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Pre-Participation Screenings Frequently Miss Occult Cardiovascular Conditions in Apparently Healthy Male Middle-Aged First-Time Marathon Runners

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Cardiology · Adult · Marathon running · Exercise · Myocardial diseases · Sports medicine

Abstract

Introduction: The optimal pre-participation screening strategy to identify athletes at risk for exercise-induced cardiovascular events is unknown. We therefore aimed to compare the American College of Sports Medicine (ACSM) and European Society of Cardiology (ESC) pre-participation screening strategies against extensive cardiovascular evaluations in identifying high-risk individuals among 35–50-year-old apparently healthy men. ***Methods:*** We applied ACSM and ESC pre-participation screenings to 25 men participating in a study on first-time marathon running. We compared screening outcomes against medical history, physical examination, electrocardiography, blood tests, echocardiography, cardiopulmonary exercise testing, and magnetic resonance imaging. ***Results:*** ACSM screening classified all participants as "medical clearance not necessary." ESC screening classified two participants as "high-risk." Extensive cardiovascular evaluations revealed ≥1 minor abnormality and/or cardiovascular condition in 17 participants, including three subjects with mitral regurgitation and one with a small atrial septal defect. Eleven participants had dyslipidaemia, six had hypertension, and two had premature atherosclerosis. Ultimately, three (12%) subjects had a serious cardiovascular condition warranting sports restrictions: aortic aneurysm, hypertrophic cardiomyopathy (HCM), and

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myocardial fibrosis post-myocarditis. Of these three participants, only one had been identified as "high-risk" by the ESC screening (for dyslipidaemia, not HCM) and none by the ACSM screening. ***Conclusion:*** Numerous occult cardiovascular conditions are missed when applying current ACSM/ESC screening strategies to apparently healthy middle-aged men engaging in their first high-intensity endurance sports event.

Introduction

The cardiovascular health benefits of moderate-intensity exercise have been extensively documented [1]. However, detrimental cardiovascular effects of endurance exercise are increasingly being recognized [2]. In particular, popular events such as marathon running [3] have been associated with increased levels of circulating cardiac biomarkers and transient dysfunction of the right ventricle [4–6]. Furthermore, prolonged elevation of cardiac troponins following strenuous exercise has been shown to be associated with increased rates of fatal and non-fatal cardiovascular disease (CVD) events in a cohort of older long-distance walkers, suggesting that exercise-induced increases in circulating troponins may not be a benign physiological response, but an early marker of CVD [6].

The American College of Sports Medicine (ACSM) and the European Society of Cardiology (ESC) provide pre-participation screening strategies to assist physicians in identifying individuals at high risk of exercise-related events [7, 8]. However, there is no consensus on optimal pre-participation screening content, taking efficacy, burden, and costs into account [9]. Comprehensive cardiovascular evaluations detect more cardiovascular risk factors and disease, but the incremental yield of individual investigations (e.g., physical examination, resting electrocardiography (ECG), exercise testing, echocardiography, and blood tests) remains unclear [9–12].

We therefore pragmatically compared ACSM and ESC pre-participation screening outcomes against baseline findings from our 2021 Amsterdam Marathon study [13] comprising comprehensive cardiovascular evaluations and the consequent sports advice in a rigorously investigated cohort of middle-aged men participating in their first marathon. The current work reports findings from the baseline measurements of our study population and the clinical implications of our findings.

Methods

Our current analysis of pre-participation screening was conducted within the framework of a study that investigated the effects of first-time marathon running in men aged 35–50 years [13]. We recruited participants who responded to announcements made through the Amsterdam University Medical Centers' newsletter, local newspapers, social media, and the Marathon organiser's website. After confirming eligibility, an online screening subsequently took place wherein potential participants could reconfirm their interest, and were given general information about the study and inclusion and exclusion criteria [13] and what informed consent would entail. After giving informed consent, participants in the 2021 Amsterdam Marathon study underwent extensive testing at baseline, pre-marathon (after 4 months of training), directly post-marathon, and after 1 month of recovery. Testing comprised a comprehensive medical history, physical examination, ECG, blood tests, cardiopulmonary exercise testing (CPET), echocardiography, cardiac magnetic resonance imaging (MRI), and clinical follow-up if indicated.

We applied the ACSM and ESC pre-participation screenings to the participants' baseline data. As outlined in the study design [13], the ACSM algorithm was applied before inclusion, while the ESC algorithm score was calculated post hoc. In short, the ACSM pre-participation screening for individuals aged 18–65 is based on (1) exercise participation 3 months prior and (2) cardiovascular, metabolic, or renal disease history/symptoms [8]. Participants are consequently classified as "no medical clearance necessary," "medical clearance recommended for vigorous-intensity exercise," or "discontinue exercise and seek medical clearance." The ESC pre-participation screening for individuals aged ≥35 years is based on current physical activity levels and cardiovascular risk profile, assessed by symptoms, medical history, family history, and calculation of Systematic Coronary Risk Evaluation (SCORE). Individuals with SCORE-estimated 10-year cardiovascular mortality ≥5% or markedly elevated individual risk factor levels mandating further clinical analysis are considered "high-risk" [7].

We classified hypertension according to the 2020 ISH Global Hypertension Practice Guidelines [14]. Dyslipidaemia was diagnosed if one or more of the following was present: total cholesterol ≥5.0 mmol/L, LDL cholesterol ≥3.37 mmol/L, triglycerides >1.7 mmol/L, lipoprotein(a) ≥125.0 nmol/L, or HDL <1.0 mmol/L [15–19]. The likelihood of familial hypercholesterolaemia was assessed using the Dutch Lipid Clinic Network score [20, 21]. All ECGs and exercise ECGs were interpreted according to the current international consensus [22]. Exercise tests were assessed according to the EACPR/AHA 2016 guideline [23], and echocardiography and MRI according to the most recent imaging recommendations [24]. We report final diagnoses in individuals where study findings prompted further clinical evaluation.

Results

We included 25 men with a mean age of 42 ± 4.4 years and exercise levels of 28.8 ± 12.8 MET-hours per week for the past 3 months. The ACSM screening algorithm classified

all participants as "medical clearance not necessary," as all participants were physically active for the past 3 months and reported no signs or symptoms or known cardiovascular, metabolic, or renal disease. One participant with hypertension for the past 8 years stated to be compliant with medication and to have well-controlled blood pressure.

All participants had SCORE <5% when applying the ESC screening algorithm. Two participants were reclassified as "high-risk" due to total cholesterol ≥8.0 mmol/L. The first participant was cleared for high-intensity exercise after extensive cardiovascular evaluation. The second participant was given restrictive sports advice due to the finding of hypertrophic cardiomyopathy (HCM) rather than due to dyslipidaemia or dyslipidaemia-associated cardiovascular conditions. In this participant, CT angiography revealed a moderate stenosis (CAD-RADS 3) [25] of the left anterior descending coronary artery.

Our comprehensive study evaluation documented eight subjects without cardiovascular conditions and 17 with ≥1 abnormality and/or cardiovascular conditions. Four (16%) subjects had minor abnormalities (three with mitral regurgitation and one with a small atrial septal defect). Cardiovascular conditions were found in 16 (64%) participants: dyslipidaemia was found in 11 (44%) subjects, and hypertension was found in six (24%) participants. One participant with strongly elevated lipoprotein(a) levels underwent CT angiography, which revealed premature atherosclerosis with calcified coronary plaque (<25% stenosis of the left anterior descending coronary artery). Of the 17 participants with abnormalities and/or cardiovascular conditions, three (12%) were ultimately diagnosed with CVD. They were given restrictive sports advice due to a dilated aortic root (46 mm), the presence of anteroseptal myocardial fibrosis that was interpreted as recovered viral myocarditis, and a rare phenotypic presentation of HCM (interventricular septum 15 mm) with a pathogenic PKP2 (class 5) mutation (c.2146-1G>C) [26, 27]. The results are summarized in Figure 1 and detailed in Table 1.

Discussion

Our extensive evaluation of male first-time marathon runners indicates that the sensitivity of internationally recommended pre-participation screenings has limitations in detecting subtle but serious CVD. In our study, the readiness and motivation to run a first marathon did not reflect optimal cardiovascular health. Indeed, in our small cohort of apparently healthy middle-aged men, we found a considerable number of serious CVDs, in addition to the majority demonstrating ≥1 CVD risk factor [28].

The number of studies comparing pre-participation algorithms with extensive cardiovascular examinations, including modalities such as MRI, is limited. New cardiovascular abnormalities have been reported to range from 2.8% [9] to 19% [10] of participants, which in some cases (0.4–7%) led to negative sports advice for (high-intensity) exercise [9–11]. In line with our current findings, Ermolao et al. [10] found that in 525 middle-aged (≥35 years old) men wherein the ACSM and European Association of Cardiovascular Prevention and Rehabilitation (EACPR; the 2011 predecessor of the 2020 ESC guidelines for pre-participation screening) screening algorithms were applied and compared with comprehensive examinations including ECG and a maximal exercise test, new cardiovascular conditions were found in 19% of the participants, of which 49% went undetected when using the EACPR algorithm, and 50% with the ACSM algorithm.

In our study, the ESC pre-participation screening identified two participants at high risk (for atherosclerotic disease). The ACSM pre-participation screening did not identify any individuals at high risk. Yet, we identified three participants with serious CVDs constituting contra-indications to intensive sports. One of the participants with a serious CVD – an uncommon presentation of phenotypic HCM – was identified as high-risk by the ESC algorithm due to total cholesterol of 8.14 mmol/L, and not due to screening-detected structural heart disease. The screening algorithms did not identify the other two participants with serious CVD (aortic aneurysm and myocardial fibrosis post-myocarditis). Exercise tests are commonly added to screening strategies, and each of our high-risk CVD participants had undergone CPET with continuous ECG monitoring without any abnormalities. Consequently, exercise test findings would not have changed the sports advice based on the ACSM or ESC algorithms. Furthermore, data on exercise recommendations for HCM are scarce, and American Heart Association (AHA) and ESC recommendations differ. However, recent studies point towards the possibility of a more liberal approach [29]. Our sports advice for these individuals was based on the AHA [30] and ESC guidelines [7], but with the final advice formulated by our national multidisciplinary team [31]. The subject with an aortic aneurysm was advised to discontinue all intensive and explosive exercise. The other two participants, with HCM and recovered myocarditis, are still under medical follow-up and are currently advised to refrain from high-intensity exercise.

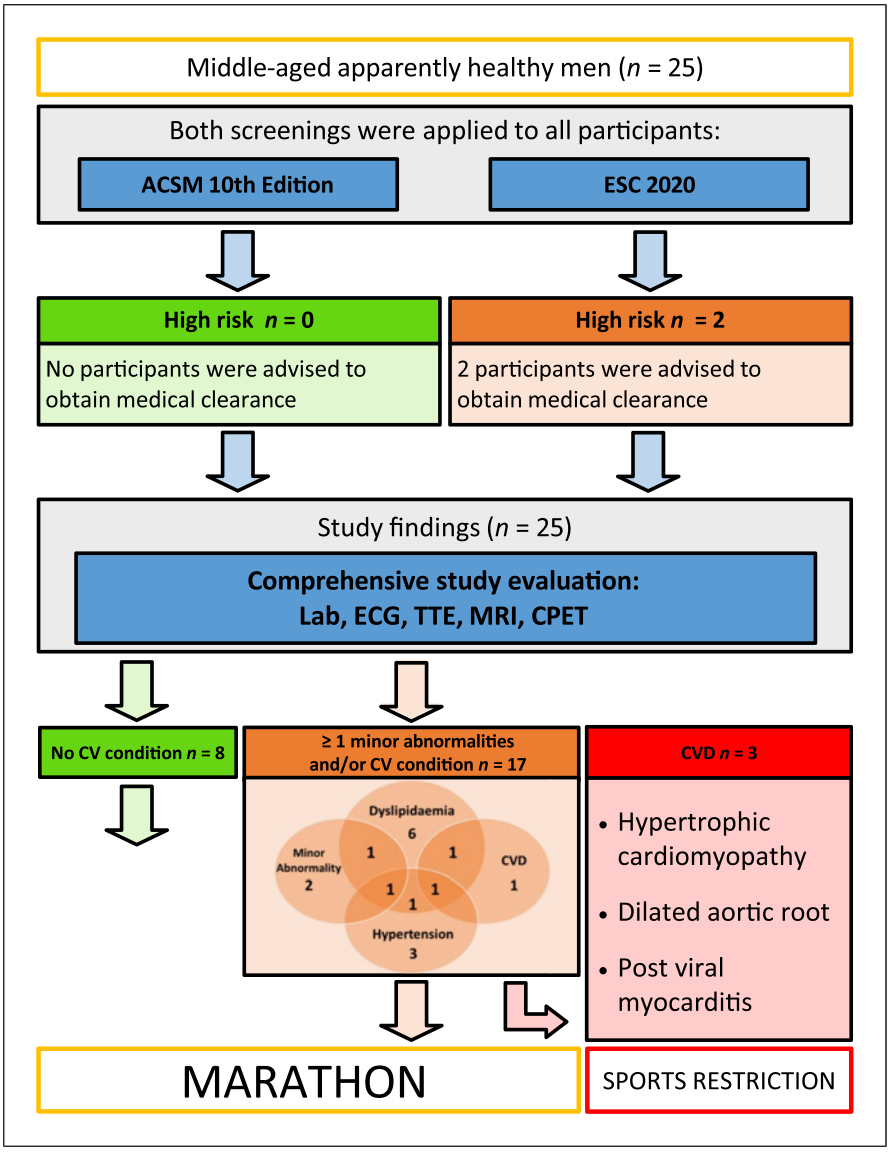

Fig. 1. Outcomes of extensive cardiovascular evaluations within the framework of a study on first-time marathon running, compared with the American College of Sports Medicine (ACSM) and European Society of Cardiology (ESC) pre-participation screening strategies. CPET, cardiopulmonary exercise test; CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; MRI, magnetic resonance imaging; TTE, transthoracic echocardiography.

Our findings highlight that pre-participation screenings in middle-aged men aim to detect the most prevalent diseases in this group, i.e., acquired, risk-factor-driven CVD, and should not be interpreted as a comprehensive screening for less prevalent, structural or (uncommon) acquired CVDs. The major advantages of the ACSM pre-participation screening are that it is easy to implement, does not require physical examinations or additional testing, and can be performed in low-resource settings, markedly lowering implementation barriers. However, in our study sample, this advantage was offset by a lack of sensitivity to several subclinical conventional risk factors (e.g., hypertension, dyslipidaemia). All participants considered themselves active during the 3 months before screening. They had no cardiac (or other screened-for) complaints and were consequently all classified as "low risk" for cardiac events during exercise. While the ESC pre-participation screening also did not classify most individuals with risk factors as "high risk," the SCORE calculation led to a higher detection rate of risk factors. These differences in screening content between the ESC and ACSM screening algorithms should be considered when implementing pre-participation screenings. Finally, the high-risk factor burden found in our study highlights the importance of not only focussing on sports eligibility but also on evaluating individual risk factors for atherosclerotic disease. This could be particularly relevant in endurance

Table 1. Outcomes of the ACSM and ESC screening algorithms and the sports advice of participants according to the clinical findings

Subject No.	Age, years	Diseases and signs or symptoms	Screening algorithm			Clinically relevant findings	Diagnosis	Final sports advice
			ACSM	ESC				
			risk category	SCORE (%)	risk category			
1	38	None	NC	0.11	Low risk	Echocardiography: mitral valve prolapse with minimal regurgitation	Mitral valve prolapse	No restrictions
2	38	None	NC	0.17	Low risk	BP 130/90 mm Hg Total cholesterol 5.42 mmol/L; triglycerides 2.32 mmol/L (DFH score: 0) Echocardiography: moderate mitral regurgitation	Hypertension grade 1 Dyslipidaemia, FH unlikely Moderate mitral regurgitation	No restrictions
3	44	None	NC	0.38	Low risk	BP 140/80 mm Hg	Hypertension grade 1	No restrictions
4	49	None	NC	1.90	High risk*	BP 150/90 mm Hg ECG: inverted T-waves V4–V6 Total cholesterol 8.14 mmol/L, LDL cholesterol 4.97 mmol/L, triglycerides 4.34 mmol/L (DFH score: 1) Echocardiography: IVS 14 mm CT angiography: moderate stenosis (CAD-RADS 3) mid-LAD MRI: IVS 15 mm, subendocardial LGE inferoseptal Genetics: pathogenic (class 5) PKP2 mutation (c.2146-1G>C)	Hypertension grade 1 Dyslipidaemia, FH unlikely Pathogenic PKP2 mutation, HCM Premature atherosclerosis	Discontinue exercise until further comprehensive evaluation
5	46	None	NC	0.75	High risk*	Total cholesterol 8.03 mmol/L, LDL cholesterol 5.67 mmol/L, lipoprotein(a) 239 nmol/L (DFH score: 3)	Dyslipidaemia, possible FH	No restrictions
6	40	None	NC	0.12	Low risk	–		No restrictions

Table 1 (continued)

Subject No.	Age, years	Diseases and signs or symptoms	Screening algorithm			Clinically relevant findings	Diagnosis	Final sports advice
			ACSM	ESC				
			risk category	SCORE (%)	risk category			
7	43	None	NC	0.20	Low risk	Small atrial septal defect, jump-rope inter-atrial septum	Small atrial septal defect	No restrictions
8	44	None	NC	0.36	Low risk	Total cholesterol 6.58 mmol/L, LDL cholesterol 4.52 mmol/L, lipoprotein(a) 82 nmol/L (DFH score: 1)	Dyslipidaemia, FH unlikely	No restrictions
9	42	None	NC	0.21	Low risk	Lipoprotein(a) 134 nmol/L (DFH score: 0)	Dyslipidaemia, FH unlikely	No restrictions
10	38	None	NC	0.14	Low risk	Total cholesterol 5.27 mmol/L, LDL cholesterol 3.48 mmol/L, lipoprotein(a) 161 nmol/L (DFH score: 0)	Dyslipidaemia, FH unlikely	No restrictions
11	35	None	NC	0.06	Low risk	–		No restrictions
12	46	None	NC	0.33	Low risk	Echocardiography: aortic root diameter 47 mm MRI: aortic root diameter 46 mm	Gene-elusive thoracic aortic aneurysm disease	Low to moderate-intensity endurance exercise; no strength training, no extreme endurance sports
13	46	None	NC	0.42	Low risk	–	–	No restrictions
14	41	None	NC	0.23	Low risk	Total cholesterol 5.31 mmol/L, lipoprotein(a) 149 nmol/L (DFH score: 0) MRI: myocardial fibrosis apical (infero) lateral and mid-septal	Dyslipidaemia, FH unlikely Probably recovered viral myocarditis	Discontinue exercise until further comprehensive evaluation
15	40	None	NC	0.22	Low risk	BP 130/90 mm Hg ECG: pathological Q waves in inferolateral leads MRI and echocardiography normal	Hypertension grade 1	No restrictions

Table 1 (continued)

Subject No.	Age, years	Diseases and signs or symptoms	Screening algorithm			Clinically relevant findings	Diagnosis	Final sports advice
			ACSM	ESC				
			risk category	SCORE (%)	risk category			
16	48	None	NC	0.58	Low risk	BP 120/90 mm Hg Total cholesterol 5.39 mmol/L, LDL cholesterol 3.46 mmol/L (DFH score: 0)	Dyslipidaemia, FH unlikely Hypertension grade 1	No restrictions
17	37	None	NC	0.09	Low risk	–	–	No restrictions
18	38	None	NC	0.12	Low risk	–	–	No restrictions
19	38	None	NC	0.15	Low risk	–	–	No restrictions
20	47	None	NC	0.69	Low risk	Total cholesterol 5.97 mmol/L, LDL cholesterol 3.38 mmol/L (DFH score: 0)	Dyslipidaemia, FH unlikely	No restrictions
21	35	None	NC	0.07	Low risk	Total cholesterol 5.17 mmol/L, LDL cholesterol 3.54 mmol/L, lipoprotein(a) 313 nmol/L (DFH score: 2) CT angiography: calcified plaque (<25% stenosis) proximal LAD	Dyslipidaemia, FH unlikely Premature atherosclerosis	No restrictions
22	46	None	NC	0.39	Low risk	–	–	No restrictions
23	42	Hypertension, stable and compliant with medication	NC	0.35	Low risk	BP: 140/70 mm Hg (with medication) MRI: mild concentric LVH (septum 12 mm)	Hypertension grade 1	No restrictions
24	39	None	NC	0.24	Low risk	Total cholesterol 7.09 mmol/L, LDL cholesterol 4.57 mmol/L, triglycerides 2.55 mmol/L (DFH score: 1) Echocardiography: dilated left atrium (LAVI 55 mL/m^2), GLS -16%, moderate mitral valve insufficiency MRI: septal wall thickness max. 12 mm	Dyslipidaemia, FH unlikely Moderate mitral regurgitation Athlete's heart	No restrictions
25	50	None	NC	0.68	Low risk	–	–	No restrictions

*Classified as high risk because of total cholesterol ≥8.0 mmol/L. NC, no medical clearance necessary; BP, blood pressure; ECG, electrocardiogram; DFH, Dutch criteria for familial hypercholesterolaemia; GLS, global longitudinal strain; IVS, interventricular septum; MRI, magnetic resonance imaging; LAD, left anterior descending; LAVI, left atrial volume index; LGE, late gadolinium enhancement.

athletes because lifelong participation in endurance exercise has been shown to be associated with more coronary plaque relative to well-matched, healthy individuals with similar risk-factor profiles [32]. Additionally, an important limitation of both approaches is that it is unknown whether the individuals classified as "high risk" are indeed at high risk because unambiguous data on the interaction between intensive sports participation and cardiac pathology in rare CVDs are lacking.

Our cohort's rates of serious CVD and risk factors are striking, considering that we aimed to include healthy first-time marathon runners. The inclusion criterion "intention to train and run for *first-time* marathon participation" could have influenced the composition of our study sample. Some of our participants may have been lifelong less active or inactive, only increasing their activity levels during the 3 months before study enrollment. Hence, they may have never provoked signs or symptoms that would have prompted cardiovascular evaluation. Joining a marathon study may also have been an incentive for individuals uncertain about their cardiovascular health and, as such, to run their first marathon in a highly monitored setting. Finally, despite implementing the recommended pre-participation screening, our rates of both structural and acquired cardiovascular condition findings are alarming and warrant replication in larger cohorts.

Conclusions

Commonly implemented pre-participation screening strategies fail to identify individuals with serious CVDs that would warrant highly restrictive sports advice. Numerous occult cardiovascular conditions are missed when applying current ACSM/ESC screening strategies to apparently healthy middle-aged men engaging in their first high-intensity endurance sports event. Our findings highlight the need for further study into the sensitivity of currently recommended screening strategies.

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Statement of Ethics

The study protocol was approved by the Amsterdam University Medical Centers Medical Ethics Review Committee (NL70800.029.19). Written informed consent was obtained from all subjects prior to study participation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

H.T.J. is responsible for the finished work and the conduct of the study. I.L. and T.G.H.W. contributed equally to this work and drafting of the article and literature research. Data collection: I.L., T.G.H.W., N.v.S., N.B., A.J.B., M.F., S.v.d.B.-F., F.H.d.H., R.-H.A.C.M.B.-B., S.M.B., and R.N.P.; data analysis: I.L., T.G.H.W., and H.T.J.; checking of the content and proofreading of the text and supervision: E.V., A.J.B., and H.T.J.; writing original draft preparation: I.L. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

Data are not publicly available due to ethical reasons. Further enquiries can be directed to the corresponding author (I.L.).

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