Thrombosis Research xxx (xxxx) xxx

Contents lists available at ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Full Length Article

Effect of regular exercise training on platelet function in patients with cardiovascular disease and healthy individuals: A systematic review

Jacobina Kristiansen [a,b,c,d,e], Erik L. Grove [c,d,*], Oliver Buchhave Pedersen [b,c,d], Steen D. Kristensen [c,d], Anne-Mette Hvas [d]

[a] Department of Medicine, National Hospital of the Faroe Islands, Tórshavn, Faroe Islands
[b] Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark
[c] Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark
[d] Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark
[e] Faculty of Health, University of the Faroe Islands, Tórshavn, Faroe Islands

ARTICLE INFO

Keywords:
Cardiovascular disease
Exercise
Platelets
Platelet activation
Platelet function test
Platelet aggregation

ABSTRACT

Introduction: Regular exercise training is essential in prevention and treatment of cardiovascular disease (CVD), yet the beneficial effects of exercise remain only partly explained. Platelets play a key role in CVD and may be affected by regular exercise training. We aimed to systematically summarise studies investigating the effect of regular exercise training on platelet function in patients with CVD and in healthy individuals.
Methods: Studies were identified by PubMed, Embase and Web of Science May 16, 2022. We selected studies investigating markers of platelet function in relation to regular exercise training in patients with CVD and in healthy individuals. Regular exercise was defined as exercise training for four weeks or more.
Results: Of the included studies, 11 investigated patients with CVD and 29 were on healthy individuals. Studies were heterogeneous regarding design, study population and methodology, and the results were ambiguous. In total, 52 different markers of platelet function were investigated with platelet aggregation, soluble P-selectin, and thromboxane B_2 (TXB_2) as the most frequently examined. When evaluating between-group changes after regular exercise, two studies found a reduced platelet aggregation in the exercise group whilst three studies did not find a difference between groups. With respect to TXB_2, three studies reported a reduction and two studies an increase in the exercise group. There were no between-group differences in the seven studies examining soluble P-selectin.
Conclusion: Regular exercise training has no clear impact on platelet function in patients with CVD or healthy individuals.
Prospero registration: CRD42022350539.

1. Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide [1]. Regular exercise training has a high priority in the prevention and treatment of CVD and has been shown to reduce cardiovascular death and rehospitalisation in patients with coronary artery disease (CAD) [2,3]. In peripheral artery disease, regular exercise training is among first line treatments in order to improve limb symptoms and

Abbreviations: 6-keto-$PGF_{1\alpha}$, plasma 6-keto-prostaglandin $F_{1\alpha}$; AA, arachidonic acid; ADMA, asymmetrical dimethyl arginine; ADP, adenosine diphosphate; CAD, coronary artery disease; CD40L, plasma CD40 ligand; COL, collagen; CVD, cardiovascular disease; EPI, epinephrine; L-arg, L-arginine levels; MPA, monocyte-platelet aggregates; MPV, mean platelet volume; PLT, platelet count; PCT, platelet crit (PLT × MPV / 10,000); PDGF, platelet derived growth factor beta-1; PDW, platelet distribution width; PRISMA, preferred reporting items for systematic reviews and meta-analyses; P-sel, P-selectin; RCT, randomised controlled trial; S1P, sphingosine-1-phosphate; SA1P, sphinganine-1-phosphate; sICAM-1, soluble intercellular adhesion molecule-1; SDMA, symmetrical dimethyl arginine; sE-sel, soluble-E-selectin; SphK, sphingosine kinase activity; sP-selectin, soluble-P-selectin; sVCAM-1, soluble vascular cell adhesion molecule-1; TRAP, thrombin receptor activating peptide; TXA_2, thromboxane A_2; TXB_2, thromboxane B_2; VCAM-1, vascular cell adhesion molecule-1; VEGF, vascular endothelial growth factor; VO_{2max}, maximal aerobic capacity; vWf, von Willebrand factor.

* Corresponding author at: Department of Cardiology, Aarhus University Hospital, 8200 Aarhus N, Denmark.
E-mail address: erikgrove@dadlnet.dk (E.L. Grove).

https://doi.org/10.1016/j.thromres.2022.12.017
Received 31 August 2022; Received in revised form 21 December 2022; Accepted 22 December 2022
Available online 30 December 2022

salvage [4]. The mechanisms explaining the benefits of regular exercise training are only sparsely understood. Regular exercise training has a wide range of potential benefits on cardiovascular risk factors such as hypertension, dyslipidaemia and overweight [2,5,6] and may possibly also have an impact on platelet function. Platelets play a crucial role in the process of coronary thrombus formation [7,8] and thus CVD patients are usually treated with antithrombotic drugs [3,9]. Paradoxically, some studies have linked acute exercise to an increased risk of thrombosis [10–12], which may be explained by exercise-induced platelet aggregation and activation of coagulation [11,12]. Furthermore, untrained people have a higher risk of cardiovascular events following strenuous exercise [2]. In contrast, regular exercise training may induce changes in the haemostatic system explaining its beneficial effects on cardiovascular health and mortality [3]. We aimed to systematically review the literature for studies investigating the effect of regular exercise training on platelet function in patients with CVD and in healthy individuals.

2. Methods

2.1. Eligibility criteria

The present review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [13]. Inclusion criteria were: 1) studies including patients with CVD or healthy individuals, 2) performance of regular exercise training (≥4 weeks), 3) evaluation of platelet function (activation, aggregation, and/or platelet turnover), 4) age ≥18 years, 5) English language, 6) randomised controlled trials, cohort, cross-sectional, or case-control studies. Exclusion criteria were: 1) Studies including individuals with risk factors without established CVD, 2) animals or in vitro studies, 3) guidelines, 4) reviews, 5) letters or editorials without original data, 6) case reports, 7) conference abstracts, 8) studies investigating the effect of pharmacotherapy on platelet function during exercise training 9) records with <10 cases that completed the study. The review was registered at PROSPERO (ID: CRD42022350539).

2.2. Literature search and data extraction

Literature search was performed in three different databases: PubMed, Embase and web of science. The literature search was performed on May 16th, 2022. The search string for PubMed was: ("Blood Platelets" (Mesh) OR "platelet" OR "thrombocyte" OR "Platelet Function Test" (Mesh) OR "Platelet Activation" (Mesh)) AND ("Exercise" (Mesh) OR "exercise"), Embase: ("exercise"/exp OR "exercise") AND

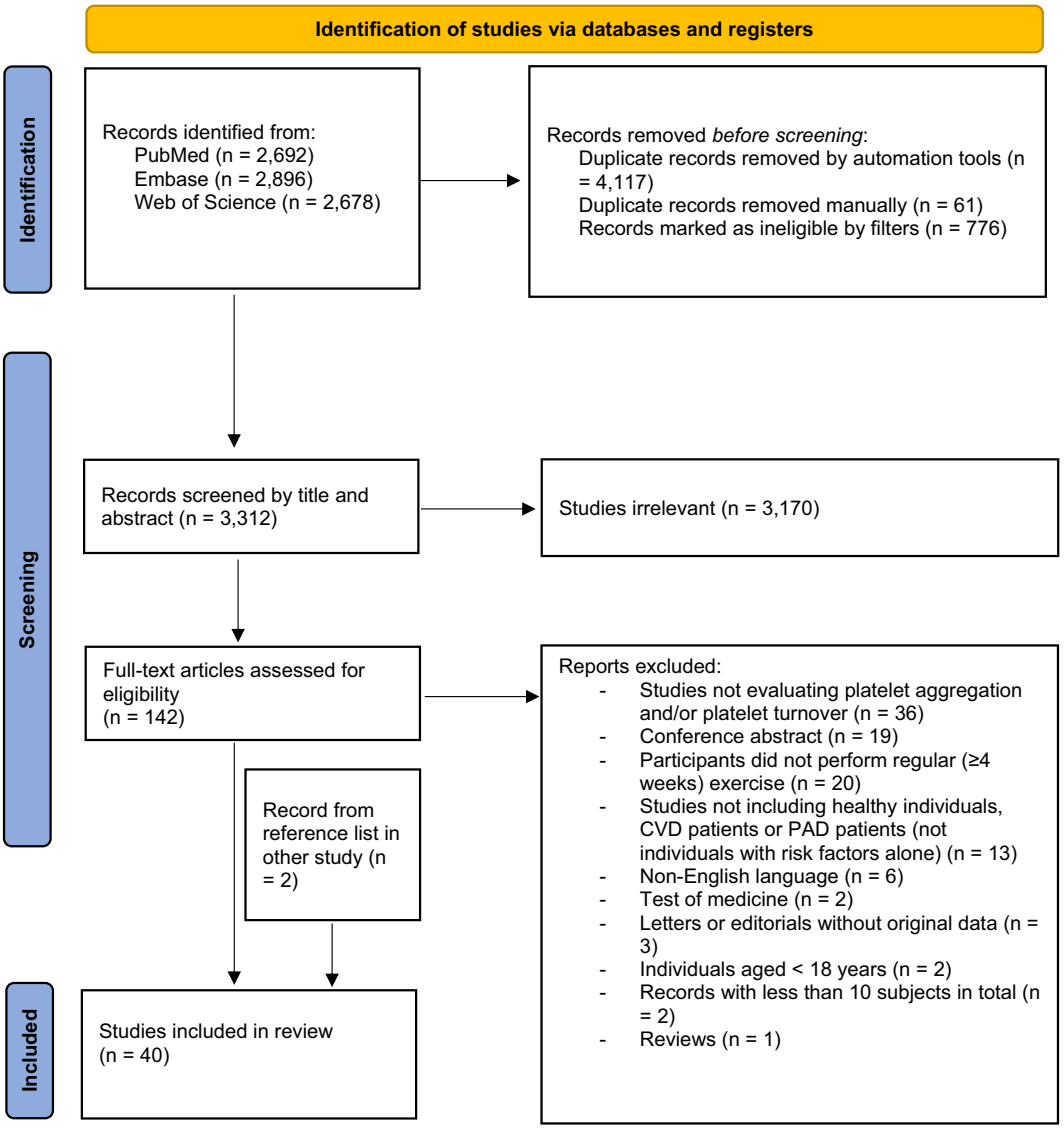

Fig. 1. Flow-diagram for literature search.

("thrombocyte"/exp OR "thrombocyte") and for web of science: ALL = (exercise) AND (ALL = (thrombocyte) OR ALL = (platelet)). The searches were without time boundaries. After duplicate screening, 30 random abstracts were independently screened by the first and last author (JK and AMH). JK made the remaining abstract screening using the Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). JK and AMH evaluated 30 random full-text records to evaluate the study selection. JK evaluated the remaining full-text records for relevance.

2.3. Data processing

Included records were divided by population in patients with CAD, ischaemic stroke or peripheral artery disease and healthy individuals. The exercise protocol for each study was presented with focus on weekly frequency, length of training period, and supervision status.

3. Results

Fig. 1 shows the flowchart of the literature searches and selection procedure. In total, 8266 records were identified. Before screening, 4178 duplicates were removed. Title and abstract screening was performed on 3312 records of which 3170 were excluded based on inclusion and exclusion criteria. The remaining 142 articles were assessed by full text of which 38 were eligible for inclusion. Furthermore, two additional records were found in the reference list of other studies. Among the included studies, 11 studies included patients with CVD and 29 studies examined healthy individuals. CVD subpopulations included CAD (n = 9) and peripheral artery disease (n = 2).

3.1. Effect of regular exercise on platelet function in CVD patients and in healthy individuals

Tables 1 and 2 summarise the characteristics and results of all 40 included studies. The total study population consisted of 2238 individuals: 1072 healthy individuals, 1047 patients with CAD and 119 patients with peripheral artery disease. Out of the 40 included studies, 12 were randomised controlled trials, 21 were cohort studies, 4 were cross-sectional studies and 3 were combined cohort- and cross-sectional studies. Randomised controlled studies were employed in 6 (55 %) of the studies on CVD patients and 6 (21 %) of the studies including healthy individuals. The mean age of patients with CVD was 62 years old, compared to 31 years for healthy individuals. Among studies on patients with CVD, 21 % of patients were women, whereas 33 % of healthy individuals were women. In the included studies, 52 different markers of platelet function were investigated, of which 41 were only measured in a few studies. In Table 3, changes of the 11 markers that were assessed in three or more studies are displayed. Some of the studies reported two different results for the same marker; one result on changes from baseline to after exercise training and another result from the comparison of changes in cases and controls.

3.2. Exercise intervention characteristics

The included studies were homogeneous concerning the type of exercise intervention. In 38 (95 %) of the studies, aerobic exercise was performed (supervised, unsupervised or retrospectively) [14–51] whilst 2 (5 %) studies performed a resistance training program [52,53]. Twenty-nine studies (73 %) performed supervised exercise training [19–26,28,32–41,43,45–53], 6 studies (15 %) did not report supervision status [14,16–18,27,44] and 5 (13 %) studies performed unsupervised exercise [15,29–31,42]. The length of the exercise intervention was varying from 1 to 9 months. Twenty-six studies (65 %) performed exercise interventions for ≤3 months [14,18–20,22,24,26,28,32,35–41,43,44,46–49,51–53], and in 14 studies (35 %) the exercise period lasted for >3 months [15–17,21,23,25,27,29–31,33,34,42,45,50]. Changes in platelet function markers following exercise did not differ between studies with ≤3 months' exercise compared with studies with >3 months of exercise training (data not shown).

3.3. Platelet aggregation

Eight studies measured platelet aggregation using light transmittance aggregometry [15,19–21,36–38,47]. Overall, eight studies reported a reduction [19–21,29,36–38,47] and seven studies reported no changes in platelet aggregation following exercise training [15,19,20,28,29,33,38]. The most frequently measured marker was ADP-induced platelet aggregation. When comparing changes from baseline to after the exercise intervention, six studies showed a decline [20,21,36–38,47], whilst three reported no changes in ADP-induced platelet aggregation (Table 3) [15,19,28]. When changes in the exercise groups were compared with changes in the control group, one study reported a decrease [37] and four studies found no differences between the two groups [20,29,33,38]. When comparing studies that reported a decrease and studies reporting no change in ADP-induced platelet aggregation following an exercise intervention, age (33 years and 34 years) and body mass index (24 in both) were similar in both groups of studies. On the contrary, there was a noticeable variation in the gender distribution across the groups, with a greater proportion of females (44 % vs 27 %) in the group that did not find any alterations in ADP-induced platelet aggregation (χ^2 (1, n = 443) = 13.4, p = 0.0003). COL-induced platelet aggregation was reduced after exercise training in four studies [19,21,29,47], whereas one study did not show any changes [28]. Regarding results on EPI-induced platelet aggregation; two studies reported a reduced aggregation [29,47] and two studies did not find any changes after regular exercise training [19,28]. All studies on platelet aggregation, with the exception of one [47], comprised healthy individuals [15,19–21,28,29,33,36–38].

3.4. Platelet activation and endothelial activation linked to platelet function

Eight different markers of endothelial and platelet activation were measured in three or more studies and are presented in Table 3 [14–20,22,25,27–33,35,36,39–50,52]. Thromboxane B_2 (TXB_2) decreased in three studies [30,31,35], increased in one study [52] and was without changes in two studies [15,25] when comparing results from baseline to after exercise training. Likewise, comparison between TXB_2 in the exercise group and the control group showed a reduction in three studies [30,31,33] and an increase in two studies [25,52] after the intervention period. Six studies investigating plasma 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) did not find a difference following exercise or between the control and the exercise group [15,25,28,29,33,40]. However, Kaufmann et al. reported a fall from baseline to after exercise training [25] and two studies demonstrated an increased 6-keto-$PGF_{1\alpha}$ [30,31]. Mean platelet volume (MPV) increased after exercise in two studies [16,22], whereas two studies reported a decrease in MPV [18,41]. In addition, three other studies did not find any changes in MPV [28,47,51]. Platelet count was unchanged in seven studies after exercise training [16,18,20,22,28,36,51], whereas two studies reported a reduction [19,46] and one study an increase [47]. Platelet micro particles were reduced in two studies [32,47], whilst two studies did not find any changes after exercise [17,32]. Von Willebrand factor (vWf) was reduced in four studies [39,43,46,48], but all except one of these studies [39] demonstrated changes within the case group from pre to post exercise training. Five studies did not find any differences in vWf [14,27,43,45,46], and they were all comparing cases with controls. Likewise, soluble P-selectin was not different in cases and controls following exercise in seven studies [33,39,42,43,45,50,51]. However, soluble P-selectin decreased in the exercise group in two studies [35,42]. Platelet-derived growth factor beta-1 (PDGF) was reduced in two studies [44,47], whilst one study did not find any change after exercise

Table 1
Studies investigating the effect of regular exercise on platelet function in patients with cardiovascular disease (n = 11).

Year Author Ref	Design Study population Number of individuals Age Females	Exercise protocol	Blood sampling	Platelet parameters	Results
2021 Durmus et al. [41]	Cohort study CAD Cases (n = 203) Controls (n = 97) 57 years Gender: 23 % Aspirin: 98 % $P2Y_{12}$ inhib: 59 %	5 times weekly 1.5 months Supervised	Pre 1.5 months	MPV	Cases vs controls: ↓MPV
2020 Heber et al. [51]	RCT CAD Cases (n = 40) Controls (n = 42) 61 years Gender: 0 % Aspirin: 100 % $P2Y_{12}$ inhib: 100 %	All: 4 times weekly 3 months Cases: HIIT+MICT Controls: MICT	Pre 1.5 months 3 months	Flow cytometry (TRAP as agonist): P-sel, CD40L, PNA, GPIIb/IIIa. MPV PLT	Cases vs controls: ↓ P-sel ↔ sP-sel ↔ CD40L ↔ PNA ↔ GPIIb/IIIa ↔ MPV ↔ PLT
2013 Keating et al. [42]	RCT CAD Cases (n = 21) Controls (n = 25) 64 years Gender: 24 % Aspirin: 98 % $P2Y_{12}$ inhib: 0 %	5–7 times weekly 5 months Supervised and unsupervised	Pre 5 months	sP-sel expression (ADP agonist)	Post vs pre, cases: ↓ sP-sel Post vs pre, controls: ↔ sP-sel Cases vs controls: ↔ sP-sel
2006 Lee et al. [43]	RCT CAD Cases (n = 81) Controls (n = 20) 60 years Gender: 19 % Aspirin: 98 % $P2Y_{12}$ inhib: 13 %	2 times weekly 3 months Supervised vs unsupervised	Pre 3 months	sP-sel vWf	Post vs pre, cases: ↔ sP-sel ↓ vWf Post vs pre, controls: ↔ sP-sel ↓ vWf Cases vs controls: ↔ sP-sel ↔ vWf
2021 Liang et al. [44]	Cohort study CAD Cases (n = 35) Controls (n = 17) 67 years Gender: 8 % Aspirin: 36 % $P2Y_{12}$ inhib: 20 %	2 months Supervised vs unsupervised	Pre 2 months	PDGF	Post vs pre, cases: ↓ PDGF Post vs pre, controls: ↔ PDGF Cases vs controls: ↓ PDGF
2011, Munk et al. [45]	RCT CAD Cases (n = 18) Controls (n = 18) 60 years Gender: 17 % Aspirin: 100 % $P2Y_{12}$ inhib: 100 %	3 times weekly 6 months Supervised	Pre 6 months	sE-sel VCAM-1 vWF sP-sel CD4-Ligand	Post vs pre, cases: ↑ sE-sel ↑ VCAM-1 ↔ vWf ↔ sP-sel ↔ CD40-ligand Post vs pre, controls: ↑ E-sel ↔ VCAM-1 ↑ vWf ↔ sP-sel ↔ CD4-ligand Cases vs controls: ↔ all parameters
1992 Suzuki et al. [46]	Cohort study CAD Cases (n = 56) Controls (n = 30) 60 years Gender: 13 %	6 times weekly 1 month Supervised	Pre 1 month	PLT vWf antigen	Post vs pre, cases: ↓ PLT ↓ vWf Antigen Post vs pre, controls:

(*continued on next page*)

Table 1 (*continued*)

Year Author Ref	Design Study population Number of individuals Age Females	Exercise protocol	Blood sampling	Platelet parameters	Results
	Aspirin: 51 % $P2Y_{12}$ inhib: 43 %				↑ PLT ↔ vWf Antigen Cases vs controls: ↓ PLT ↔ vWf Antigen
2017 Toth-Zsamboki et al. [47]	Cohort study CAD Cases (n = 84) Controls (n = 51) 61 years Gender: 22 % Aspirin: 33 % $P2Y_{12}$ inhib: 20 %	5 times weekly 3 months Supervised vs unsupervised	Pre 3 months	PLT MPV Platelet aggregation (COL, ADP, EPI and AA as agonists) PDGF Platelet micro particles	Post vs pre, cases: ↑ PLT ↔ MPV ↓ Platelet aggregation (COL, ADP, EPI) ↔ Platelet aggregation (AA) ↓ PDGF ↓ Platelet micro particles Post vs pre, controls: ↑ PLT ↔ MPV ↔ Platelet aggregation (COL, ADP, AA) ↓ Platelet aggregation (EPI) ↔ PDGF ↔ Platelet micro particles
2009 Vona et al. [48]	RCT CAD Cases (n = 159) Controls (n = 50) 57 years Gender: 26 % Aspirin: 100 % $P2Y_{12}$ inhib: NR	4 times weekly 1 month Supervised	Pre 1 month	vWf	Post vs pre, cases: ↓ vWf Post vs pre, controls: ↔ vWf
2017 Januszek et al. [49]	Cohort study Intermittent claudication (n = 66) 65 years Gender: 38 % Aspirin: NR $P2Y_{12}$ inhib: NR	3 months Supervised	Pre 3 months	PDGF AA PDGF AB/BB	Post vs pre: ↔ PDGF AA ↔ PDGF AB/BB
2012 Schlager et al. [50]	RCT Intermittent claudication: cases (n = 27) Controls (n = 26) 70 years Gender: 38 % Aspirin: 85 % $P2Y_{12}$ inhib: 40 %	2 times weekly 6 months Supervised	Pre 3 months 6 months 12 months	sP-sel MPA	Post vs pre, cases: ↔ sP-sel ↔ MPA Post vs pre, controls: ↔ sP-sel ↔ MPA Cases vs controls: ↔ sP-sel ↔ MPA

Studies evaluating two or more subgroups were labelled as cases and controls. Cases were defined as the group who exercised. If both groups exercised, the population termed cases exercised more than controls and we only presented the exercise protocol for the case group.
Abbreviations: AA: arachidonic acid, ADP: adenosine 5′diphosphate, CAD: coronary artery disease, COL: collagen, EPI: epinephrine, Inhib: inhibitor, HIIT: high-intensity interval training, MICT: moderate-intensity continuous training, MPA: monocyte-platelet aggregates, MPV: mean platelet volume, PDGF: platelet derived growth factor beta-1, PLT: platelet count, PNA: platelet–neutrophil aggregates, P-sel: P-selectin, RCT: Randomised controlled trial, sE-sel: soluble E-selectin, sP-sel: soluble P-selectin, VCAM-1: vascular cell adhesion molecule-1, vWf: von Willebrand factor.

intervention [49].

4. Discussion

In the present review, we identified 40 studies investigating the effect of regular exercise on platelet function in patients with CVD and in healthy individuals. We chose to elaborate on platelet function markers that were measured in at least three studies. Most of the studies investigating platelet function did not find any changes following regular exercise training.

Whilst some of the benefits of regular exercise training on risk factors are well-known, there is still a significant portion of its effects that are not fully understood. For more than half a century, we have known that acute strenuous exercise affects platelets [54,55], and it has been hypothesised that this effect may in part account for the increased risk of sudden cardiac death associated with strenuous exertion [11,56]. In contrast, regular exercise has been shown to reduce the risk of cardiovascular death [2]. Accordingly, we investigated if the beneficial effects of regular exercise may be partly explained by reduced platelet aggregation. As aspirin and other antiplatelet drugs are cornerstones in the

Table 2
Studies investigating the effect of regular exercise on platelet function in healthy individuals (n = 29).

Year, author Ref.	Design Study population Number of patients Age Gender (% females)	Exercise protocol	Blood sampling	Platelet analysis	Results
1991, Ågren et al. [15]	RCT Cases (n = 27) Controls (n = 23) 21 years Gender: 100 %	3 times weekly 3.5 months Unsupervised	Pre 3.5 months	Platelet aggregation (ADP as agonist) TXB_2 6-Keto-$PGF_{1\alpha}$	Post vs pre, cases: ↔ Platelet aggregation (ADP), TXB_2, 6-keto-$PGF_{1\alpha}$ Post vs pre, controls: ↔ Platelet aggregation (ADP), TXB_2, 6-keto-$PGF_{1\alpha}$ Cases vs controls: ↔ Platelet aggregation (ADP), TXB_2, 6-keto-$PGF_{1\alpha}$
2017, Bachero-Mena et al. [16]	Cohort study Active (n = 13) 23 years Gender 0 %	Daily 8 months NR	Pre 4 months 8 months	PLT MPV	8 months vs pre: ↑ MPV ↔ PLT 8 months vs 4 months: ↑ MPV ↔ PLT 4 months vs pre: ↔ MPV ↔ PLT
2017, Bittencourt et al. [17]	Cross-sectional study Cases (n = 25) Controls (n = 24) NR NR	Daily NR	Single time point	Platelet micro particles	Cases vs controls: ↔ Platelet micro particles
2019, Boyali et al. [18]	Cohort study Active (n = 21) 20 years Gender: 57 %	5 times weekly 2 months NR	Pre 2 months	PLT MPV PCT PDW	Post vs pre: ↔ PLT ↓ MPV ↓ PCT ↔ PDW
1996, Burri et al. [19]	Cohort study Inactive (n = 10) 28 years Gender: 100 %	6 times weekly 3 months Supervised	Pre 1.5 months 3 months	PLT Platelet aggregation (ADP, COL and EPI as agonists)	1.5 months vs pre: ↔ PLT ↓ Platelet aggregation (COL) ↔ Platelet aggregation (ADP, EPI) 3 months vs 1.5 months: ↔ PLT ↑ Platelet aggregation (ADP, COL) ↔ Platelet aggregation (EPI) 3 months vs pre: ↓ PLT ↔ Platelet aggregation (ADP, EPI) ↓ Platelet aggregation (COL)
2004, Coppola et al. [20]	Cohort study Cases (n = 15) Controls (n = 15) 43 years Gender: 27 %	3 times weekly for 3 months Supervised	Pre 3 months	PLT Platelet aggregation (ADP as agonist)	Post vs pre, cases: ↔ PLT ↓ Platelet aggregation (ADP) Cases vs controls: ↔ PLT ↔ Platelet aggregation (ADP)
2004, Di Massimo et al. [21]	Cohort study Inactive (n = 12) 25 years Gender: 0 %	3 times weekly 5 months Supervised	Pre 5 months	Platelet aggregation (ADP and COL as agonists) NO_x level	Post vs pre: ↓ Platelet aggregation (ADP) ↓ Platelet aggregation (COL) ↑ NO_x
2020, Erdogan et al. [22]	Cohort study Active (n = 16) NR Gender: 0 %	3 times weekly for 3 months Supervised	Pre 3 months	PLT PCT MPV PDW	Post vs pre: ↔ PLT ↔ PCT

(*continued on next page*)

Table 2 (*continued*)

Year, author Ref.	Design Study population Number of patients Age Gender (% females)	Exercise protocol	Blood sampling	Platelet analysis	Results
2018, Haynes et al. [23]	RCT Cases (n = 14) Controls (n = 13) 60 years Gender: 82 %	3 times weekly for 6 months Supervised	Pre 6 months	MPA (ADP, TRAP, AA as agonists)	↑ MPV ↑ PDW 6 months vs pre, cases: ↔ MPA (ADP, TRAP, AA) 6 months vs pre, controls: ↑ MPA (ADP) ↔ MPA (TRAP, AA) Cases vs controls: ↓ MPA (ADP) ↔ MPA (TRAP, AA)
2016, Heber et al. [24]	A: Cross-sectional study Cases (n = 28) Controls (n = 34) 23 years Gender: 100 % B: Cohort study Cases (n = 17) Controls (n = 17) NR Gender: 100 %	A: NR, based on VO_{2max} at inclusion B: 3 times weekly 2 months Supervised	A: Single time point B: Pre 2 months	Flow cytometry (P-sel, CD40L, ROS) [unstimulated and TRAP as agonist]	A: Cases vs control ↓ P-sel (unstimulated) ↑ P-sel (TRAP) ↔ CD40L (unstimulated) ↑ CD40L (TRAP) ↑ ROS (TRAP) B: Post vs pre, cases ↓ P-sel (unstimulated) ↑ P-sel (TRAP) ↔ CD40L (unstimulated) ↓ CD40L (TRAP) ↔ ROS (TRAP) C: Post vs pre, controls ↔ P-sel (unstimulated, TRAP) ↔ CD40L (unstimulated, TRAP) ↔ ROS (TRAP)
2000, Hilberg et al. [14]	Cohort study Cases (n = 24) Controls (n = 10) 22–38 years Gender: 100 %	2 times weekly 3 months NR	Pre 3 months	vWf	Post vs pre, cases ↔ vWf Cases vs controls ↔ vWf
1997, Kauffman et al. [25]	Cohort study Cases (n = 10) Controls (n = 6) 66 years Gender: 50 %	3 times weekly 4 months Supervised	Pre 4 months	6-Keto-$PGF_{1\alpha}$ TXB_2	Post vs pre, cases ↓ 6-Keto-$PGF_{1\alpha}$ ↔ TXB_2 Post vs pre, controls ↓ 6-Keto-$PGF_{1\alpha}$ ↔ TXB_2 Cases vs controls ↔ 6-Keto-$PGF_{1\alpha}$ ↑ TXB_2
2018, Książek et al. [26]	Cohort study Inactive (n = 17) 20 years Gender: 0 %	3 times weekly 2 months Supervised	Pre 2 months	Sphingosine Sphinganine S1P SA1P Ceramide SphK PLT	Post vs pre ↑ Sphingosine ↑ Sphinganine ↔ S1P ↑ SA1P ↔ Ceramide ↑ Sphingosine kinase activity ↔ PLT
2006, Lippi et al. [27]	Cross-sectional study Cases (n = 89) Controls (n = 43) 28 years Gender: 0 %	Daily NR	Single time point	Platelet aggregation (COL-ADP and COL-EPI as agonist) vWf	Cases vs controls: ↓ Platelet aggregation (COL-ADP) ↔ Platelet aggregation (COL-EPI) ↔ vWf
2018, Lundberg Slingsby et al. [29]	Cross-sectional study Cases (n = 14) Controls (n = 13) 52 years Gender: 0 %	2–4 h weekly >15 years Unsupervised	Single time point	Platelet aggregation (AA, ADP, COL, EPI, TRAP, TXA_2 as agonists) 6-Keto $PGF_{1\alpha}$	Cases vs controls: ↓ Platelet aggregation (COL, EPI) ↔ Platelet aggregation (AA, ADP, TRAP6, TXA_2) ↔ 6-Keto PGF1α

(*continued on next page*)

Table 2 (*continued*)

Year, author Ref.	Design Study population Number of patients Age Gender (% females)	Exercise protocol	Blood sampling	Platelet analysis	Results
2017, Lundberg Slingsby et al. [28]	Cohort study Inactive (n = 49) 51 years Gender: 100 %	3 times weekly 3 months Supervised	Pre 3 months	Platelet aggregation (ADP, EPI, TRAP, TXA_2 and COL as agonists) 6-Keto $PGF_{1\alpha}$ PLT MPV	Post vs pre ↔ 6-Keto $PGF_{1\alpha}$ ↔ PLT ↔ MPV ↔ Platelet aggregation (ADP, EPI, TRAP, TXA_2 and COL)
2021, Medvedev et al. [30]	A: Cross-sectional study Cases (n = 46) Controls (n = 42) 21 years Gender: 0 % B: Cohort study Inactive (n = 42) 22 years Gender: 0 %	A: 3 times weekly NR B: 3 times weekly 6 months Unsupervised	A: Single time point B: Pre 3 months 6 months	TXB_2 6-Keto-$PGF_{1\alpha}$	A: Cases vs controls ↓ TXB_2 ↑ 6-Keto-$PGF_{1\alpha}$ B: 3 months vs pre ↔ TXB_2 ↔ 6-Keto-$PGF_{1\alpha}$ C: 6 months vs pre ↓ TXB_2 ↑ 6-Keto-$PGF_{1\alpha}$
2021, Medvedev et al. [31]	A: Cross-sectional study Cases (n = 35) Controls (n = 38) 48 years Gender: 0 % B: Cohort study Inactive (n = 38) 48 years Gender: 0 %	A: 4 times weekly NR B: 4 times weekly 6 months Unsupervised	A: Single time point B: Pre 3 months 6 months	TXB_2 6-Keto-$PGF_{1\alpha}$	A: Cases vs controls ↓ TXB_2 ↑ 6-Keto-$PGF_{1\alpha}$ B: 3 months vs pre ↔ TXB_2 ↔ 6-Keto-$PGF_{1\alpha}$ C: 6 months vs pre ↓ TXB_2 ↑ 6-Keto-$PGF_{1\alpha}$
2007, Murakami et al. [32]	RCT Cases (n = 28) Controls (n = 21) 52 years Gender: 48 %	3 times weekly 3 months Supervised	Pre 3 months	Platelet microparticles	3 months vs pre, cases: ↓ Platelet microparticles 3 months vs pre, controls: ↓ Platelet microparticles Cases vs controls: ↔ Platelet microparticles
2017, Podgórska et al. [33]	Cross-sectional study Cases (n = 25) Controls (n = 54) 25 years Gender: 0 %	Daily Supervised	Single time point	Platelet aggregation (AA and ADP as agonists) 6-Keto-$PGF_{1\alpha}$ TXB_2 Soluble markers (sP-Sel, VEGF, sICAM-1, sVCAM-1, sE-Sel, ADMA, SDMA, L-arg, Serpin E1)	Cases vs controls: ↔ Platelet aggregation (AA and ADP) ↓ TXB^2 ↔ 6-Keto-$PGF_{1\alpha}$ ↓ sICAM-1 ↔ sP-Sel, VEGF, sVCAM-1, sE-Sel, ADMA, SDMA, L-arg, Serpin E1
1993, Ponjee et al. [34]	Cohort study Inactive (n = 34) 37 years Gender: 41 %	3 times weekly 9 months Supervised	Pre 6 months 9 months	Platelet factor 4 β-Thrombo-globulin	6 months vs pre: ↑ Plasma platelet factor 4 ↔ β-Thromboglobulin 9 months vs pre ↑ Plasma platelet factor 4 ↔ β-Thromboglobulin
2013, Santilli et al. [35]	Cohort study Inactive (n = 22) 51 years Gender: 32 %	2 times weekly 2 months Supervised	Pre 2 months	8-iso-$PGF_{2\alpha}$ TXB_2 sCD40L sP-sel	2 months vs pre ↓8-iso-$PGF_{2\alpha}$ ↓ TXB_2 ↓ sCD40L ↓ s-P-sel
2018 Tagawa et al. [52]	Cohort study Cases (n = 17) Controls (n = 7) 25 years Gender: 0 %	3 times weekly 1 month Supervised	Pre 1 month	TXB_2	Post vs pre, cases: ↑ TXB_2 Post vs pre, controls: ↔ TXB_2

(*continued on next page*)

Table 2 (*continued*)

Year, author Ref.	Design Study population Number of patients Age Gender (% females)	Exercise protocol	Blood sampling	Platelet analysis	Results
					Cases vs controls: ↑ TXB_2 in cases
2011 Trenerry et al. [53]	Cohort study Active (n = 13) 19 years Gender: 0 %	3 times weekly 3 months Supervised	Pre 3 months	VEGF	Post vs pre: ↔ VEGF
2004 Wang et al. [36]	Cohort study Inactive (n = 10) 22 years Gender: 0 %	5 times weekly 2 months Supervised	Pre 2 months	PLT Platelet aggregation (ADP as agonist) Platelet $[Ca^{2+}]_I$ (unstimulated and ADP)	Post vs pre: ↔ PLT ↓ Platelet aggregation (ADP) ↓ $[Ca^{2+}]_I$ (unstimulated, ADP)
1997 Wang et al. [37]	RCT Cases (n = 8) Controls (n = 8) 22 years Gender: 100 %	5 times weekly 2 months Supervised	Pre 2 months	Platelet adhesiveness Platelet aggregation (ADP as agonist) Platelet $[Ca^{2+}]_I$ (unstimulated and ADP) Platelet cGMP	Post vs pre, cases: ↓ Platelet adhesiveness ↓ Platelet aggregation (ADP) ↓ $[Ca^{2+}]_I$ (unstimulated, ADP) ↑ cGMP Post vs pre, controls: ↔ Platelet adhesiveness ↔ Platelet aggregation (ADP) ↔ $[Ca^{2+}]_I$ (unstimulated, ADP) ↔ cGMP Cases vs controls: ↓ Platelet adhesiveness ↓ Platelet aggregation (ADP) ↓ $[Ca^{2+}]_I$ (unstimulated, ADP) ↑ cGMP
1995 Wang et al. [38]	RCT Cases (n = 11) Controls (n = 12) 21 years Gender: 0 %	5 times weekly 2 months Supervised	Pre 2 months	Platelet adhesiveness Platelet aggregation (ADP as agonist)	Post vs pre, cases: ↓ Platelet adhesiveness ↓ Platelet aggregation (ADP) Post vs pre, controls: ↔ Platelet adhesiveness ↔ Platelet aggregation (ADP) Cases vs controls: ↓ Platelet adhesiveness ↔ Platelet aggregation (ADP)
2005 Wang et al. [39]	RCT Cases (n = 15) Controls (n = 15) 24 years Gender: 0 %	5 times weekly 2 months Supervised	Pre 2 months	Platelet aggregation (induced by shear stress) sP-sel vWf	Post vs pre, cases: ↓ Platelet aggregation ↓ vWf ↔ sP-sel Post vs pre, controls: ↔ Platelet aggregation ↔ vWf ↔ sP-sel Cases vs controls: ↓ Platelet aggregation ↓ vWf ↔ sP-sel
2010 Zoladz et al. [40]	Cohort study Inactive (n = 12) 23 years Gender: 0 %	4 times weekly 1 month Supervised	Pre 1 month	6-Keto-$PGF_{1\alpha}$	Post vs pre: ↔ 6-Keto-$PGF_{1\alpha}$

Cohort studies investigating one group only were labelled active or inactive describing their level of physical activity at inclusion. Studies evaluating two or more subgroups were labelled as cases and controls. Cases were defined as the group who exercised. If both groups exercised, the population termed cases exercised more than controls and we only presented the exercise protocol for the case group.

Abbreviations: 6-keto-$PGF_{1\alpha}$: plasma 6-keto-prostaglandin $F_{1\alpha}$, AA: arachidonic acid, ADMA: asymmetrical dimethyl arginine, ADP: adenosine 5′diphosphate, CD40L: plasma CD40 ligand, COL: collagen, EPI: epinephrine, L-arg: L-arginine levels, MPA: monocyte-platelet aggregates, MPV: mean platelet volume, NR: not reported, PLT: platelet count, PCT: platelet crit (PLT × MPV / 10,000), PDW: platelet distribution width, RCT: randomised controlled trial, S1P: sphingosine-1-phosphate, SA1P: sphinganine-1-phosphate, sICAM-1: soluble intercellular adhesion molecule-1, SDMA: symmetrical dimethyl arginine, sE-sel: soluble-E-selectin, SphK: sphingosine

kinase activity, sP-selectin: soluble-P-selectin, sVCAM-1: soluble vascular cell adhesion molecule-1, TRAP: thrombin receptor activating peptide, TXA_2: thromboxane A_2, TXB_2: thromboxane B_2, VEGF: vascular endothelial growth factor, VO_{2max}: maximal aerobic capacity, vWf: von Willebrand factor.

Table 3
Alteration in platelet function following regular exercise training from baseline to after exercise intervention (within-group) and comparing cases and controls (between-group).

Marker	Healthy individuals		Cardiovascular disease	
	Within-group	Between-group	Within-group	Between-group
Platelet aggregation (ADP)	↓ [20,21,36–38] ↔ [15,19,28]	↓ [37] ↔ [20,29,33,38]	↓ [47]	
Platelet aggregation (COL)	↓ [19,21] ↔ [28]	↓ [29]	↓ [47]	
Platelet aggregation (EPI)	↔ [19,28]	↓ [29]	↓ [47]	
TXB_2	↓ [30,31,35] ↔ [15,25] ↑ [52]	↓ [30,31,33] ↑ [25,52]		
6-Keto-$PGF_{1\alpha}$	↓ [25] ↔ [15,28,40] ↑ [30,31]	↔ [25,29,33] ↑ [30,31]		
Mean platelet volume	↓ [18] ↔ [28] ↑ [16,22]		↔ [47]	↓ [41] ↔ [51]
Platelet count	↓ [19] ↔ [16,18,20,22,28,36]	↔ [20]	↓ [46] ↑ [47]	↓ [46] ↔ [51]
Micro particles	↓ [32]	↔ [17,32]	↓ [47]	
vWf	↓ [39] ↔ [14]	↓ [39] ↔ [14,27]	↓ [43,46,48] ↔ [45]	↔ [43,45,46]
sP-selectin	↓ [35] ↔ [39]	↔ [33,39]	↓ [42] ↔ [43,45,50]	↔ [42,43,45,50,51]
PDGF			↓ [44,47] ↔ [49]	↓ [44]

Only platelet activity and aggregation markers examined in at least three studies across study populations are presented.
↑: Higher after exercise or higher in exercise group (cases) than controls.
↓: Lower after exercise or lower in exercise group (cases) than controls.
↔: Unchanged after exercise or no difference between exercise group (cases) and controls.
If markers were measured more than twice during the intervention, we only included comparison between baseline and post intervention blood samples in this table.
Abbreviations: ADP: adenosine diphosphate, COL: collagen, EPI: epinephrine, PDGF: platelet derived growth factor beta, TXB_2: thromboxane B_2, vWf: von Willebrand factor.

medical treatment of CVD, most recent and ongoing studies are performed in CVD patients treated with antiplatelets, which may influence the observed effect of regular exercise training on platelet function.

Platelet aggregation induced by ADP was the most frequently measured platelet parameter, and most studies employed light transmittance aggregometry. Ten studies investigated platelet aggregation in healthy individuals [15,19–21,28,29,36–38] whilst only Toth-Zsamboki et al. [47] studied platelet aggregation following regular exercise in CVD patients. In healthy individuals, five studies reported between-group differences [20,29,33,37,38], whilst eight studies performed statistical analyses on within-group differences [15,19–21,28,36–38]. The same pattern was seen throughout the review; the majority of studies reported only on outcomes from within-group comparisons despite including a control group. Within-group analysis in randomised controlled trials is known to be substantially misleading, hence between-group differences should ideally be reported in these studies [57]. A control group is typically also included in cohort studies so that your intervention can be compared to it [58]. However, when evaluating within-group differences in healthy individuals, the majority of studies reported a decreased ADP-induced platelet aggregation [20,21,36–38], whereas three studies did not find any changes in platelet aggregation after regular exercise [15,19,28]. This stands in contrast to results from the between-group differences, where Wang et al. was the only study reporting a decrease in ADP-induced platelet aggregation after regular exercise [37], whilst four studies did not find any changes [20,29,33,38]. Notably, among the five studies reporting a decrease in ADP-induced platelet aggregation, all but one evaluated only within-group differences. Overall, the findings indicate no consistent effect of regular exercise training on ADP-induced platelet aggregation in healthy individuals. Toth-Zsamboki et al. [47] aimed to investigate how platelet aggregation was affected by complex life-style modifications (cases) and traditional unsupervised rehabilitation (controls) in patients with CAD. In addition to supervised exercise training for three months, the intervention consisted of dietary education, stress management and lifestyle coaching and education. The study reported a reduced platelet aggregation in cases but not in controls. These results suggest that the observed effect in cases was explained by a combination of several factors such as selection bias, dietary changes and improvement in stress. Hence, this study investigating platelet aggregation following regular exercise in patients with CVD is not investigating pure exercise, thus making it difficult to determine whether the observed effect is caused by exercise training or dietary modifications.

A reduction in COL-induced platelet aggregation following regular exercise was reported in three studies [19,21,29] and only Lundberg Slingsby et al. reported no effect in healthy individuals. Thus, regular exercise training may possible reduce COL-induced platelet aggregation, but this needs further investigation. No studies reported an increased platelet aggregation after regular exercise, indicating that regular exercise does not induce a platelet-driven increased thrombotic risk.

TXB_2 is an inactive metabolite of the platelet-activating TXA_2. TXB_2 was measured in seven studies only including healthy individuals [15,25,30,31,33,35,52]. The outcomes, however, may not be comparable because TXB_2 was measured in different liquids including plasma [25,30,31,33], serum [52] and urine [35]. There are also several other potential sources of error due to preanalytic variables and to the choice of anticoagulant used [59]. However, a within-group decrease was found in three studies [30,31,35] whereas two studies reported no change in TXB_2 [15,25] and one study observed an increase [52]. The

results were similar for the between-group differences. Three studies reported a decrease in TXB_2 [30,31,33] and two studies found an increase after regular training [25,52]. Overall, the studies indicate that regular exercise training may reduce TXB_2 in healthy individuals but there are also conflicting results, and it needs further investigation in randomised studies with a fitting sample size. Studies including CVD patients are also warranted.

At sites of vascular injury, vWF recruits platelets via binding to the platelet receptor glycoprotein Ib_α, thus vWF is crucial for the initial phase of the primary haemostasis. Overall, the majority of between-group analyses reported no effect of exercise training [14,27,43,45,46] whereas the majority of the within-group investigations found a decrease in vWF after regular exercise [39,43,46,48]. These outcomes indicate that there were no substantial changes in vWF after regular exercise training in either patients with CVD or healthy individuals, but an eventual effect cannot be excluded and needs to be investigated further.

PDGF is produced, stored and released by platelets upon activation. Three studies reported on PDGF in CVD; two studies found a decrease following supervised regular exercise training compared with unsupervised exercise [44,47], whilst one study found no change in PDGF [49]. Despite small sample sizes, these findings may indicate a beneficial effect of exercise training in PDGF in patients with CVD but needs further investigation.

The vast majority of studies evaluating other platelet parameters such as EPI-induced platelet aggregation, platelet count, MPV, micro particles, sP-selectin, and the prostacyclin metabolite 6-keto-$PGF_{1\alpha}$ had conflicting findings or reported no differences in these markers after regular exercise training. Thus, regular exercise training did not seem to affect these parameters.

We included both patients with CVD and healthy individuals in our literature search. Whilst there were more studies conducted on healthy individuals, the studies on patients with CVD were generally considered more reliable due to the use of randomised controlled trials with a larger total sample size. However, when comparing the results in CVD patients and healthy individuals, they are very similar with mostly no changes detected following exercise and some studies demonstrating changes in platelet function. Whilst platelet aggregation is the most frequently measured marker in healthy individuals, only one non-randomised study examined platelet aggregation in patients with CVD. Studies on healthy individuals predominantly measured platelet aggregation, TXB_2 and 6-keto-$PGF_{1\alpha}$ whilst studies on patients with CVD more often examined vWf, soluble P-selectin and PDGF. Of the four markers investigated in patients with peripheral artery disease, regular exercise training had no effect on PDGF AA, PDGF AB/BB, soluble P-selectin, or monocyte-platelet aggregates. We did not find a trend towards a better effect on the markers for platelet function if the length of the exercise intervention was >3 months in neither healthy individuals nor patients with CVD.

As illustrated in Table 1, patients with CVD were treated with aspirin and many of them received dual antiplatelet treatment, which obviously has an influence on platelet function. Thus, platelet inhibition by aspirin and $P2Y_{12}$ inhibitors may abolish the effect of regular exercise on the included measures of platelet function and thereby explain the lack of response in the articles included in this review. However, the effect of regular exercise may also have been overestimated. A common feature for the studies performed in patients with CVD was that the studies were initiated within three months after an acute coronary syndrome and/or coronary artery revascularisation [43,45–48,51]. It has previously been reported that platelets may be active for several months following ST segment elevation myocardial infarction [60], and any reduction in platelet function may thus be explained by changes over time after myocardial infarction rather than an intervention with regular exercise.

Aging increases platelet activity [61], and it also raises the risk of vascular and thrombotic disorders [61]. Whilst patients with CVD were older than healthy individuals, they also had vascular disease, making it difficult to examine how age could potentially modify the effect of exercise on platelet function. However, we did not find that patients with CVD had a different response to regular exercise than healthy individuals.

More women than men die from CVD in Europe despite the fact that the prevalence of CVD is higher in men and men are more likely to die from premature CVD [62]. Previous studies have shown that platelet aggregation levels are higher in women than in men [63–65]. In the present review, women were substantially underrepresented in the study populations. On the contrary, women were overrepresented in the studies that reported no impact of regular exercise compared with those reporting a decrease in ADP-induced platelet aggregation in healthy individuals. Therefore, one may hypothesise that regular exercise training affects platelet function differently in men than in women, with a potential benefit in men but not in women. However, the pooled population is still small and heterogeneous, thus hampering the possibility of making firm conclusions.

In the present literature review, we searched three large international databases and, therefore, the possibility that we overlooked any relevant publications is very low. Moreover, we included all markers on platelet function without predefining methodologies or pre-analytical parameters. The fact that most studies involved exercise training under supervision is also a strength, increasing the probability that all participants carried out the intervention as intended. However, this review is not without limitations. The studies were very heterogeneous regarding which markers of platelet function they examined and that makes it difficult to make a consensus and conclusion. Most studies were non-randomised trials, which limits their internal validity. As a result, it may be challenging to distinguish between the benefits of regular exercise training and other factors. Even though many studies included a control group, not all studies used statistical tests to compare the outcomes between the exercise group and the control group. In general, the sample size was low in the studies investigating healthy individuals, which increases the risk of missing a true effect. Furthermore, patients with CVD received antiplatelet therapy, which have likely challenged the possibility of identifying exercise-related differences in platelet function.

5. Conclusion

In conclusion, this review shows that regular exercise training has no clear effect on platelet function, neither in patients with CVD nor healthy individuals. TXB_2 levels may be reduced in healthy individuals following regular exercise, however the current literature does not support that reduced platelet function explains the beneficial effects of regular exercise training in patients with CVD and healthy individuals. Importantly, most studies were small, heterogeneous and non-randomised making it difficult to draw firm conclusions. Larger randomised controlled trials testing the effect of regular exercise training on platelet function in both patients with CVD and healthy individuals are warranted.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- AMH has received speaker's fees from Astellas, CSL Behring, Bayer, Boehringer-Ingelheim, Bristol-Myers Squibb, and Leo Pharma and unrestricted research support from Octapharma, CSL Behring, and Leo Pharma.
- ELG has received speaker honoraria or consultancy fees from Alexion Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, MSD, MundiPharma, and Lundbeck Pharma. He is an investigator in clinical trials sponsored by AstraZeneca and Bayer,

and has received unrestricted research grants from Boehringer Ingelheim.
- SDK is National Coordinating Investigator of SOS-AMI (Idorsia).
- OBP and JK reported no conflict of interest.

Acknowledgements

The salary of JK was funded by Aarhus University, Denmark and OBP's salary was funded by Department of Clinical Biochemistry, Aarhus University Hospital, Denmark.

References

[1] World Health Organization, Cardiovascular diseases (CVDs), Available from: http://www.who.int/mediacentre/factsheets/fs317/en/, 2015.
[2] A. Pelliccia, S. Sharma, S. Gati, et al., 2020 ESC guidelines on sports cardiology and exercise in patients with cardiovascular disease, Eur. Heart J. 42 (1) (2021) 17–96, https://doi.org/10.1093/eurheartj/ehaa605 [published Online First: 2020/08/30].
[3] G. Dibben, J. Faulkner, N. Oldridge, et al., Exercise-based cardiac rehabilitation for coronary heart disease, Cochrane Database Syst. Rev. 11 (11) (2021), Cd001800, https://doi.org/10.1002/14651858.CD001800.pub4 [published Online First: 20211106].
[4] V. Aboyans, J.B. Ricco, M.E.L. Bartelink, et al., 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the european Society for Vascular Surgery (ESVS): document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesEndorsed by: the european stroke organization (ESO)The task force for the diagnosis and treatment of peripheral arterial diseases of the european Society of Cardiology (ESC) and of the european Society for Vascular Surgery (ESVS), Eur. Heart J. 39 (9) (2018) 763–816, https://doi.org/10.1093/eurheartj/ehx095.
[5] A.J. Alves, Y. Wu, S. Lopes, et al., Exercise to treat hypertension: late breaking news on exercise prescriptions that FITT, Curr. Sports Med. Rep. 21 (8) (2022) 280–288, https://doi.org/10.1249/jsr.0000000000000983 [published Online First: 20220801].
[6] R.I. Doewes, G. Gharibian, F.A. Zadeh, An updated systematic review on the effects of aerobic exercise on human blood lipid profile, Curr. Probl. Cardiol. (2022), 101108, https://doi.org/10.1016/j.cpcardiol.2022.101108 [published Online First: 20220108].
[7] M.K. Freynhofer, V. Bruno, J. Wojta, et al., The role of platelets in athero-thrombotic events, Curr. Pharm. Des. 18 (33) (2012) 5197–5214, https://doi.org/10.2174/138161212803251899.
[8] T. Gremmel, A.L. Frelinger III, A.D. Michelson, Platelet physiology, Semin. Thromb. Hemost. 42 (3) (2016) 191–204, https://doi.org/10.1055/s-0035-1564835 [published Online First: 20160229].
[9] P. Giannuzzi, A. Mezzani, H. Saner, et al., Physical activity for primary and secondary prevention. Position paper of the working group on cardiac rehabilitation and exercise physiology of the european Society of Cardiology, Eur. J. Cardiovasc. Prev. Rehabil. 10 (5) (2003) 319–327, https://doi.org/10.1097/01.hjr.0000086303.28200.50.
[10] L.N. Olsen, M. Fischer, P.A. Evans, Does exercise influence the susceptibility to arterial thrombosis? An integrative perspective, Front. Physiol. 12 (2021), 636027, https://doi.org/10.3389/fphys.2021.636027 [published Online First: 20210223].
[11] J.J. Posthuma, P.E. van der Meijden, H. Ten Cate, Short- and Long-term exercise induced alterations in haemostasis: a review of the literature, Blood Rev. 29 (3) (2015) 171–178, https://doi.org/10.1016/j.blre.2014.10.005, 10.1016/j.blre.2014.10.005. Epub 2014 Nov 6.
[12] A.M. Hvas, S. Neergaard-Petersen, Influence of exercise on platelet function in patients with cardiovascular disease, Semin. Thromb. Hemost. 44 (8) (2018) 802–812, https://doi.org/10.1055/s-0038-1673618, 10.1055/s-0038-1673618. Epub 2018 Sep 28.
[13] A. Liberati, D.G. Altman, J. Tetzlaff, et al., The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, PLoS Med. 6 (7) (2009), e1000100, https://doi.org/10.1371/journal.pmed.1000100 [published Online First: 20090721].
[14] T. Hilberg, P.E. Nowacki, G. Müller-Berghaus, et al., Changes in blood coagulation and fibrinolysis associated with maximal exercise and physical conditioning in women taking low dose oral contraceptives, J. Sci. Med. Sport 3 (4) (2000) 383–390, https://doi.org/10.1016/s1440-2440(00)80005-5.
[15] J.J. Agren, H. Pekkarinen, H. Litmanen, et al., Fish diet and physical fitness in relation to membrane and serum lipids, prostanoid metabolism and platelet aggregation in female students, Eur. J. Appl. Physiol. Occup. Physiol. 63 (5) (1991) 393–398, https://doi.org/10.1007/bf00364468.
[16] B. Bachero-Mena, F. Pareja-Blanco, J.J. Gonzalez-Badillo, Enhanced strength and sprint levels, and changes in blood parameters during a complete athletics season in 800m high-level athletes, Front. Physiol. (2017) 8, https://doi.org/10.3389/fphys.2017.00637.
[17] C.R.O. Bittencourt, M.C.O. Izar, C.N. França, et al., Effects of chronic exercise on endothelial progenitor cells and microparticles in professional runners, Arq. Bras. Cardiol. 108 (3) (2017) 212–216, https://doi.org/10.5935/abc.20170022.
[18] E. Boyali, T. Sevindi, M.F. Yuksel, et al., The effects of preparation period exercises on the hematological parameters of the taekwondo athletes, Phys. Educ. Stud. 23 (1) (2019) 9–15, https://doi.org/10.15561/20755279.2019.0102.
[19] B.J. Burri, M. Van Loan, N.L. Keim, Moderate exercise training and low-energy diets are associated with small changes in indices of platelet aggregation and blood coagulation in overweight women, Nutr. Res. 16 (9) (1996) 1451–1458, https://doi.org/10.1016/0271-5317(96)00157-1.
[20] L. Coppola, A. Grassia, A. Coppola, et al., Effects of a moderate-intensity aerobic program on blood viscosity, platelet aggregation and fibrinolytic balance in young and middle-aged sedentary subjects, Blood Coagul. Fibrinolysis 15 (1) (2004) 31–37, https://doi.org/10.1097/00001721-200401000-00006.
[21] C. Di Massimo, P. Scarpelli, M. Penco, et al., Possible involvement of plasma antioxidant defences in training-associated decrease of platelet responsiveness in humans, Eur. J. Appl. Physiol. 91 (4) (2004) 406–412, https://doi.org/10.1007/s00421-003-0998-9 [published Online First: 20031118].
[22] R. Erdogan, Effects of endurance workouts on thyroid hormone metabolism and biochemical markers in athletes, Brain 11 (3) (2020) 136–146, https://doi.org/10.18662/brain/11.3/114.
[23] A. Haynes, M.D. Linden, E. Robey, Beneficial impacts of regular exercise on platelet function in sedentary older adults: evidence from a randomized 6-mo walking trial, J. Appl. Physiol. (1985) 125 (2) (2018) 401–408, https://doi.org/10.1152/japplphysiol.00079.2018 [published Online First: 20180412].
[24] S. Heber, A. Assinger, R. Pokan, et al., Correlation between cardiorespiratory fitness and platelet function in healthy women, Med. Sci. Sports Exerc. 48 (6) (2016) 1101–1110, https://doi.org/10.1249/mss.0000000000000882.
[25] R.D. Kauffman, G.S. Sforzo, B. Frost, et al., The effects of exercise training on resting prostacyclin and thromboxane A(2) in older adults, J. Aging Phys. Act. 5 (1) (1997) 59–70, https://doi.org/10.1123/japa.5.1.59.
[26] M. Książek, M. Charmas, A. Klusiewicz, et al., Endurance training selectively increases high-density lipoprotein-bound sphingosine-1-phosphate in the plasma, Scand. J. Med. Sci. Sports 28 (1) (2018) 57–64, https://doi.org/10.1111/sms.12910 [published Online First: 20170601].
[27] G. Lippi, M. Montagnana, G.L. Salvagno, et al., Comparison of platelet function between sedentary individuals and competitive athletes at rest, Thromb. J. 4 (2006) 10, https://doi.org/10.1186/1477-9560-4-10 [published Online First: 20060817].
[28] M.H. Lundberg Slingsby, M. Nyberg, J. Egelund, et al., Aerobic exercise training lowers platelet reactivity and improves platelet sensitivity to prostacyclin in pre- and postmenopausal women, J. Thromb. Haemost. 15 (12) (2017) 2419–2431, https://doi.org/10.1111/jth.13866 [published Online First: 20171027].
[29] M.H. Lundberg Slingsby, L. Gliemann, M. Thrane, et al., Platelet responses to pharmacological and physiological interventions in middle-aged men with different habitual physical activity levels, Acta Physiol (Oxf) 223 (1) (2018), e13028, https://doi.org/10.1111/apha.13028 [published Online First: 20180119].
[30] I.N. Medvedev, V.Y. Karpov, M.V. Eremin, et al., The functional characteristics of the organism of physically inactive students who have started regular physical training, J. Biochem. Technol. 12 (2) (2021) 33–37, https://doi.org/10.51847/LdHG6l2l5q.
[31] I.N. Medvedev, V.Y. Karpov, M.V. Eremin, et al., Hematological parameters in mature age men who have begun regular sports walking, Biochem. Biophys. Res. Commun. 14 (3) (2021) 1015–1019, https://doi.org/10.21786/bbrc/14.3.17.
[32] T. Murakami, H. Horigome, K. Tanaka, et al., Impact of weight reduction on production of platelet-derived microparticles and fibrinolytic parameters in obesity, Thromb. Res. 119 (1) (2007) 45–53, https://doi.org/10.1016/j.thromres.2005.12.013 [published Online First: 20060215].
[33] K. Podgórska, A. Derkacz, E. Szahidewicz-Krupska, et al., Effect of regular aerobic activity in young healthy athletes on profile of endothelial function and platelet activity, Biomed. Res. Int. 2017 (2017), 8715909, https://doi.org/10.1155/2017/8715909 [published Online First: 20170529].
[34] G.A. Ponjee, E.M. Janssen, J.W. van Wersch, Prolonged physical conditioning and blood platelet release markers: a longitudinal study, Haemostasis 23 (5) (1993) 269–274, https://doi.org/10.1159/000216886.
[35] F. Santilli, N. Vazzana, P. Iodice, et al., Effects of high-amount-high-intensity exercise on in vivo platelet activation: modulation by lipid peroxidation and AGE/RAGE axis, Thromb. Haemost. 110 (6) (2013) 1232–1240, https://doi.org/10.1160/th13-04-0295 [published Online First: 20130912].
[36] J.S. Wang, S.E. Chow, Effects of exercise training and detraining on oxidized low-density lipoprotein-potentiated platelet function in men, Arch. Phys. Med. Rehabil. 85 (9) (2004) 1531–1537, https://doi.org/10.1016/j.apmr.2003.08.112.
[37] J.S. Wang, C.J. Jen, H.I. Chen, Effects of chronic exercise and deconditioning on platelet function in women, J. Appl. Physiol. (1985) 83 (6) (1997) 2080–2085, https://doi.org/10.1152/jappl.1997.83.6.2080.
[38] J.S. Wang, C.J. Jen, H.I. Chen, Effects of exercise training and deconditioning on platelet function in men, Arterioscler. Thromb. Vasc. Biol. 15 (10) (1995) 1668–1674 [published Online First: 1995/10/01].
[39] J.S. Wang, Y.S. Li, J.C. Chen, et al., Effects of exercise training and deconditioning on platelet aggregation induced by alternating shear stress in men, Arterioscler. Thromb. Vasc. Biol. 25 (2) (2005) 454–460, https://doi.org/10.1161/01.Atv.0000151987.04607.24 [published Online First: 20041129].
[40] J.A. Zoladz, J. Majerczak, K. Duda, et al., Endurance training increases exercise-induced prostacyclin release in young, healthy men - relationship with VO2max, Pharmacol. Rep. 62 (3) (2010) 494–502, https://doi.org/10.1016/S1734-1140(10)70305-4.

[41] İ. Durmuş, E. Kalaycıoğlu, M. Çetin, et al., Exercise-based cardiac rehabilitation has a strong relationship with mean platelet volume reduction, Arq. Bras. Cardiol. 116 (3) (2021) 434–440, https://doi.org/10.36660/abc.20190514.
[42] F.K. Keating, D.J. Schneider, P.D. Savage, et al., Effect of exercise training and weight loss on platelet reactivity in overweight patients with coronary artery disease, J. Cardiopulm. Rehabil. Prev. 33 (6) (2013) 371–377, https://doi.org/10.1097/hcr.0000000000000015.
[43] K.W. Lee, A.D. Blann, K. Jolly, et al., Plasma haemostatic markers, endothelial function and ambulatory blood pressure changes with home versus hospital cardiac rehabilitation: the Birmingham rehabilitation uptake maximisation study, Heart 92 (12) (2006) 1732–1738, https://doi.org/10.1136/hrt.2006.092163.
[44] G. Liang, X. Huang, J. Hirsch, et al., Modest gains after an 8-week exercise program correlate with reductions in non-traditional markers of cardiovascular risk, Front. Cardiovasc. Med. 8 (2021), 669110, https://doi.org/10.3389/fcvm.2021.669110 [published Online First: 2021/07/06].
[45] P.S. Munk, U.M. Breland, P. Aukrust, et al., High intensity interval training reduces systemic inflammation in post-PCI patients, Eur. J. Cardiovasc. Prev. Rehabil. 18 (6) (2011) 850–857, https://doi.org/10.1177/1741826710397600 [published Online First: 20110218].
[46] T. Suzuki, K. Yamauchi, Y. Yamada, et al., Blood coagulability and fibrinolytic activity before and after physical training during the recovery phase of acute myocardial infarction, Clin. Cardiol. 15 (5) (1992) 358–364.
[47] E. Toth-Zsamboki, Z. Horvath, L. Hajtman, et al., Cardiac rehabilitation programme as a non-pharmacological platelet inhibitory tool in acute coronary syndrome survivors, Eur. J. Prev. Cardiol. 24 (11) (2017) 1148–1156, https://doi.org/10.1177/2047487317704937.
[48] M. Vona, G.M. Codeluppi, T. Iannino, et al., Effects of different types of exercise training followed by detraining on endothelium-dependent dilation in patients with recent myocardial infarction, Circulation 119 (12) (2009) 1601–1608, https://doi.org/10.1161/CIRCULATIONAHA.108.821736.
[49] R. Januszek, P. Mika, R. Nowobilski, et al., Soluble endoglin as a prognostic factor of the claudication distance improvement in patients with peripheral artery disease undergoing supervised treadmill training program, J. Am. Soc. Hypertens. 11 (9) (2017) 553–564, https://doi.org/10.1016/j.jash.2017.06.009 [published Online First: 20170628].
[50] O. Schlager, A. Hammer, A. Giurgea, Impact of exercise training on inflammation and platelet activation in patients with intermittent claudication, Swiss Med. Wkly. 142 (2012), w13623, https://doi.org/10.4414/smw.2012.13623 [published Online First: 20120814].
[51] S. Heber, B. Fischer, M. Sallaberger-Lehner, et al., Effects of high-intensity interval training on platelet function in cardiac rehabilitation: a randomised controlled trial, Heart 106 (1) (2020) 69–79, https://doi.org/10.1136/heartjnl-2019-315130 [published Online First: 2019/07/19].
[52] K. Tagawa, S.G. Ra, H. Kumagai, et al., Resistance training-induced decreases in central arterial compliance is associated with increases in serum thromboxane B-2 concentrations in young men, Artery Res. 23 (2018) 63–70, https://doi.org/10.1016/j.artres.2018.08.001.
[53] M.K. Trenerry, P.A. Della Gatta, A.E. Larsen, et al., Impact of resistance exercise training on interleukin-6 and JAK/STAT in young men, Muscle Nerve 43 (3) (2011) 385–392, https://doi.org/10.1002/mus.21875 [published Online First: 20101209].
[54] E. Ikkala, G. Myllylae, H.S. Sarajas, Haemostatic changes associated with exercise, Nature 199 (1963) 459–461, https://doi.org/10.1038/199459a0.
[55] M.S. El-Sayed, Effects of exercise on blood coagulation, fibrinolysis and platelet aggregation, Sports Med. 22 (5) (1996) 282–298, https://doi.org/10.2165/00007256-199622050-00002.
[56] A.P. Burke, A. Farb, G.T. Malcom, et al., Plaque rupture and sudden death related to exertion in men with coronary artery disease, JAMA 281 (10) (1999) 921–926, https://doi.org/10.1001/jama.281.10.921.
[57] J.M. Bland, D.G. Altman, Comparisons against baseline within randomised groups are often used and can be highly misleading, Trials 12 (2011) 264, https://doi.org/10.1186/1745-6215-12-264 [published Online First: 20111222].
[58] J.W. Song, K.C. Chung, Observational studies: cohort and case-control studies, Plast. Reconstr. Surg. 126 (6) (2010) 2234–2242, https://doi.org/10.1097/PRS.0b013e3181f44abc.
[59] H. Helgadóttir, Í. Ólafsson, K. Andersen, et al., Stability of thromboxane in blood samples, Vasc. Health Risk Manag. 15 (2019) 143–147, https://doi.org/10.2147/vhrm.S204925 [published Online First: 20190604].
[60] G. Scalone, I. Coviello, L. Barone, Evidence of increased platelet reactivity in the first six months after acute ST segment elevation myocardial infarction, Thromb. Res. 128 (2) (2011) 174–178, https://doi.org/10.1016/j.thromres.2011.03.018, 10.1016/j.thromres.2011.03.018. Epub 2011 Apr 6. [published Online First: 2011/04/08].
[61] J. Le Blanc, M. Lordkipanidzé, Platelet function in aging, Front. Cardiovasc. Med. 6 (2019) 109, https://doi.org/10.3389/fcvm.2019.00109 [published Online First: 20190807].
[62] N. Townsend, D. Kazakiewicz, F. Lucy Wright, et al., Epidemiology of cardiovascular disease in Europe, Nat. Rev. Cardiol. 19 (2) (2022) 133–143, https://doi.org/10.1038/s41569-021-00607-3.
[63] K. Kurrelmeyer, L. Becker, D. Becker, Platelet hyperreactivity in women from families with premature atherosclerosis, J. Am. Med. Wom. Assoc. (1972) 58 (4) (2003) 272–277.
[64] T.W. Meade, M.V. Vickers, S.G. Thompson, et al., Epidemiological characteristics of platelet aggregability, Br. Med. J. (Clin. Res. Ed.) 290 (6466) (1985) 428–432, https://doi.org/10.1136/bmj.290.6466.428.
[65] J. Cowman, E. Dunne, I. Oglesby, et al., Age-related changes in platelet function are more profound in women than in men, Sci. Rep. 5 (2015) 12235, https://doi.org/10.1038/srep12235 [published Online First: 20150716].