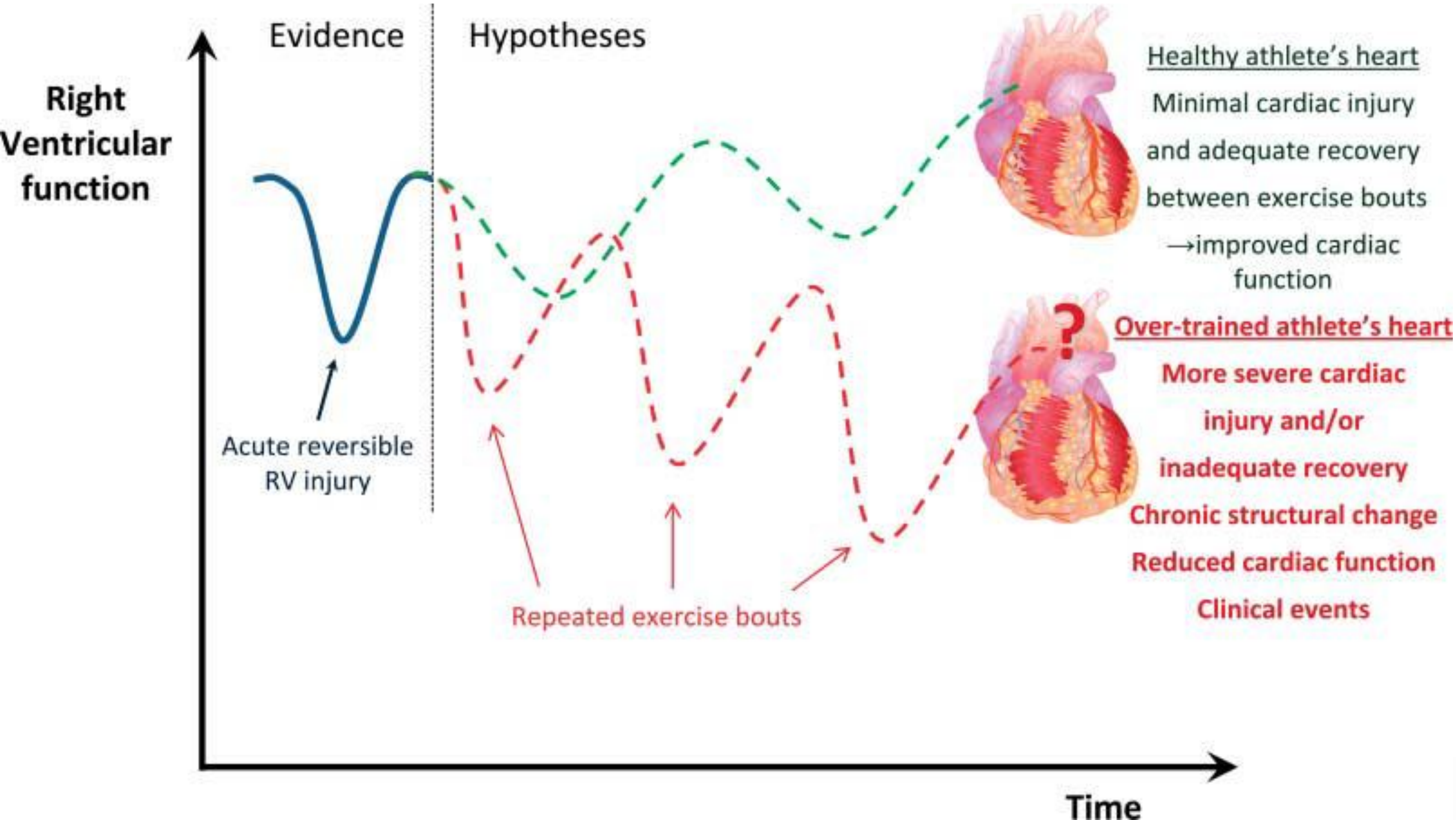
Exercise-induced arrhythmogenic right ventricular cardiomyopathy: fact or fallacy?

Sanjay Sharma* and Abbas Zaidi



European Heart Journal (2008) 29, 1903–1910
doi:10.1093/eurheartj/ehn163

CLINICAL RESEARCH
Sports cardiology

Running: the risk of coronary events†

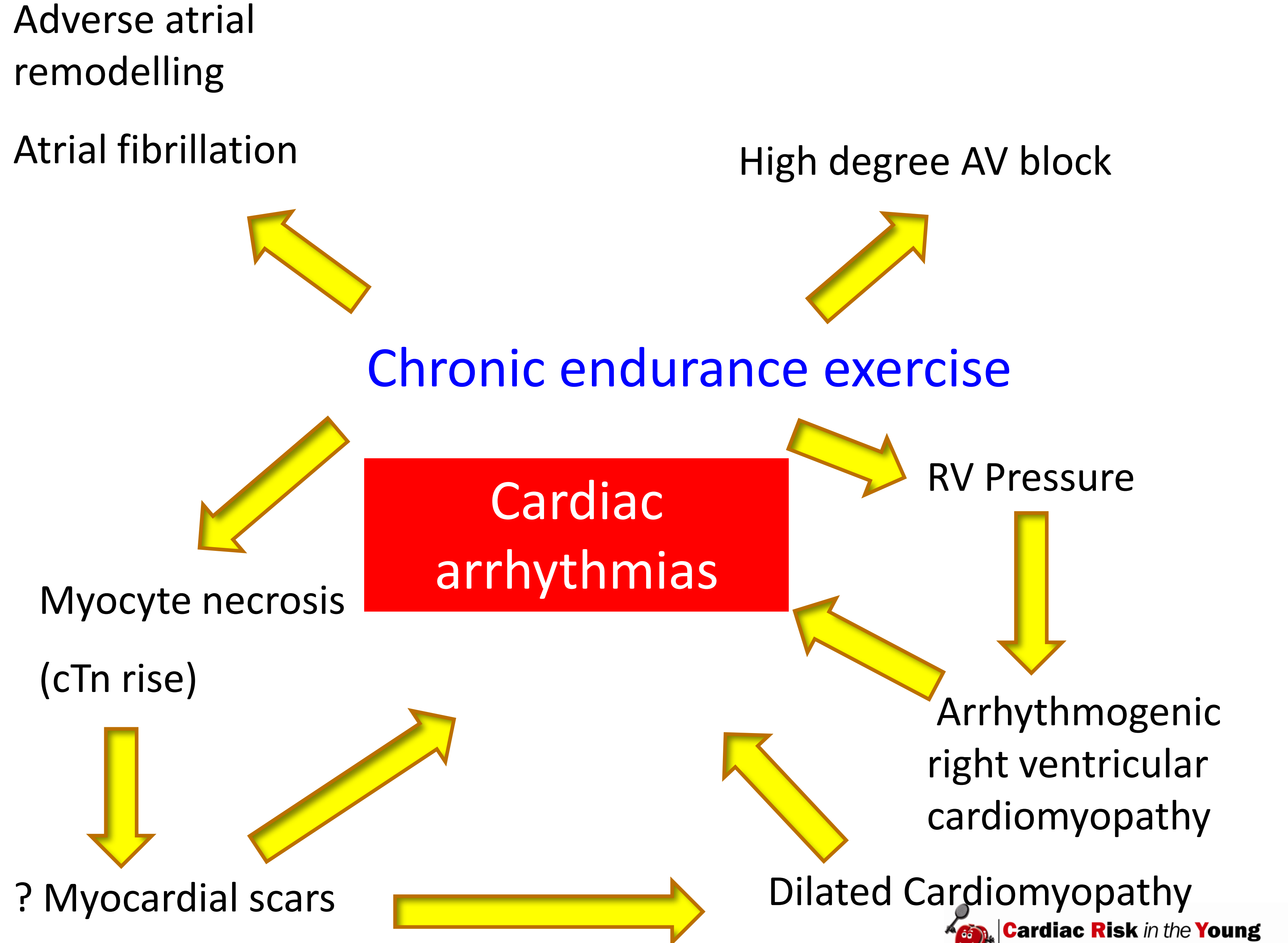
Prevalence and prognostic relevance of coronary atherosclerosis in marathon runners

108 Males aged 50-72 years old

High calcium scores and late gadolinium enhancement in presumably healthy middle aged marathon runners compared with Framingham risk matched controls

Marathon running associated with a 2-fold increase in LGE.

56% runners were current or former smokers



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Long-Term Clinical Consequences of Intense, Uninterrupted Endurance Training in Olympic Athletes

Antonio Pelliccia, MD,* Norimitsu Kinoshita, MD,† Cataldo Pisicchio, MD,* Filippo Quattrini, MD,* Fernando M. DiPaolo, MD,* Roberto Ciardo, MD,* Barbara Di Giacinto, MD,* Emanuele Guerra, MD,* Elvira De Blasiis, MD,* Maurizio Casasco, MD,* Franco Culasso, PhD,‡ Barry J. Maron, MD§

Rome, Italy; Yokohama, Japan; and Minneapolis, Minnesota

114 athletes (78% Male)
Mean age 22 ± 4
Continuous intensive physical training for at least 2 consecutive Olympics (2-5)
Mean training period 8.6 ± 3 years (4-17)

Rowers and canoeists (n=55), cyclists (n=19), cross-country skiing (n =15) long distance running/marathon (n=9), swimming (n=6) triathlon (n=2)

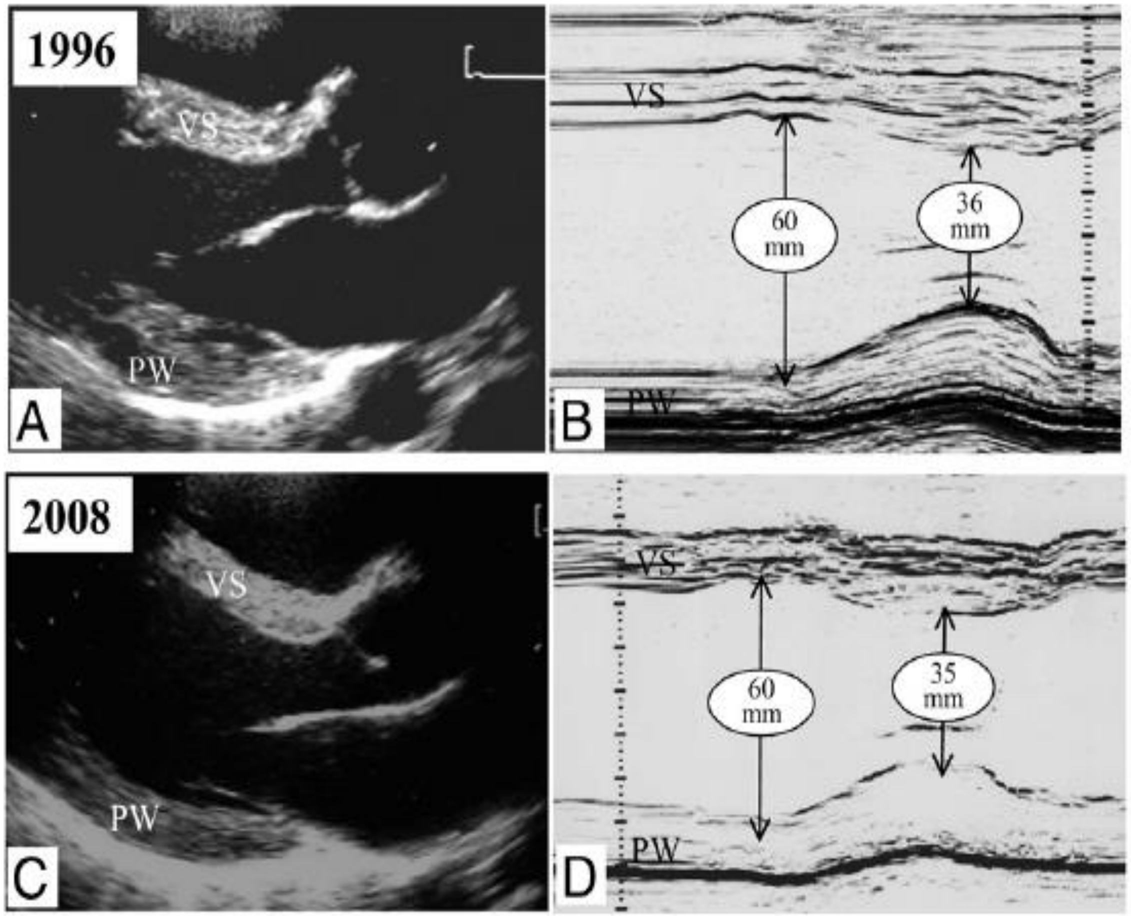

Figure 1 Serial Echocardiographic Views of the LV in an Elite Italian Marathon Runner

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Impact of Lifelong Exercise "Dose" on Left Ventricular Compliance and Distensibility

Paul S. Bhella, MD,*† Jeffrey L. Hastings, MD,* Naoki Fujimoto, MD,* Shigeki Shibata, MD, PhD,* Graeme Carrick-Ranson, PhD,* M. Dean Palmer, MS,* Kara N. Boyd, MS,* Beverley Adams-Huet, MS,‡ Benjamin D. Levine, MD*‡

Aging is associated with decreased left ventricular compliance and distensibility.

4-5 sessions of intensive exercise for 30 minutes per week over 25 years prevented such age related changes.

Lower doses of exercise did not retard this normal aging process.

Masters athletes exhibited the most compliant ventricles.

and may reduce the risk of hypertension and heart failure with preserved ejection fraction

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Centre for Sports Cardiology

Dose of Jogging and Long-Term Mortality

The Copenhagen City Heart Study

Schnohr et al. JACC 2015

Peter Schnohr, MD, DMSc,* James H. O'Keefe, MD,† Jacob L. Marott, MSc,* Peter Lange, MD, DMSc,*‡
Gorm B. Jensen, MD, DMSc*§

DOSE OF JOGGING	NO. OF PARTICIPANTS	ALL-CAUSE MORTALITY DEATHS
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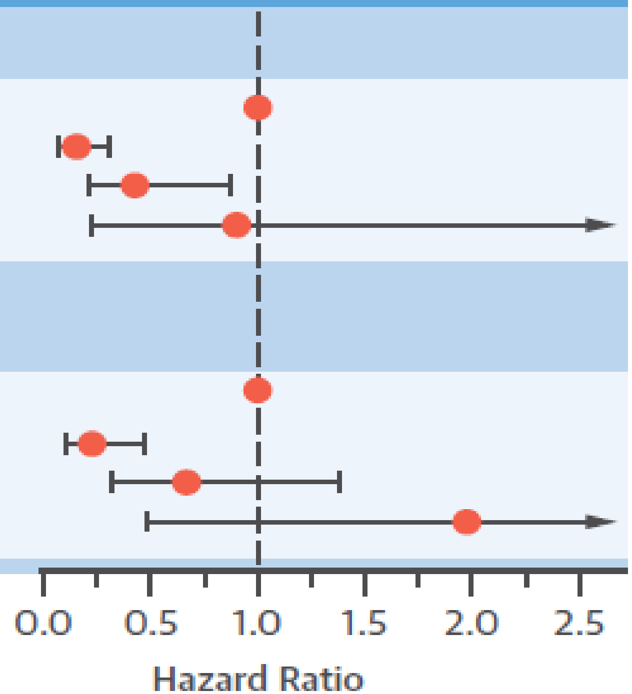

Elite Endurance Athletes Live Longer than Non Athletes

Strenuous endurance exercise improves life expectancy: it's in our genes

Jonatan R Ruiz,[1] Maria Morán,[2,3] Joaquín Arenas,[2–4] Alejandro Lucia[5]

European Heart Journal
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FASTTRACK CLINICAL RESEARCH

Mortality of French participants in the Tour de France (1947–2012)

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Review

Mortality and longevity of elite athlete

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Table 1 Summary of the main studies assessing the association between sports participation (usually at the university or elite competition level) and life expectancy

Reference	Former athletes (cases)*	Non-athletes (controls)	Main conclusion	Main results (in numbers)
Hartley and Llewellyn[4]	Oarsmen (n=767) who participated in between 1829 and 1928 in the Oxford–Cambridge boat race	Standard mortality tables for men	Higher longevity in cases	Total number of deaths in controls was 87.8%, 75.7%, 88.1% and 93.5% of expected during 1829–1862, 1863–1893, 1894–1923 and 1924–1928 periods respectively
Rook[5]	Cambridge University athletes (n=834, sprint and endurance runners, cricketers and rugby players)	'Intellectuals' (academically distinguished) and random controls, both from Cambridge (total n=761)	Similar longevity in cases and controls	Similar mean age at death in all groups (67–68 years); only intellectuals lived slightly (~1.5 years) longer
Dublin[7]	4976 athletes, most graduating between 1880 and 1905 in 10 leading US universities (baseball, crew, football, track, 2+ sports)		US men's 'table of mortality'	8.5% reduction in death rate compared with expected data for age-matched American male (based on data from insured men)
Montoye et al[8]	Michigan State University athletes (letter winners in varsity of sports) born between 1855 and 1919 (n=629)	Non-athletic University mates (n=583)	Similar longevity in cases and controls	Mean life expectancy of 65.36 years in athletes and 65.57 years in controls
Prout[9]	Harvard and Yale University oarsmen (n=172) matriculating during 1882–1902	Random classmates (n=172)	Cases lived longer	Cases lived 67.5 years on average, whereas controls lived 61.6 years
Ishiko[10]	Japanese University athletes (n=1655)	Tokyo university graduates (all medical doctors, n=3000) and average Japanese population	Cases lived longer than the two control groups	Numbers not provided, ~70% of cases alive at 68–72 years versus less than 50% in the two control groups (as estimated from figure)
Schnohr[1]	Danish athletic champions in 15 different sports (n=297, born between 1880 and 1910)	General Danish male population	Lower risk of death before 50 years of age in cases	~39% lower risk of death between 25 and 49 years of age in athletes, but thereafter similar death ratio than for the general population
Polednak[11]	Harvard athletes (lettermen, n=631) who attended Harvard college between 1880 and 1912 (baseball, football, crew, track, or combination of 2+ sports)	–	No differences in longevity between sports, but differences related to the extent of participation in sports (see next column)	Major university athletes (3+ letters) died slightly earlier and significantly more often from CAD (45.7%) than 'minor' or recreational athletes (1–2 letters, 40.2% and 38.1% respectively)
Beaglehole and Stewart[12]	New Zealand international rugby players (n=822; playing between 1884 and 1980)	New Zealand life tables for males	Similar life expectancy in cases and controls, but the non-Maori players lived longer	Non-Maori players had increased (~10 years) longevity
Waterbor et al[13]	US white baseball players (n=985; started playing between 1911 and 1915)	US white male population	Cases lived slightly longer than controls	All-cause SMR was reduced by 6% in cases
Karvonen et al[14]	396 Finnish champion endurance skiers born between 1845 and 1910	Finnish male population	Cases lived longer than controls	Cases has a median LE of 73.0 years (2.8–4.3 more years than Finnish males)
van Saase et al[15]	Non-professional Dutch male ice skaters (n=2259) able to finish ultra-endurance (200 km) races	Male Dutch population	Cases lived longer than controls	All-cause SMR was reduced by 24% (95% CI 32 to 15) in cases over a 33-year follow-up
Sarna et al[16]	Finnish elite athletes active during 1920–1965 (n=2613, including endurance sports, team games, track and field jumpers and sprinters and power athletes)	Age- and area-of-residence-matched men (n=1712)	Cases, especially endurance athletes, lived longer than controls	The mean LE was 75.6 years in endurance athletes, 73.9 years in team games and track and field sprinters, 71.5 years in power athletes and 69.9 years in controls
Kujala et al[17]	Subcohort of athletes (n=2009) within the above cohort[17]	Finnish general population	The 'protective' effect of elite exercise participation is sports-dependent (highest in sports requiring high $\dot{V}O_{2max}$)	All-cause SMR and CAD-SMR were much reduced in endurance athletes (−43% and −44%) but not so much in power athletes (−10% and −5%)
Chakravarty et al[18]	Northern California runners aged ≥50 years (n=538; men and women)	Demographically matched group of non-runners (n=423, 25–70 years)	Controls lived longer (and had less disability in late life)	Runners demonstrated a survival benefit over a 21-year follow-up (HR 0.61; 95% CI 0.45 to 0.82).

Except in the study by Chakravarty et al,[18] athletic and control cohorts did not include women.
*All subjects were former athletes, except in the study by Chakravarty et al.[18]
CAD, coronary artery disease; LE, life expectancy; SMR, standard mortality ratio; $\dot{V}O_{2max}$, maximal oxygen uptake.

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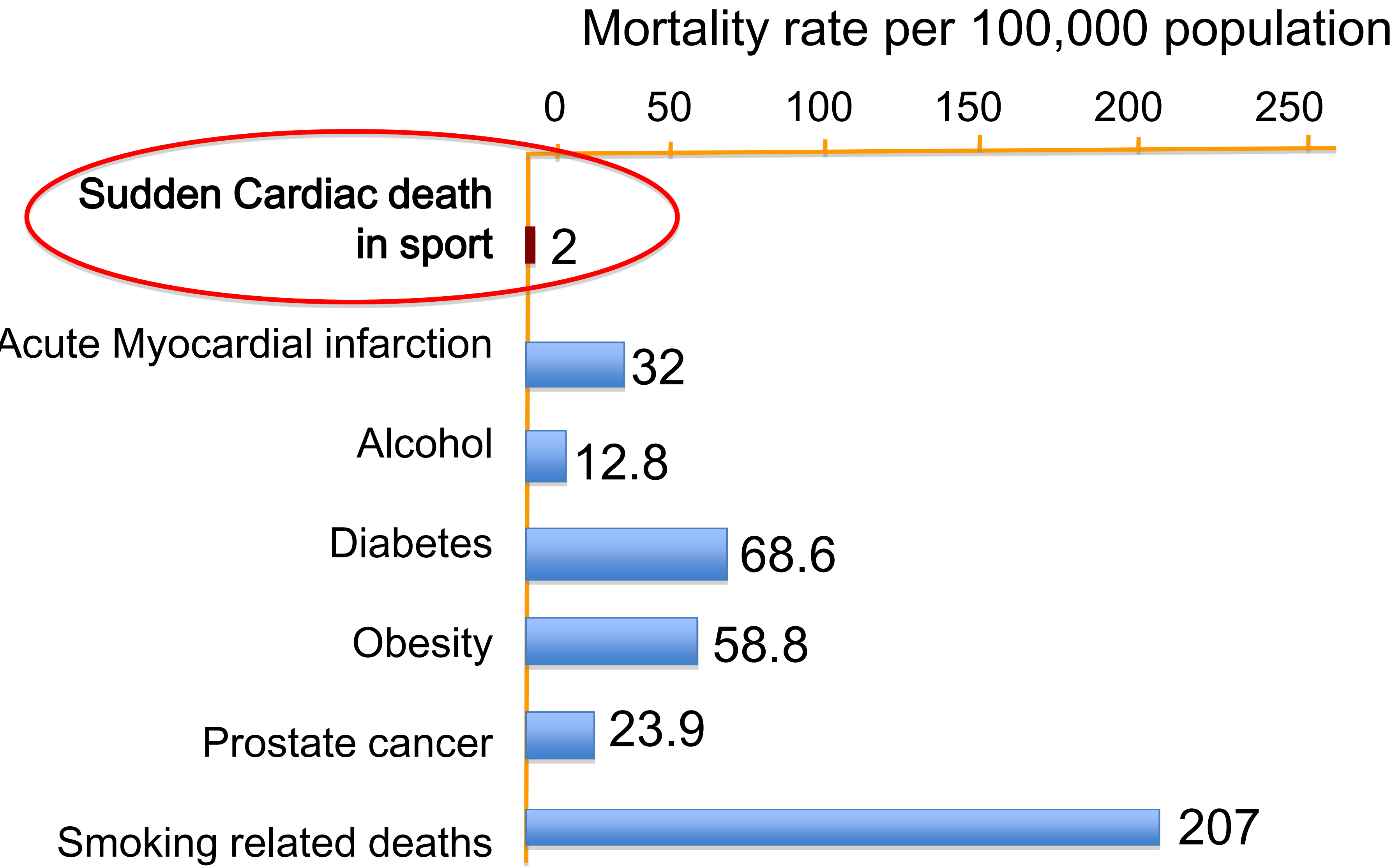

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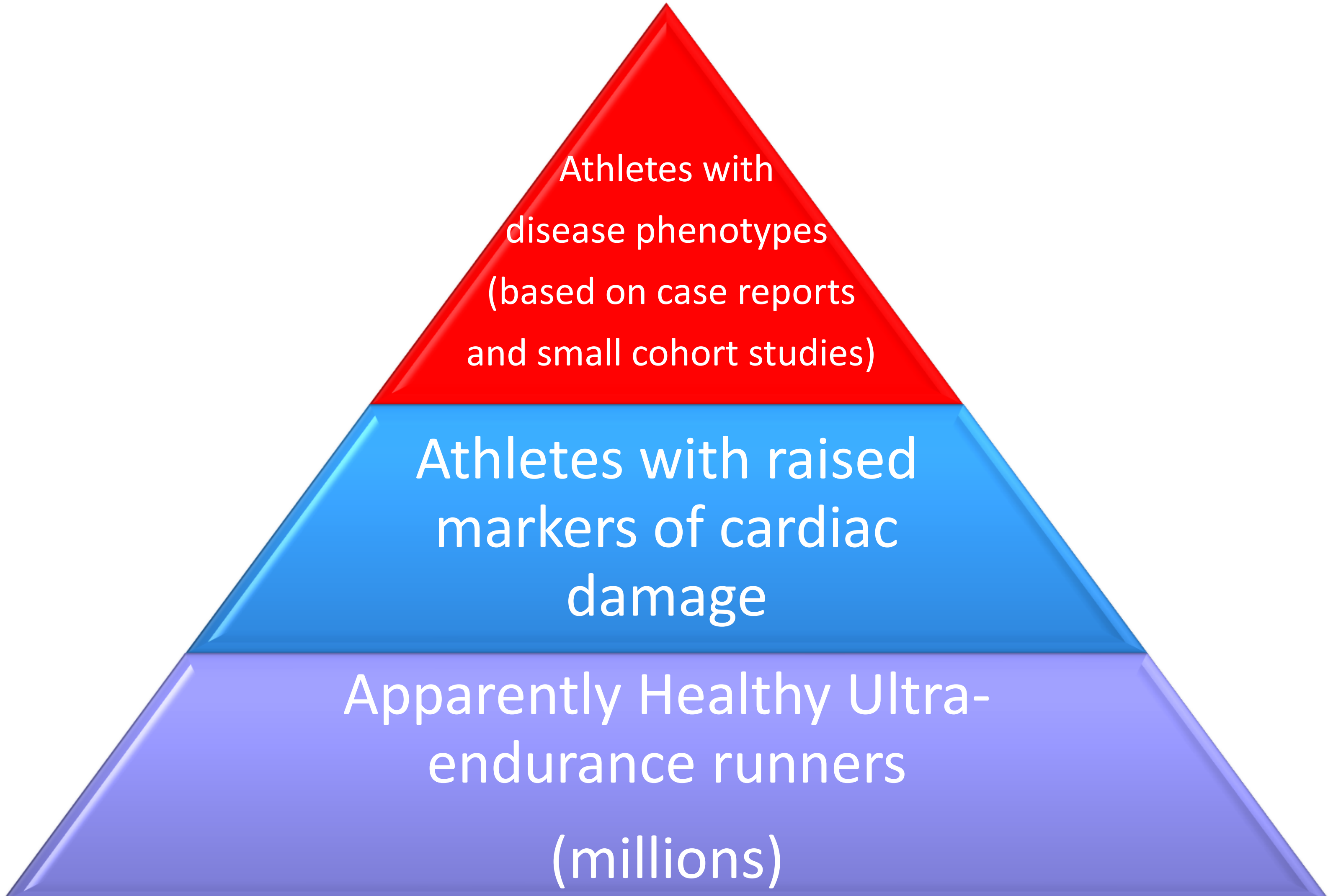
Marathon Runners
Died age 51 May he rest in peace

Numerator versus Denominator



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Prospective Studies

CARDIOTOXIC
?

Conclusions

Moderate exercise has cardiovascular benefits.

Long term endurance exercise promotes atrial fibrillation in some athletes.

Larger prospective studies are necessary to confirm or refute whether life long endurance exercise exerts a plethora of deleterious effects on an otherwise normal heart.

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