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Relationship between objectively measured physical activity and subclinical cardiovascular disease: a systematic review

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ABSTRACT

Introduction The association of physical activity (PA) with subclinical cardiovascular disease (CVD) is unclear. Clarifying this relationship may inform cardiovascular prevention strategies.

Methods We performed a systematic review (CRD42021226089) using Medline, Embase, CINAHL and Cochrane (1 January 2000 to 1 September 2023). Studies published with adult populations exploring the relationship between objectively measured PA and subclinical CVD were included. Subclinical CVD was assessed using: ankle-brachial index (ABI); arterial stiffness; carotid artery disease; coronary artery atherosclerosis; endothelial function; and measures of cardiac structure and function. The Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) and Cochrane Risk of Bias tools were used for quality review.

Results Of 68 included studies, most supported an inverse relationship between PA and subclinical CVD. Arterial stiffness was the most common outcome (n=40), and 33 studies suggested that less sedentary behaviour (SB), increased PA and/or higher intensity PA was associated with less arterial stiffness. Ten studies of carotid artery disease (total n=18), six of endothelial function (n=10), two of coronary artery disease (n=3) and all of ABI (n=6) suggested that PA or less SB is associated with less subclinical disease. Five studies assessing cardiac structure/function (n=6) suggested alterations in structure/function with PA.

Conclusions PA reduces the risk of CVD events, and this systematic review demonstrates that some of the benefits may be mediated by an inverse association between PA and subclinical CVD. Interventions to increase PA are important for CVD prevention, so we provide a comprehensive overview of which surrogate outcome measures may be most useful to assess future CVD prevention interventions.

PROSPERO registration number CRD42021226089.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Higher levels of objectively-measured physical activity are associated with reduced risk of cardiovascular events.

⇒ Individual studies have assessed the relationship between objectively measured physical activity and a variety of different measures of subclinical cardiovascular disease or dysfunction.

WHAT THIS STUDY ADDS

⇒ This systematic review synthesises the breadth of individual studies and the directional nature of associations between physical activity and six measures of subclinical disease: coronary artery disease, arterial stiffness, endothelial function, peripheral artery atherosclerosis, carotid artery atherosclerosis and cardiac structure and function.

INTRODUCTION

Cardiovascular disease (CVD) continues to be a leading cause of morbidity and mortality globally, and its prevalence has been rising in recent decades.[1] Between 1990 and 2019, the global prevalence of CVD nearly doubled from 271 million to 523 million.[1] Based on data from 2018, CVD was estimated to affect 9.3% of the US population (26.1 million individuals), with prevalence increasing with older age.[2 3] Despite its significant contribution to disease burden and health expenditures, CVD and its adverse health consequences may be largely preventable through targeted interventions for modifiable risk factors such as physical inactivity.

The inverse relationship between higher levels or longer duration of physical activity (PA) and risk of CVD events is well established.[4] What is less clear is whether this relationship is primarily mediated by changes in subclinical CVD (eg, vascular dysfunction, atherosclerotic plaque or abnormal cardiac structure and function) or other potential mediators of risk, such as inflammation, sympathetic tone and thrombogenesis (figure 1). While there is evidence describing the relationship between intentional exercise and subclinical vascular disease, the impact of daily PA on subclinical disease is less established.[5 6]

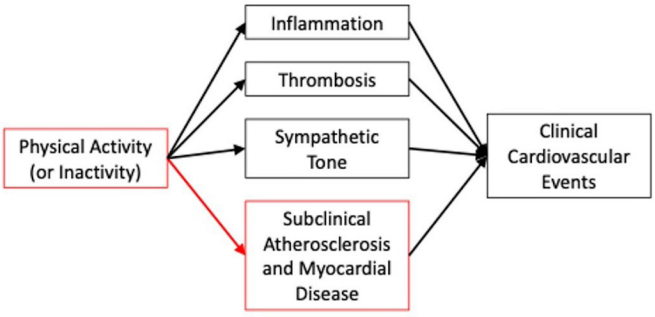

Figure 1 Directed acyclic graph of potential mediators of the relationship between physical activity and clinical cardiovascular events. This systematic review focuses on subclinical disease.

Subclinical CVD is a powerful predictor of future development of clinical CVD, and the prevalence of subclinical CVD increases with age.[7] Identification of subclinical CVD and its associated risk factors may help decrease the progression to clinical CVD events and CVD-related disability and mortality.[8]

Much of the published literature focuses on self-reported PA, which is subject to bias.[9] Wearable activity monitors are tools that objectively measure activity levels.[10] Accelerometers are the gold-standard measurement of PA and are often used in research due to their increased accuracy, reliability and validity compared with simpler options, such as pedometers, self-reported activity and direct observation.[9–11] Accelerometers are able to quantify the magnitude and duration of acceleration by using piezoelectric transducers and microprocessors, and just several days of wear have been shown to be a reliable measure of 2–3 years of activity.[12]

We aimed to describe the association between objectively-measured PA and markers of subclinical CVD, defined as vascular dysfunction, atherosclerotic plaque or abnormal cardiac structure and function, by performing a systematic review of the literature. A better understanding of this relationship may inform the use of subclinical CVD measures as surrogate outcomes for CVD prevention interventions that aim to promote PA and decrease sedentary time among populations.

METHODS

This prospectively registered (PROSPERO CRD42021226089, registered 14 January 2021) systematic review follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2020 guidelines, and institutional review board approval was not needed for this review.[13] The study protocol is available on request.

Equity, diversity and inclusion statement

The investigator team included members of two genders, junior and senior researchers, career researchers, physicians at different stages of training and researchers trained in nursing. With non-restrictive exclusion criteria, we include manuscripts that analysed data for different genders, ages, races, ethnicities, socioeconomic statuses, countries and geographies. Thus, we include studies of diverse participant samples. We present overall trends in this analysis and do not draw conclusions about subgroups of populations. We encourage future interpreters of this systematic review to use our analysis to guide their review of the literature that focuses on their population of interest.

Search strategy

A comprehensive list of search terms was developed by a main reviewer (EB) under the direct supervision of CVD and PA experts (CTL and ARW). Searches were performed in Medline, Embase, CINAHL and Cochrane for publications from 1 January 2000 through 1 September 2023 (online supplemental table 1).

No restrictions or filters involving date, language, article type, text availability, duplication or other limitations were applied to the original search. Next, search results were narrowed to English language, peer-reviewed full-text articles and human studies. Excluded publications included research letters, letters to the editor, editorials, commentaries, systematic reviews/meta-analyses, case reports, case series and meeting abstracts. Study designs included in this systematic review were longitudinal observation studies, randomised/non-randomised controlled/uncontrolled trials, cohort studies and cross-sectional studies. There was no geographic limitation to the included studies. Additionally, the reference lists for all included studies and related systematic reviews/meta-analyses were searched for additional sources meeting the inclusion criteria.

Data management

Search results were imported into Covidence, a systematic review management software (Veritas Health Innovation, Melbourne, Australia).[14] Title and abstract screening was performed independently by two reviewers (AN and EB) using Covidence, according to the inclusion criteria outlined in box 1. These included: subjects 18 years or older without pre-existing CVD (studies that

Box 1 Inclusion criteria for primary studies

⇒ Study published between 1 January 2000 and 1 September 2023.
⇒ Subjects were at least 18 years of age.
⇒ Subjects had no known pre-existing vascular disease.
⇒ Outcome measures include one or more of the following: (1) ankle-brachial index, (2) carotid or popliteal artery plaque/stenosis and intima-media thickness, (3) aortic stiffness, (4) measures of cardiac structure and function (echocardiography, CT, MRI), (5) endothelial function and (6) coronary artery atherosclerosis (coronary calcium and coronary CT angiography).
⇒ Accelerometry/actigraphy data are available for included subjects.
⇒ The direct relationship between objectively measured physical activity (PA) and subclinical cardiovascular disease (CVD) is reported.
⇒ The study is peer reviewed.

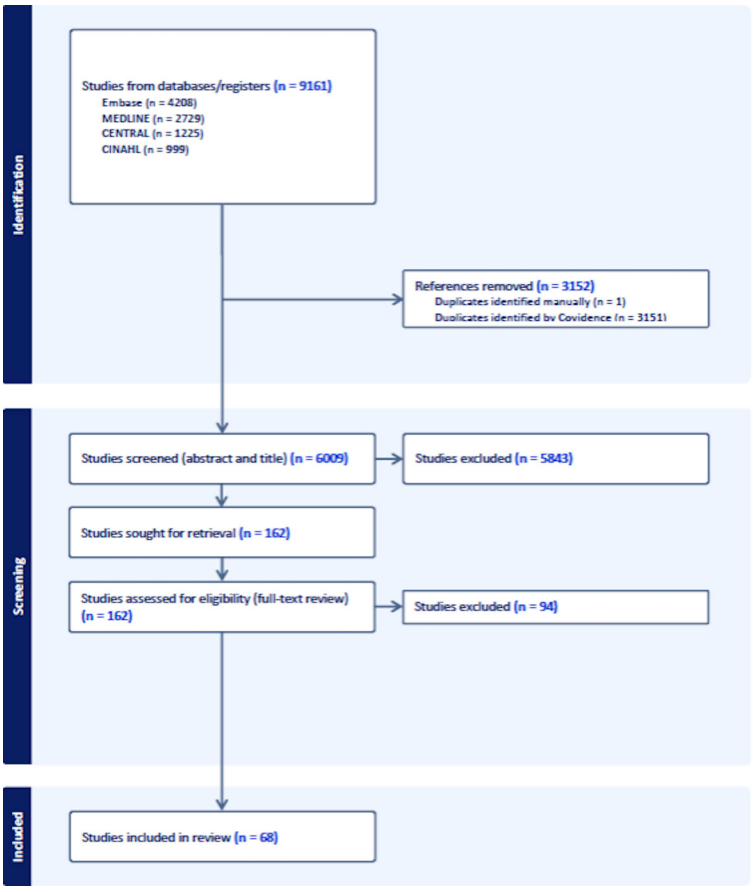

Figure 2 Flow diagram of study selection.

included adolescents and young adults in which the majority of patients were 18 years of age or older were not excluded), a primary exposure variable of objectively measured PA using the validated tool of actigraphy/accelerometry and outcomes of subclinical CVD. After initial abstract screening and adjudication of discrepancies between the two reviewers, full-text papers were reviewed independently by the two reviewers (AN and EB). Disputes were resolved during adjudication meetings with experts (ARW, CTL and CHD). Once all disputes had been settled, the two reviewers verified the list of studies included.

In conjunction with the criteria listed in box 1, reasons for exclusion included duplicates identified manually or by Covidence, studies with the wrong exposure, wrong outcome, wrong intervention, wrong study design, wrong comparator, wrong patient population or data not reported. Meeting abstracts and manuscripts not written in English were also excluded (figure 2).

Exposures

The primary exposure was objectively measured PA using the validated tool of actigraphy/accelerometry. Studies that reported actigraphy/accelerometry data as an independent predictor of subclinical CVD were included. Studies that measured PA using self-reported measures or pedometer data without accelerometer data were excluded.

Outcomes

Subclinical CVD was the primary outcome and was derived from definitions proposed by the Cardiovascular Health Study[7]: (1) abnormal ankle-brachial index (ABI), (2) carotid or popliteal artery plaque/stenosis or intima-media thickness (IMT) of the internal or common carotid artery (CCA), (3) abnormalities noted on measures of cardiac structure and function (echocardiography, CT, MRI), (4) arterial stiffness, (5) endothelial dysfunction and (6) coronary artery atherosclerosis (coronary calcium and coronary CT angiography).

Data extraction

Data were extracted from included papers separately by AN and EB using a data extraction spreadsheet. Discrepancies were adjudicated between the reviewers (AN and EB). The following data were extracted for each included study: publication details (title, author(s), journal, publication date, publication location, publication type and funding source), methods (including study design, type of accelerometer, PA outcome measure(s) reported and subclinical CVD outcome), participant details (number, pertinent characteristics of the population and

demographics), outcomes and limitations (including types of bias present).

Quality assessment

Quality assessment was performed by two reviewers (AN and EB). The included studies were assessed using the Cochrane Risk of Bias tool for randomised controlled trials and the Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) tool for non-randomised controlled trials.[15 16]

Data synthesis

A narrative synthesis of the existing literature was performed without meta-analysis due to the heterogeneity of exposure and outcome measures. We reported findings according to outcome measure, including the following *a priori* categories: arterial stiffness, endothelial function, carotid artery disease, coronary artery atherosclerosis, peripheral artery atherosclerosis and cardiac structure and function (online supplemental table 2).

RESULTS

Study selection

Our search yielded an initial 9161 records for title and abstract screening, of which 162 studies underwent full-text review; 68 studies met the inclusion criteria (figure 2).

Study characteristics

Of the included studies, study samples ranged from 22 to 7,688 subjects, and there was marked variability with regard to characteristics of study participants; for example, some studies focused on specific populations (eg, individuals with diabetes or pregnancy). Study characteristics are described in online supplemental table 3. The majority of studies included were observational studies and therefore subject to bias and/or residual confounding.

Accelerometry wear time ranged from 1 day to 1 year. PA was classified as sedentary behaviour (SB), habitual PA (HPA), light PA (LPA), moderate PA (MPA), moderate to vigorous physical activity (MVPA) and vigorous PA (VPA), as defined by counts per minute on accelerometry. Studies assessed duration in each category of PA.

As a wide range of outcome measures were assessed, a descriptive systematic review was performed. Most studies examined a single outcome (n=57), while other studies included two or more outcomes (n=11). Figure 3A–C graphically demonstrate the number of studies assessing each measure of subclinical CVD and further indicates the proportion of these studies that suggested an association between PA or SB and disease.

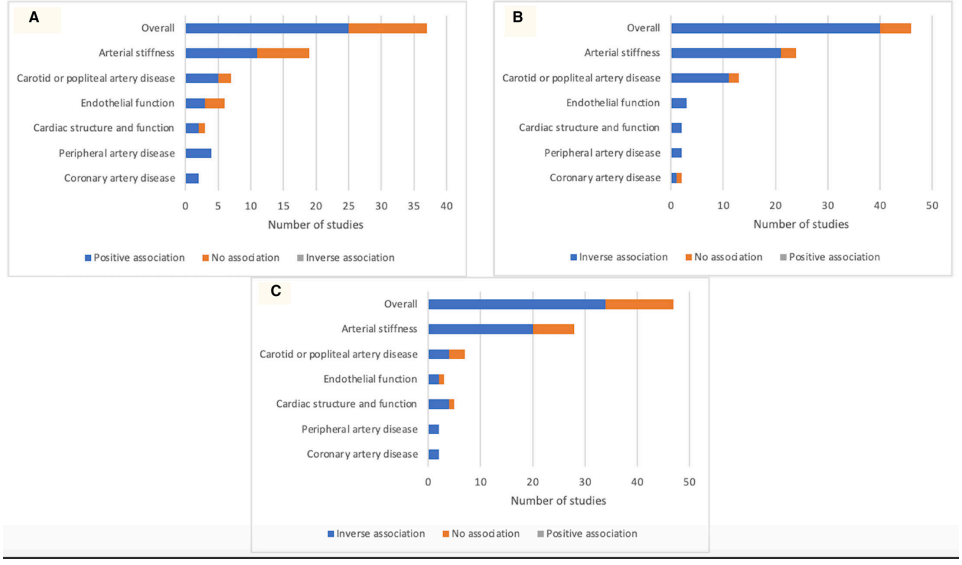

Figure 3 (A) Association between subclinical cardiovascular disease (CVD) and sedentary behaviour (SB), by marker of disease. Included in the figure are 37 analyses assessing the relationship between subclinical CVD and SB. Indication of the presence of an association includes all studies with a positive association between SB and subclinical CVD, regardless of strength of the association, significance or controlling for confounders. (B) Association between subclinical CVD and habitual or low-intensity physical activity, by marker of disease. Included in the figure are 46 analyses assessing the relationship between subclinical CVD and physical activity. Indication of the presence of an association includes all studies with an inverse association between physical activity and subclinical CVD, regardless of strength of the association, significance or controlling for confounders. (C) Association between subclinical CVD and higher intensity physical activity, by marker of disease. Included in the figure are 47 analyses assessing the relationship between subclinical CVD and higher intensity physical activity. Indication of the presence of an association includes all studies with an inverse association between higher intensity physical activity and subclinical CVD, regardless of strength of the association, significance or controlling for confounders.

Arterial stiffness (*n*=40)

The relationship between arterial stiffness and objectively measured PA was reported in 40 studies. Most studies measured arterial stiffness using pulse-wave velocity (PWV), some in addition to tonometry (eg, augmentation index or AIx) and only three studies assessed tonometry but not PWV.

Cruickshank *et al* and Funck *et al* suggested that time in PA of non-specific intensity was related to decreased arterial stiffness as measured by PWV.[17 18] However, higher intensity of PA did not further decrease carotid-femoral PWV (cfPWV) in Funck's analysis, which was not designed to investigate intensity of PA.[18] Several other studies also suggested an inverse dose–response relationship between time in PA and arterial stiffness,[19–26] although this was not always statistically significant.[27] In a smaller cross-sectional study, O'Donovan *et al* found significant inverse associations between HPA and PA of different intensities with AIx and PWV.[28] Additionally, some studies found an inverse association between LPA and arterial stiffness,[25 29] while others did not.[30 31]

Many studies suggested that higher intensities of PA, including MPA, MVPA or VPA, were inversely associated with arterial stiffness.[21 23 32–41] Several studies that found a significant inverse relationship between higher intensity PA and arterial stiffness found no significant relationship with lower intensities of PA and/or total PA.[21 23 32 36 38 41 42] In contrast, Gando *et al* suggested no relationship between arterial stiffness with VPA, while there was an inverse relationship for MPA and LPA in older subjects.[43] Several studies found no relationship between higher intensity PA with arterial stiffness.[23 44–49] Some studies investigated specific patient populations, with differing results for subsets of patients.[50 51] For example, Fernberg *et al* suggested a strong inverse association between AIx and MVPA in women and the total population, but not in men.[51]

Several studies also found a significant positive association between SB and arterial stiffness.[21 26 28 29 32 35 36 40 52] Gomez-Sanchez *et al* investigated SB and showed a positive correlation with vascular ageing, a term that included arterial stiffness.[53] While the small (*n*=47) analysis by Morillas-de-Laguno (2018) suggested inverse associations between total PA and PA of all intensities with arterial stiffness, as well as a positive association between SB and arterial stiffness, these reports were not significant, potentially due to underpowering of the study.[54] Other analyses did not find an association between SB and arterial stiffness.[31 40 44 51 55]

Endothelial function (*n*=10)

Ten studies explored the relationship between PA and endothelial function. Studies used change in flow-mediated dilation (FMD) or reactive hyperaemic flow as markers for endothelial function.

Of studies assessing change in FMD, Kohlbrenner *et al* found an inverse relationship between daily PA and FMD in a cohort of patients with chronic obstructive pulmonary disease (COPD).[56] Reyes *et al* also found a higher FMD response in active versus inactive pregnant women, defined by time in MVPA.[57] Suboc *et al* found a similar correlation in participants with ≥20 min/day of MPA in bouts, which was not statistically significant, perhaps due to underpowering of the study (*n*=96).[46] Suboc *et al* also found that MPA in bouts, rather than overall time in MPA, was associated with change in FMD.[47] Similarly, Shivgulam *et al* noted MPA, habitual prolonged sedentary bouts and sedentary breaks, but not total sedentary time, were associated with change in popliteal FMD.[58] On the other hand, Lane-Cordova *et al* reported no relationship between change in FMD with PA; however, their reporting of results was limited.[59]

Four studies investigated reactive hyperaemic flow velocity as a measure of endothelial function. While Duran *et al* did not see worsened hyperaemic flow velocity with SB, Wipfli *et al* found a non-significant correlation.[60 61] Baier *et al* found that daily PA is associated with improved hyperaemic flow velocity in patients with diabetes and control patients.[62] Andersson *et al* measured both change in FMD and reactive hyperaemia and found no consistent relationship between SB or MVPA and endothelial function.[55]

Peripheral artery atherosclerosis (*n*=6)

A low ABI (≤0.90) is a gold-standard screening tool for peripheral artery disease.[63 64] Five studies demonstrated the inverse relationship between exercise and peripheral artery atherosclerosis, as defined by a low ABI. Parsons *et al* showed that the total amount of time spent in MVPA is associated with decreased peripheral artery atherosclerotic risk, while increased LPA and decreased SB are also associated with decreased risk of peripheral artery atherosclerosis.[65] Similarly, two large cross-sectional studies demonstrated that increased time in SB is associated with low ABI, while one of them also indicated that increased time in PA is less suggestive of peripheral artery atherosclerosis.[53 66 67] Another study suggested that those with low ABI spent more time in SB and less time in LPA or MVPA, although these relationships are not statistically significant.[68] Finally, Chiu *et al* found that a lower daily volume of PAs was associated with lower ABI scores.[69]

Carotid artery atherosclerosis (*n*=18)

Eighteen studies assessed subclinical carotid artery atherosclerosis through measures of carotid IMT (cIMT) and/or beta index. Kozàkovà *et al* found that SB was related to worsened CCA but not internal carotid artery IMT, while all intensities of PA, particularly VPA, were associated with lower CCA IMT.[70] Five other studies showed that increased time spent in PA, of non-specific or light intensity, was related to reduced risk of carotid artery atherosclerosis.[26 27 34 71 72] Parsons *et al* found an association between increased SB and worse cIMT, while an inverse relationship was found between LPA and MVPA with cIMT, although MVPA did not have a stronger association than LPA.[65] Several studies (n=5) found no

relationship between cIMT and PA.[20 49 73–75] Other studies (*n*=4) found a negative association between cIMT and PA and/or a positive association between cIMT and SB, but not after adjusting for confounders.[19 21 76 77] MVPA was found to improve Young's elastic modulus of the carotid artery in one study, while another study found no association between cIMT and LPA, MVPA or SB, but did find decreased popliteal IMT with MVPA.[78 79]

Coronary artery atherosclerosis (*n*=3)

Three papers explored coronary artery calcification (CAC) as measured by CT as a marker of subclinical CVD. Gabriel *et al* showed that women without detectable CAC were statistically significantly more likely to spend more time per day in MVPA than those with prevalent CAC, while increased LPA and decreased SB showed non-significant associations with decreased CAC.[80] Hamer *et al* showed a weak inverse relationship between MVPA and CAC that did not persist after adjustment for confounders and a weak non-significant positive association between SB and CAC.[81] Webel *et al* found no association between objectively measured PA and CAC.[82]

Cardiac structure and function (*n*=6)

Five studies evaluated cardiac structure and function using echocardiography, while one assessed cardiac MRI (CMR).[27 55 83–86] Most studies suggested better myocardial function with increased PA. Thangada *et al* demonstrated that MVPA was associated with increased stroke volume and left ventricular (LV) end diastolic volume (EDV), and VPA was associated with larger LV mass (LVM) on CMR.[83] They did not observe an association between PA and left atrial (LA) size, while Heitmann *et al* found increased LA volume index (LAVI) with higher levels of PA in participants <70 years with normal diastolic function.[83 84] Berdy *et al*[85] found that higher levels of both LPA and MVPA were associated with increased LAVI. SB was associated with worsening LV myocardial mechanics, worsening LA pressure and right ventricular function.[85] Andersson *et al* showed the Third Generation Framingham Heart Study indicated that more time spent in LPA or MVPA is associated with greater LVM, largely due to increased LV wall thickness, while SB was associated with lower LV wall thickness and LVM.[55] In a smaller study, subjects with increased MVPA demonstrated higher LVM.[27] Suboc *et al* found that engagement in MVPA after a 12-week intervention in healthy adults had no impact on cardiac function, including septal wall thickness, LV EDV, LV end systolic volume, or diastolic or systolic function.[86]

Quality assessment results

The results from the quality assessment scoring are depicted in online supplemental table 4. Of the six randomised controlled trials, three were classified as having low risk for bias, one was classified as having some concern for risk of bias and two were classified as having high concern for risk of bias. Reasons for lower ratings were due to concern for risk of bias arising randomisation or deviation from the intended intervention group, which often occurred in insufficient reporting of (1) randomisation procedures, (2) baseline characteristics from each randomisation group and (3) adherence to intended intervention, as well as a high percentage of the study population with missing data. Of the 62 non-randomised experimental or observational studies, 4 were classified as having low risk of bias, 39 moderate risk of bias, 18 serious risk of bias and 1 as having a critical risk of bias. The primary reasons for worse quality scores among the non-randomised studies were potential for confounding, classification bias and missing data.

DISCUSSION

Substantial data have established that increasing PA through intentional exercise or daily activities may prevent and mitigate cardiovascular morbidity and mortality.[87] However, the mediators of this effect on clinical outcomes were not previously elucidated. Notably, no prior systematic review to our knowledge has previously investigated the relationship between objectively measured PA and a comprehensive list of markers of subclinical CVD. This study demonstrated that the majority of the published literature describes an inverse relationship between increased PA and risk of subclinical CVD and a positive relationship between sedentary time and risk of various types of subclinical CVD.

These findings are similar to those published by Germano-Soares *et al*, whose meta-analysis demonstrated a negative association between time spent in PA and cfPWV, and a positive association between time spent in SB and cfPWV.[88] Our study expands on this review by including a comprehensive array of measures of subclinical CVD, beyond arterial stiffness to include measures of carotid artery plaque/stenosis and IMT, endothelial function, cardiac structure and function, ABI and coronary artery atherosclerosis.

While the majority of studies described an inverse relationship between increased PA and risk of subclinical CVD, there was heterogeneity in the strength and direction of these associations. Notably, some studies found no association between risk of subclinical CVD and engagement in PA or SB. The discrepancy in findings may be explained by several factors. The heterogeneity of populations studied (eg, sex, age, comorbidities, geography), study design (eg, accelerometry wear time and location, presence of an exercise intervention, blinding of investigators) and low power in some studies are potential reasons for the lack of associations between measures of PA or SB and subclinical CVD measures. Subpopulation analyses suggest that this heterogeneity may be a reason for varying strength of results among different study groups.[29 43] Therefore, it is difficult to quantitatively assess whether one type of PA or reducing SB is universally more effective at reducing subclinical CVD. Additionally, we cannot rule out the possibility that publication bias may have contributed to a higher volume of literature describing positive associations.

Subclinical CVD is a powerful predictor of future development of clinical CVD, and the prevalence of subclinical CVD increases with age.[7] Identification of subclinical CVD and its associated risk factors may help decrease the progression to clinical CVD events and CVD-related disability and mortality.[8] The findings in this review are noteworthy, as they support the notion that the inverse relationship between time or intensity of PA and risk of CVD may be mediated by changes in subclinical CVD, as opposed to inflammation, thrombosis or other proposed mechanisms. As such, enhanced public health efforts towards promoting engagement in PA at an early age may have significant impacts on reducing risk of various types of CVD in adulthood.[29 43 88]

Limitations

While the breadth of our systematic review protocol provides the opportunity to consolidate a narrative of the current literature on this topic, the heterogeneity of both measures of PA, as well as included outcome measures, rendered it impossible to do a meaningful meta-analysis of all included studies. The included studies represent a range of different populations and sample sizes; however, the lack of participant-level characteristics prevents us from making conclusions about the relationship between PA or SB and subclinical CVD in any specific subgroup.

CONCLUSION

In conclusion, this systematic review consolidates contemporary research describing the relationship between objectively measured PA, including time spent in PA and different intensities of PA, or SB and subclinical CVD. Despite a wide array of study designs and populations, most studies suggested that decreased SB, increased PA and higher intensity PA were associated with less subclinical CVD. No studies suggested a positive association between PA and increased subclinical disease. We hope that by summarising existing data, our study can inform the choice of outcome measures in the design of future research and interventions assessing CVD prevention.

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