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Does exercise prevent major non-communicable diseases and premature mortality? A critical review based on results from randomized controlled trials

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Observational studies show that physical activity is strongly associated with a reduced risk of premature mortality and major non-communicable diseases. We reviewed to which extent these associations have been confirmed in randomized controlled trials (RCTs) for the outcomes of mortality, cardiovascular disease (CVD), type 2 diabetes (T2D), and fracture. The results show that exercise does not reduce all-cause mortality and incident CVD in older adults or in people with chronic conditions, based on RCTs comprising ~50,000 participants. The results also indicate a lack of effect on cardiovascular mortality in people with chronic conditions, based on RCTs comprising ~11,000 participants. Furthermore, there is inconsistent evidence regarding the effect of exercise on fractures in older adults, based on RCTs comprising ~40,000 participants. Finally, based on RCTs comprising ~17,000 participants, exercise reduces T2D incidence in people with prediabetes when combined with dietary modification, although evidence for the individual effect of exercise is lacking. Identified shortcomings of the current evidence include risks of publication bias, lack of high-quality studies in certain high-risk populations, and inconstant evidence with respect to some outcomes. Thus, additional large trials would be of value, especially with fracture as the primary outcome. In conclusion, according to current RCT evidence, exercise can prevent T2D assuming it is combined with dietary intervention. However, the current evidence shows that exercise does not prevent premature mortality or CVD, with inconsistent evidence for fractures.

Keywords: exercise, health, morbidity, mortality, physical activity

Introduction

The world's population is ageing rapidly. In 2020, there were 727 million older adults (≥65 years), representing 9% of the total population. By 2050, the total number of older adults is estimated to double, with 16% of the total population being older adults [1]. Age is a strong risk factor for major non-communicable diseases (NCDs) and can thereby diminish healthy ageing by causing severe complications and premature mortality [2–5]. Thus, the demographic shift towards an ageing population suggests that the prevention of NCDs is essential.

The World Health Organization (WHO) suggests that 80% of major NCDs could be prevented by targeting lifestyle risk factors including physical inactivity [6] and that five million deaths each year could be averted if people were sufficiently physically active [7]. They also state that a quarter of the world's population is currently physically inactive [7], which in turn is estimated to be responsible for 5.5% of hip fracture burden [8] and 4.5–7.6% of global T2D, CVD and mortality [9]. Consequently, WHO has established global guidelines wherein physical activity is highlighted as a powerful preventive measure to counteract these outcomes [10]. However, most of the evidence that

underpins these guidelines and estimates relies on data from observational studies. Thus, a plausible question is how well the strong associations correspond to actual effects shown in randomized controlled trials (RCTs).

Comparing the epidemiological evidence with RCT evidence is important to ensure that interventions aiming to prevent major NCDs and premature mortality are designed appropriately and provided to high-risk populations where the largest effects could be expected. If the findings are discrepant, it is important to try to understand and describe the reasons in order to advance the field further. For example, is there a lack of adequate studies, have the existing studies been of insufficient quality, or have existing high-quality RCTs simply failed to show an effect of physical activity on the selected outcomes of interest? Another aspect pertains to credibility. Physical activity and exercise have been proposed as a 'polypill' against chronic disease, and another term that is increasingly used in the field is 'exercise is medicine'. Yet, if the aim is for physical activity and exercise to be prescribed for primary and secondary prevention of chronic disease, similar to medications, evidence from RCTs needs to be taken into higher consideration. For instance, in pharmacological research, observational studies are primarily viewed as hypothesis generating, whereas the emphasis is on clinical trials when determining true effects and causality.

In this paper, we reviewed RCTs that have investigated the effects of exercise on mortality and selected major NCDs including CVD, T2D, and fractures. In broader discussions, we use the term 'physical activity', as it refers to all movements causing an increase in energy expenditure. When referring to structured interventions and results from RCTs we use the term 'exercise' [11]. In this review, the specific areas of investigation were as follows: (1) Does exercise prevent CVD and premature mortality in older adults? (2) Does exercise prevent CVD and premature mortality in people with chronic conditions? (3) Does exercise prevent T2D in people with prediabetes? (4) Does exercise prevent fractures in older adults? We then aimed to provide explanations to the potential discrepant findings between RCTs and observational studies, and also describe how the effects of exercise compare to those of medications.

Why is the physical activity and health paradigm so strong? A historical glance

The foundation for the epidemiological field on physical activity and health was laid in the mid-1900s by the pioneering researchers Jeremy Morris and Ralph Paffenberger. In a study of London bus workers, Morris and colleagues found that cardiovascular mortality was lower amongst the more active bus conductors compared to the more sedentary bus drivers, with similar results observed when comparing postal delivery workers to the sedentary clerks [12]. These results were corroborated by Paffenberger, who in a study of San Francisco longshoremen found that cardiovascular mortality was lower in those with higher energy expenditure compared to those with lower energy expenditure [13]. These studies were followed up by observed beneficial associations of also leisure-time physical activity. In a study of college alumni, Paffenberger found that those who reported higher energy expenditure had a lower risk of myocardial infarction [14]. Although the first public recommendations related to physical activity were released already in the 1970s, these focused on improving fitness and performance [15,16]. However, with further advancements and data on the association between physical activity and health, the recommendations evolved and in the 1990s these were reshaped to guidelines that emphasized physical activity for health promotion [17]. Fast forward to today and it can be concluded that there has been an exponential increase in physical activity research, of which >80% are observational studies [18]. In 2020, the WHO launched the most recent guidelines on physical activity, which include specific quantitative recommendations on physical activity to reduce the risk of mortality and a variety of NCDs in specific populations, including in older adults and people with chronic conditions [10].

Observational studies have shown that self-reported physical activity is associated with up to 30–40% lower risk of all-cause and cardiovascular mortality, 25% lower risk of T2D and CVD, and 30% lower risk of fracture [19–22]. However, recent studies based on accelerometer-measured data have shown that the strength of the associations may be more than two-fold of that previously observed from self-reported data [23–25]. The observational studies also suggest

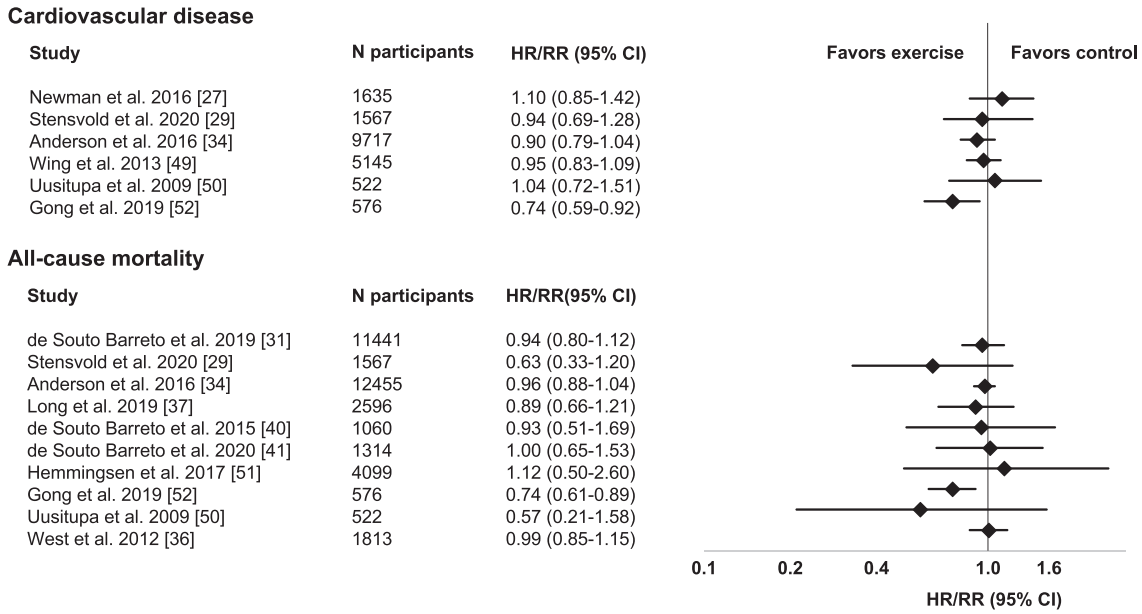

Fig. 1 *Effects of exercise on incident cardiovascular disease and all-cause mortality in the randomized controlled trials and meta-analyses of randomized controlled trials. CI, confidence interval; HR, hazard ratio; RR, relative risk.*

that the majority of benefits occur early on the physical activity spectra, although performing a larger proportion of the activity at a higher intensity may yield additional benefits [25,26]. Altogether, observational studies have consistently estimated large risk reductions from physical activity, and it is proposed that doing something is better than doing nothing and that additional benefits may be attained by increasing the amount and the intensity of the activity [10]. This would imply that providing a variety of interventions, whether they aim to promote low- to moderate-intensity physical activity or high-intensity exercise, would effectively prevent major NCDs and premature mortality. However, to what extent is this supported by current evidence from RCTs?

Does exercise prevent CVD and premature mortality in older adults?

It is well known that older adults are underrepresented in clinical research and the field of physical activity is no exception. Between 1950 and 2019, less than 10% of all physical activity research was conducted in populations specifically aged 60 years or above [18]. Specifically, to our knowledge, only two RCTs have specifically investigated the effects of long-term exercise on CVD or all-cause mortality in general older populations.

The LIFE Study is a US multicenter study in which sedentary older adults were randomized to an intervention group receiving exercise or a control group receiving a successful ageing program, for a median of 2.6 years. Participants eligible for inclusion were required to be sedentary and to have functional limitations. The intervention group received supervised center-based exercise twice per week together with home-based exercise three to four times per week. The control group attended health education workshops. Adherence to the intervention was 63%. The primary outcome of the LIFE Study was major disability, but a composite CVD endpoint (defined as a variety of subtypes of CVD including cardiovascular mortality) was also investigated. The results showed that exercise did not reduce CVD compared to the control group (hazard ratio [HR], 1.10; 95% confidence interval [CI], 0.85–1.42) (Table 1, Fig. 1) [27]. The authors proposed that the lack of effect may have been caused by limited statistical power and short follow-up, as well as an insufficient intervention intensity. Yet, at follow-up, the intervention group reported 104 additional minutes of self-reported walking/weight training and 40 additional minutes of accelerometer-measured moderate physical

Table 1. *Effects of exercise on cardiovascular disease incidence and all-cause mortality in older adults*

Study	Design	No. of participants	Mean age	Intervention duration	Outcome	Number of events I/C	Cumulative incidence (%)	HR/RR (95% CI)
Newman et al. [27]	RCT	1635 (I: 818, C: 817)	78.7	Median 2.6 years	Composite CVD	121/113	14.8% versus 13.8%	1.10 (0.85–1.42)
de Souto Barreto et al. [31]	Meta-analysis	11,441 (I: 5677, C: 5764)	73.1	Mean 1.4 years	All-cause mortality	406/453	7.1% versus 7.9%	0.94 (0.80–1.12)
Stensvold et al. [29]	RCT	1567 (I_1: 400, I_2: 387, C: 780)	72.8	5 years	All-cause mortality	I_1: 37 I_2: 23 C: 12	I_1: 4.7% I_2: 5.9% C: 3.0%	0.63 (0.33–1.20)[a] 0.51 (0.25–1.02)[b] 1.24 (0.33–1.20)[c]
					Composite CVD	I_1: 125 I_2: 58 C: 61	I_1: 16.0% I_2: 15.0% C: 15.3%	0.94 (0.69–1.28)[a] 0.98 (0.69–1.41)[b] 0.96 (0.70–1.31)[c]

Abbreviations: C, control group; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; I, intervention group; RCT, randomized controlled trial; RR, relative risk.
[a]High-intensity exercise versus control.
[b]High-intensity exercise versus moderate-intensity exercise.
[c]Moderate-intensity exercise versus control.

activity in 1 week compared to the control group [28].

The Generation 100 Study investigated the effect of supervised exercise for 5 years on the primary outcome of all-cause mortality in a Norwegian older population. The participants were randomized to a control group receiving recommendations on physical activity, an intervention group receiving moderate-intensity continuous training (MICT), or an intervention group receiving high-intensity interval training (HIIT). Adherence to the prescribed exercise at the 5-year follow-up was 69% in the control group, 51% in the MICT group and 47% in the HIIT group. Compared to controls, neither MICT (HR, 1.24; 95% CI, 0.73–2.10), nor HIIT (HR, 0.63; 95% CI, 0.33–1.20) resulted in significantly lower all-cause mortality (Table 1, Fig. 1) [29]. Comparing HIIT to MICT showed a non-significant trend towards lower all-cause mortality with HIIT (HR, 0.51; 95% CI, 0.25–1.02) [29]. The authors also analyzed the effects on a composite CVD endpoint, for which the number of cases was greater. Still, neither MICT (HR, 0.96; 95% CI, 0.70–1.31) nor HIIT (HR, 0.94; 95% CI, 0.69–1.28) reduced CVD compared to controls (Table 1, Fig. 1). Also, no effect was seen comparing HIIT to MICT (HR, 0.98; 95% CI, 0.69–1.41) [29]. The authors proposed several explanations for the lack of effects, such as that the control group exercised at a higher level and intensity than intended for, which may have biased the results and attenuated the true effect. Also, absolute mortality was less than half of that in the general population, which may have limited the statistical power, although there was a lack of effect also on CVD for which the cumulative incidence and the total number of events were greater [29]. Furthermore, the healthy volunteer bias may have been present as less than 10% of participants reported low physical activity at baseline and nearly 90% reported good overall health, which was significantly different compared to those who declined participation in the study [30]. It could be postulated that the intervention would have been more effective in a sedentary population, yet the LIFE Study that specifically included sedentary older adults did not show an effect. In sum, the results of these two RCTs, which together comprised around 3200 older adults, show that long-term exercise does not prevent CVD and premature mortality in older adults. These findings add to those from a previous meta-analysis of 29 trials, which showed that moderate-intensity exercise interventions lasting >1 year were not

associated with reduced mortality compared to control groups (HR, 0.96; 95% CI, 0.85–1.09) (Table 1, Fig. 1) [31].

In light of the above, it is of interest that an even larger and longer study is currently ongoing. The WHISH is a large pragmatic RCT in the US that is investigating the effects of a multicomponent unsupervised exercise intervention lasting 5–9 years on incident CVD in a diverse cohort of nearly 50,000 older women (mean age, 79.7) [32]. The intervention is based on the physical activity recommendations for older adults as well as behaviour change theories and is delivered through a variety of channels including example standard mail, telephone, email, and online platforms. The participants are provided with training calendars, pedometers, and resistance training equipment [32]. The primary outcome is a composite CVD endpoint (stroke, myocardial infarction or cardiovascular mortality). A major strength of the WHISH Study is the randomized consent design meaning that participants were randomized prior to being invited to the study and providing consent [32]. This may have reduced the possibility that only the most active participants choose to participate in the study, minimizing healthy volunteer bias. Of the 24,657 participants randomized to the intervention group, less than 4% opted out. Consequently, the WHISH Study will be an essential piece in the puzzle of creating knowledge regarding whether a large-scale, pragmatic exercise intervention will effectively prevent CVD in a large general population of older individuals.

Does exercise prevent CVD and premature mortality in people with chronic conditions?

The high prevalence of people living with major NCDs, together with the fact that prevalent NCD is one of the strongest risk factors for mortality or recurrent disease events, emphasizes the importance of secondary prevention in such populations. A 2014 overview of six systematic reviews concluded that in people with various subtypes of CVD, exercise was not effective for reducing all-cause mortality [33]. Since then, updated reviews and meta-analyses of RCTs have produced new evidence and also elucidated the knowledge gaps that remain to be filled. A 2016 meta-analysis of 47 trials determined the effects of moderate to vigorous exercise-based cardiac rehabilitation (CR) compared to no exercise on mortality and recurrent CVD in individuals with coronary heart disease. The median intervention duration was 0.5 years and the median follow-up was 0.5 years. Exercise-based CR did not reduce all-cause mortality (risk ratio [RR], 0.96; 95% CI, 0.88–1.04) (Table 2, Fig. 1), but reduced cardiovascular mortality (RR, 0.74; 95% CI, 0.64–0.86) [34]. However, the effect was only present in a subset of studies with 1–3 years follow-up (RR, 0.77; 95% CI, 0.63–0.93) and was stronger in studies with >3 years follow-up (RR, 0.58; 95% CI, 0.43–0.78) [34]. As for recurrent myocardial infarction, exercise-based CR had no effect across all studies (RR, 0.90; 95% CI, 0.79–1.04), although an effect was seen in a subset of studies with >3 years follow-up (RR, 0.67; 95% CI, 0.50–0.90) [34]. The evidence was deemed to be of low to moderate quality because of poorly described randomization and blinding procedures, as well as indications of publication bias. Importantly, the meta-analysis did not include the results from the final follow-up of the largest study, which appears to have had an impact on the results with respect to cardiovascular mortality. Specifically, in the NEHDP study, participants were randomized to a 3-year long exercise intervention or to a control group that was to maintain normal routines. At the final follow-up after 19 years, the intervention did not reduce cardiovascular mortality (RR, 1.16; 95% CI, 0.88–1.52 (Table 2)) [35]. These figures are in sharp contrast to those reported in the meta-analysis from this study, where there were 14 deaths in the exercise group compared to 20 in the control group at the earliest follow-up (RR, 0.71; 95% CI, 0.31–1.38). Importantly, the NEDHP also showed that the effects of the intervention waned over time [35], which also contradicts the meta-analysis where the effects appeared stronger in studies with longer follow-up. This important finding further supports the suspicion about publication bias regarding the findings in the meta-analysis. Another large study not included in the meta-analysis was the RAMIT study where patients were randomized to cardiac rehabilitation including exercise or usual care after myocardial infarction. During 7–9 years of follow-up, the intervention did not reduce all-cause mortality compared to usual care (RR, 0.99; 95% CI, 0.85–1.15) (Table 2, Fig. 1) [36]. Although cardiovascular mortality was not reported, admissions for heart disease were similar after 1 year (30% versus 29%), suggesting no effect on cardiovascular mortality [36]. Furthermore, because most participants have been middle-aged men, generalizability to women and older men cannot be established. Another meta-analysis of 27 trials

Table 2. *Effects of exercise on incident cardiovascular disease, all-cause mortality, and cardiovascular mortality in people with chronic conditions*

Study	Design	Participant condition	No. of participants	Mean age	Intervention duration	Outcome	No. of events I/C	Cumulative incidence (%)	HR/RR (95% CI)
Anderson et al. [34]	Meta-analysis	Coronary heart disease	12,455 (I: 6424, C:6031)	49–71	Median 0.5 years	All-cause mortality	838/865	13.1% versus 14.3%	0.96 (0.88–1.04)
			7469 (I: 3850, C: 3619)			CVD mortality	292/375	7.6% versus 10.4%	0.74 (0.64–0.86)
			9717 (I: 4951, C: 4766)			Myocardial infarction	356/387	7.2% versus 8.1%	0.90 (0.79–1.04)
West et al. [36]	RCT	Myocardial infarction	1813 (I: 903, C: 910)	64	6–8 weeks and 7–9 years of follow-up	All-cause mortality	245/243	27.1% versus 26.7%	0.99 (0.85–1.15)
Dorn et al. [35]	RCT	Myocardial infarction	651 (I:323, C: 328)	52	3 years and 19 years of follow-up	CVD mortality	104/109	Not specified	1.16 (0.88–1.52)
Long et al. [37]	Meta-analysis	Heart failure	2596 (I: 1302, C: 1294)	51–81	Range: 0.2–2.3 years	All-cause mortality	67/75	5.1% versus 5.8%	0.89 (0.66–1.21)
O'Connor et al. [38]	RCT	Heart failure	2331 (I: 1159, C: 1172)	59	Median 2.5 years	CVD mortality	131/143	11% versus 12%	0.92 (0.74-1.15)
Wing et al. [49]	RCT	Overweight and T2D	5145 (I: 2575, C: 2570)	58.7	Median 9.6 years	Composite CVD	403/418	15.7% versus 18.7%	0.95 (0.83–1.09)
Uusitupa et al. [50]	RCT	Overweight and prediabetes	522 (I: 265, C: 257)	55	Median 4 years	All-cause mortality	6/10	2.3% versus 4.0%	0.57 (0.21–1.58)
						Composite CVD	57/54	22.2% versus 21.8%	1.04 (0.72–1.51)
de Souto Barreto et al. [40]	Meta-analysis	Dementia	1060 (I: 553, C: 507)	Older adults, not specified	Mean 0.4 years	All-cause mortality	Not specified	Not specified	0.93 (0.51–1.69)
de Souto Barreto et al. [41]	Meta-analysis	Dementia	1314 (I: 771, C: 543)	80.8	Mean 0.5 years	All-cause mortality	45/31	5.8% versus 5.7%	1.00 (0.65–1.53)

(*Continued*)

Table 2. *Continued*

Study	Design	Participant condition	No. of participants	Mean age	Intervention duration	Outcome	No. of events I/C	Cumulative incidence (%)	HR/RR (95% CI)
Hemmingsen et al. [51]	Meta-analysis	Prediabetes	4099 (I: 2049, C: 2050)	45–63	Mean 3.6 years	All-cause mortality	12/10	0.6% versus 0.5%	1.12 (0.50–2.60)
Gong et al. [52]	RCT	Prediabetes	576 (I: 438, C: 138)	45–47	6 years and 30 years of follow-up	All-cause mortality	185/76	45.5% versus 56.3%	0.74 (0.61–0.89)
						CVD mortality	89/40	25.6% versus 35.2%	0.67 (0.48–0.94)
						Composite CVD	195/80	52.9% versus 66.5%	0.74 (0.59–0.92)

Abbreviations: C, control group; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; I, intervention group; RCT, randomized controlled trial; RR, relative risk; T2D, type 2 diabetes.

determined the effect of moderate to vigorous exercise-based CR compared to no exercise on all-cause mortality in adults with heart failure. Intervention duration ranged from 0.2 to 2.3 years and the median follow-up was 0.5 years. Results showed that exercise-based CR did not reduce all-cause mortality (RR, 0.89; 95% CI, 0.66–1.21) (Table 2, Fig. 1) [37]. Concerns regarding randomization procedures together with a small number of events caused the evidence to be judged as low quality. A subgroup analysis of six trials with >1-year follow-up showed a non-significant trend towards a small effect (RR, 0.88; 95% CI, 0.75–1.02, high-quality evidence) [37]. Again, generalizability to women and older men is unclear. Amongst the included studies, the HF-ACTION Study also reported cardiovascular mortality [38]. In that study, predominantly middle-aged men and women were randomized to a control group receiving only usual care, or to an intervention group receiving usual care plus aerobic exercise. The exercise was initially supervised for three times per week and was later fully home-based for five times per week. At a median follow-up of 2.5 years, the intervention did not reduce cardiovascular mortality compared to usual care (HR, 0.92; 95% CI, 0.74–1.15) [38]. Altogether, results from these studies suggest that exercise in patients with coronary heart disease and heart failure does not reduce all-cause or cardiovascular mortality.

A 2015 systematic review found no evidence regarding the effects of exercise on mortality in people with dementia [39], although another systematic review and meta-analysis of 10 trials where at least half of participants had dementia found that short-term exercise of mainly moderate intensity did not reduce mortality compared to controls (RR, 0.93; 95% CI, 0.51–1.69) [40] (Table 2, Fig. 1). This result was corroborated in an individual-level patient data meta-analysis of six trials, which found that moderate to vigorous exercise did not reduce mortality in older adults with dementia (HR, 1.00; 95% CI, 0.65–1.53) [41] (Table 2, Fig. 1). However, because both meta-analyses found signs of publications bias and included few cases of death, larger RCTs with sufficient power were requested. In addition, other reviews have highlighted the lack of data regarding the effects of exercise on recurrent CVD and mortality in other clinical populations of interest in relation to healthy ageing, including those with stroke [42], angina [43], atrial fibrillation [44], and chronic kidney disease [45]. All these conditions mentioned impose a significant

burden and will likely increase in conjunction with population ageing [5, 46, 47], hence RCTs targeting populations with these conditions are warranted.

There have also been RCTs conducted on individuals with obesity, T2D, and prediabetes. The Look AHEAD Study is a US multicenter weight-loss study that investigated the effects of an intensive lifestyle intervention on CVD in overweight or obese individuals with T2D. Participants were randomized to a diabetes support group or an intervention group and were followed for a median of 9.6 years. The intervention targeted weight loss through caloric restriction and >175 min/week of home-based moderate-intensity exercise. The primary outcome was a composite CVD endpoint (stroke, myocardial infarction, hospitalization for angina, or cardiovascular mortality). Although the intervention caused positive effects on cardiovascular risk factors [48], it did not reduce CVD (HR, 0.95; 95% CI, 0.83–1.09) (Table 2, Fig. 1) [49]. Similar results were found in a smaller study from Finland, where middle-aged, overweight men and women with prediabetes were randomized to an intensive lifestyle intervention or a control group for 4 years, after which the participants were followed for an average of 10 years. The intervention aimed to achieve weight loss through dietary intervention, as well as ≥30 min/day of moderate-intensity exercise including both aerobic and resistance training. Comparing the groups, there was no significant difference in incident CVD (HR, 1.04; 95% CI, 0.72–1.51) and all-cause mortality (HR, 0.57; 95% CI, 0.21–1.58) (Table 2, Fig. 1) [50].

Later, a meta-analysis of 10 trials determined the separate and combined effects of diet and exercise compared to standard/no treatment on the primary outcome of all-cause mortality in individuals with prediabetes. Secondary outcomes included incident CVD and cardiovascular mortality. The mean intervention duration was 3.6 years. The results showed that combined exercise plus dietary interventions did not reduce all-cause mortality (RR, 1.12; 95% CI, 0.50–2.60) (Table 2, Fig. 1) or cardiovascular mortality (RR, 0.94; 95% CI, 0.24–3.65) [51]. However, only 22 all-cause deaths and eight deaths from CVD were included in the analysis. Also, the evidence was judged as very low quality due to inconsistency, imprecision and other risks of bias including publication bias. In sum, this meta-analysis shows that based on very low-quality evidence, exercise plus dietary interventions are not effective for reducing all-cause or cardiovascular mortality in people with prediabetes. It further highlights the absence of evidence regarding the effects of exercise as a single intervention on these outcomes and on incident CVD. Since the publication of this meta-analysis, one of the included trials, the Da Qing Study, has reported long-term effects. In the study, a small sample of middle-aged men and women with prediabetes were randomized to diet, exercise, diet plus exercise, or a control group, for a 6-year intervention and 30 years of extended follow-up (Table 2). Compared to the control group, the combined intervention group (all three interventions analyzed together as one group) had a lower risk of incident CVD and all-cause mortality (Table 2, Fig. 1), as well as cardiovascular mortality. However, stratified analyses showed that the effects were only significant in women [52]. However, the small sample should be considered when interpreting the results and their potentiality of generalizability, including also the risk of a different form of bias with such a long follow-up time. Altogether, the evidence suggests that exercise plus dietary interventions do not prevent incident CVD or premature mortality in individuals with overweight and prediabetes. However, additional research would be valuable given that the conclusions are based mostly on low-quality evidence and few cases of death, and studies in older populations are specifically lacking.

Does exercise prevent T2D in people with prediabetes?

At least 460 million people are estimated to live with T2D, which is likely an underestimation as many are unaware of their diagnosis [4]. The prevalence is also estimated to continue to grow rapidly during the next decades [4] due to population ageing, thus prevention of T2D is important and especially so in older people. In a meta-analysis of 11 trials, combined exercise plus dietary interventions lasting ≥2 years strongly reduced the incidence of T2D compared to standard/no treatment amongst individuals with prediabetes (RR, 0.57; 95% CI, 0.50–0.64 (Table 3, Fig. 2)) [51]. The evidence was judged to be of moderate quality due to some risk of other biases including early termination of studies. Similar results were shown in another meta-analysis of seven trials (RR, 0.53; 95% CI, 0.41–0.67 (Table 3, Fig. 2)) [53]. This study judged the evidence to be of high quality, although publication bias was not assessed. The results of both these meta-analyses extended those of a larger

Table 3. *Effects of combined exercise plus dietary interventions on type 2 diabetes incidence in middle-aged adults with prediabetes*

Study	Design	No. of participants	Mean age	Intervention duration	No. of events I/C	Cumulative incidence, % or incidence rate	HR/RR (95% CI)
Hemmingsen et al. [51]	Meta-analysis	4511 (I: 2122, C: 2389)	45–63	Mean 3.8 years	315/614	14.9% versus 25.7%	0.57 (0.50–0.64)
Uusitupa et al. [53]	Meta-analysis	4090 (I: not specified, C: not specified)	Middle-aged, not specified	Mean 3.2 years	2466 in total	Total 60.3%	0.53 (0.41–0.67)
Haw et al. [54]	Meta-analysis	8959 (I: not specified, C: not specified)	57	Mean 2.6 years	541/776	7.4/100 PY versus 11.4/100 PY	0.59 (0.51–0.69)
The Da Qing Study	RCT	576 (I: 438, C: 138)	45–47	6 years	58/90	46% versus 67.7%	0.49 (0.33–0.73)
Pan et al. 1997 [57]							
Li et al. 2008 [55]				6 years and 20 years of follow-up	Total 435	43% versus 66%	0.57 (0.41–0.81)
Li et al. 2014 [56]				6 years and 23 years of follow-up	Total 436	72.6% versus 89.9%	0.55 (0.40–0.76)
Gong et al. 2019 [52]				6 years and 30 years of follow-up	Not specified	88.7% versus 95.9%	0.61 (0.45–0.83)

Abbreviations: C, control group; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; I, intervention group; PY, person-years; RCT, randomized controlled trial; RR, relative risk.

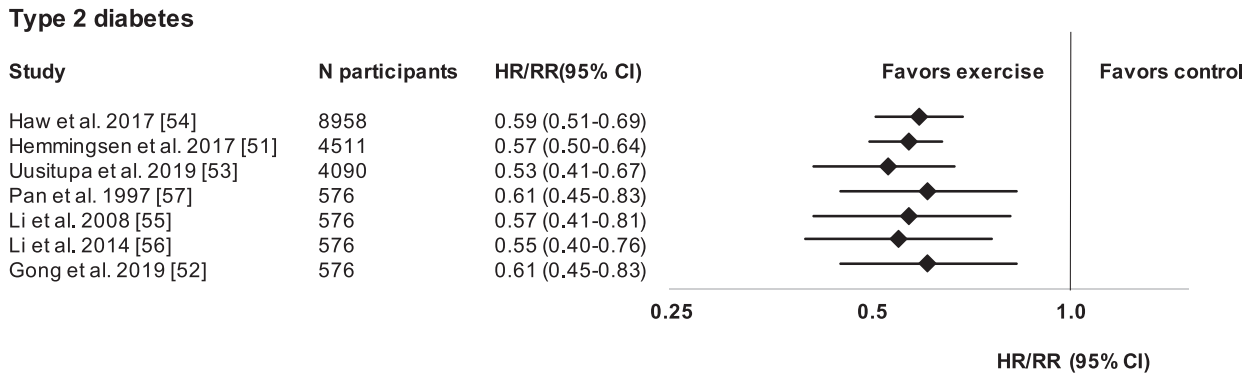

Fig. 2 *Effects of exercise plus diet on incident type 2 diabetes in the randomized controlled trials and meta-analyses of randomized controlled trials. CI, confidence interval; HR, hazard ratio; RR, relative risk.*

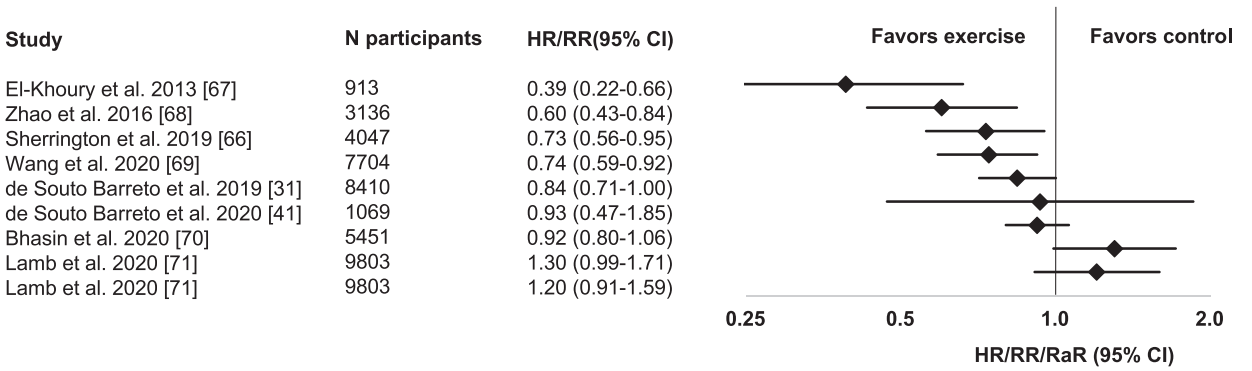

Fig. 3 *Effects of exercise on incident fracture in the randomized controlled trials and meta-analyses of randomized controlled trials. CI, confidence interval; HR, hazard ratio; RaR, rate ratio; RR, relative risk.*

meta-analysis of 19 trials where the average intervention duration was shorter (RR, 0.59; 95% CI, 0.51–0.69 (Table 3, Fig. 2)) [54]. This meta-analysis also explored the sustainability of effects based on four trials with a mean extended follow-up of 7.2 years and showed a greater effect immediately after the intervention (RR, 0.55; 95% CI, 0.43–0.70) compared to after the extended follow-up (RR, 0.72; 95% CI, 0.60–0.86) [54]. In the Da Qing Study, a similar effect was found after up to 20, 23, and 30 years of extended follow-up [52, 55, 56, 57] (Table 3, Fig. 2).

Furthermore, an important finding from these meta-analyses was the observed lack of studies on the effects of exercise as a single intervention on T2D incidence. In the Da Qing Study, the exercise-only group was encouraged to perform one to two exercise sessions per week according to preference, ranging from mild to very high intensity. The results showed that exercise alone reduced T2D compared to the control group (HR, 0.63; 95% CI, 0.50–0.80) [57]. In contrast, a smaller study of 123 individuals with prediabetes showed that a physical activity intervention did not significantly reduce T2D incidence compared to standard treatment over 3 years (RR, 0.66; 95% CI, 0.26–1.61), although this could be due to lack of statistical power [58]. Altogether, moderate- to high-quality evidence shows that both short- and long-term lifestyle interventions including both exercise and diet reduce the incidence of T2D in middle-aged individuals with prediabetes. Evidence regarding the effects of exercise as a single intervention is promising, although very limited, and has not been investigated in older populations.

Does exercise prevent fractures in older adults?

At least nine million fragility fractures occur every year [59], causing chronic pain, disability and premature mortality [60, 61]. Most fractures are attributed to falls [62] and deaths attributed to falls are increasing [63]. Several meta-analyses have shown that fall prevention exercise reduces the rate of falls in the short-term [64–66], suggesting that this could potentially translate into the prevention of fractures. A 2013 meta-analysis of six trials found that multi-component exercise strongly reduced the rate of fall-related fractures compared to no exercise in community-dwelling older adults (rate ratio [RaR], 0.39; 95% CI, 0.22–0.66 (Table 4, Fig. 3)) [67]. However, the sample was small and comprised few male participants, which together with a high risk of bias related to the ascertainment of fracture in three of the trials makes the findings rather uncertain. A 2016 meta-analysis of 15 trials also found an effect from exercise compared to no exercise (RR, 0.60; 95% CI, 0.43–0.84 (Table 4, Fig. 3)) [68]. Although there were no indications of publication bias, the number of fractures was few, and most studies had fractures as a secondary endpoint or only as a mere observation. Thus, the authors stated that larger RCTs with the primary outcome fracture in older adults are needed. A later meta-analysis of 10 trials on community-dwelling older adults included a larger number of participants and found a smaller, yet significant effect of exercise on fracture incidence (RR, 0.73; 95% CI, 0.56–0.95 (Table 4, Fig. 3)) [66]. However, the evidence was judged as low quality due to few events and risk of publication bias, and again, larger RCTs were requested to allow conclusions to be drawn.

Table 4. *Effects of exercise on fracture incidence in older adults*

Study	Design	Population	No. of participants	Mean age	Intervention duration	Number of events I/C	Cumulative incidence, % or incidence rate	HR/RR/RaR (95% CI)
de Souto Barreto et al. [41]	Meta-analysis	Older adults with dementia	1069	80.8	Mean 0.5 years	19/15	2.9% versus 3.5%	0.93 (0.47–1.85)
El-Khoury et al. [67]	Meta-analysis	Community-dwelling older adults	913 (I: 455, C: 458)	73	Mean 0.8 years	Not specified	Not specified	0.39 (0.22–0.66)
Zhao et al. [68]	Meta-analysis	Adults aged ≥50	3136	53.6-85.1	Mean 1.33 years	54/89	3.2% versus 6.9%	0.60 (0.43–0.84)
Sherrington et al. [66]	Meta-analysis	Community-dwelling older adults	4047 (I: 2057, 1990)	76	Mean 1.25 years	Not specified	4.7/100 PY versus 6.4/100 PY	0.73 (0.56–0.95)
Wang et al. [69]	Meta-analysis	Adults aged ≥50	7704	Not specified	Mean 1.27 years	194/230	4.4% versus 7.0%	0.74 (0.59–0.92)
de Souto Barreto et al. [31]	Meta-analysis	Predominantly community-dwelling older adults	8410 (I: 4138, C: 4272)	76	Mean 1.4 years	221/270	5.3% versus 6.3%	0.84 (0.71–1.00)
Bhasin et al. [70]	Pragmatic RCT	Community-dwelling older adults	5451 (I: 2802, C: 2649)	80	3.3 years	291/301	4.9/100 PY versus 5.3/100 PY	0.92 (0.80–1.06)[a]
Lamb et al. [71]	Pragmatic RCT	Community-dwelling older adults	9803 (I_1: 3301, I_2: 3279, C: 3223)	78	1.5 years	I_1: 173 I_2: 152 C: 133	I_1: 3.5/100 PY I_2: 3.1/100 PY C: 2.8/100 PY	1.30 (0.99–1.71)[a] 1.20 (0.91–1.59)[b]

Abbreviations: C, control group; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; I, intervention group; RaR, rate ratio; RCT, randomized controlled trial; RR, relative risk; T2D, type 2 diabetes.
[a]Multifactorial (including exercise) versus control (I_1 versus C).
[b]Exercise versus control (I_2 versus C).

Another meta-analysis of 20 trials found a similar effect of exercise compared to no exercise (RR, 0.74; 95% CI, 0.59–0.92 (Table 4, Fig. 3)), with individual RRs ranging between 0.19 and 3.00 [69]. Still, publication bias could not be ruled out and larger RCTs were requested. Another meta-analysis of 19 trials examined the effect of multicomponent exercise compared to no exercise on fractures in a larger number of community-dwelling older adults. The exercise was shown to have a small, borderline significant effect (RR, 0.84; 95% CI, 0.71–1.00 (Table 4, Fig. 3)) [31]. Again, the authors stated the need for larger RCTs before conclusions could be drawn. Finally, a recent individual-level patient data meta-analysis of four trials showed that exercise did not reduce fractures in older adults with dementia compared to no exercise (HR, 0.93; 95% CI, 0.47–1.85 (Table 4, Fig. 3)) [41]. There was no sign of publication bias, but the small number of trials and events suggest that larger RCTs are warranted.

Consequently, two very large pragmatic RCTs recently investigated the effects of fall prevention interventions on fractures in representative samples of older adults. The STRIDE Study was a pragmatic cluster-RCT conducted across 86 primary care practices in the United States that investigated the effectiveness of a multifactorial intervention for the prevention of serious fall injuries in community-dwelling older adults [70]. The primary outcome was time until first adjudicated serious fall injury, including fall-related fractures other than thoracic or lumbar vertebral fracture, joint dislocation and other injuries after a fall that led to hospitalization. Participants at increased risk of fall injury were randomized to an intervention group and a control group. The intervention group received a multifactorial intervention that lasted for up to 3.3 years and included assessment and recommendations for the management of risk factors (such as strength and balance), development of a personalized care plan to target specific risk factors and implementation of the care plan. The control group received enhanced usual care. Of all serious fall injuries, fractures accounted for two-thirds of cases. The results showed that the intervention did not reduce the risk of serious fall injuries (HR, 0.92; 95% CI, 0.80–1.06 (Table 4, Fig. 3)) [70]. A limitation of the study was that adherence to the behaviour part of the intervention, such as exercise for improving strength and balance, was not monitored. Thus, it cannot be ruled out that participants did not achieve sufficient exercise stimuli. On the other hand, the pragmatic design of the study reflects what effects can be expected in real-life settings, which together with the population-based representative sample increases the external validity of the findings from this study.

The PreFIT Study was conducted in 63 general practices across England and investigated the effect of advice by mail, screening for falls, and targeted interventions in community-dwelling older adults [71]. The primary outcome was the rate of fractures over 1.5 years, defined as fracture diagnosis at hospital admissions, emergency department and clinic visits. Participants were randomized to an advice-by-mail group, an exercise intervention group and a multifactorial intervention group. Participants in the advice-by-mail group received a booklet on fall prevention. Those in the exercise group were prescribed the Otago Exercise Program that included home-based exercises to improve strength and balance at least twice a week, and behaviour change strategies were used to promote intervention adherence. The multifactorial group received the same exercise program, as well as other components such as a professional assessment of fall risk, a home environment interview, a medication review, and home modifications. Participants in both intervention groups also received a validated fall-risk questionnaire. During follow-up, 86% of intervention participants improved or maintained their strength and 72% improved or maintained balance. Compared to the advice-by-mail group, neither the exercise (RaR, 1.20; 95% CI, 0.91–1.59) nor the multifactorial intervention (RaR, 1.30; 95% CI, 0.99–1.71) reduced the rate of fractures (Table 4, Fig. 3) [71]. The results were similar in a nested analysis of participants who were at increased risk of falls (RaR, 0.94; 95% CI, 0.65–1.35 and RaR, 1.26; 95% CI, 0.89–1.78) [71]. Important strengths of the PreFIT and STRIDE include the pragmatic design and the population-based representative sample, but data regarding intervention adherence was a limitation. In sum, although several meta-analyses have shown that exercise may reduce fall-related fractures in community-dwelling older adults, these are based primarily on studies reporting fractures as secondary outcomes or simple observations. Also, some of them could not rule out publication bias and all of them requested large RCTs to draw conclusions. In contrast, large pragmatic RCTs that have investigated the effects of

exercise or multifactorial interventions including exercise on a fracture as a primary outcome have failed to show a beneficial effect. Altogether, there is inconsistent evidence on exercise as a potent preventive measure against fractures on a population level and in real-world settings.

Why do the findings from RCTs differ from those of observational studies?

Based on observational research during the last 70 years, the paradigm that physical activity is crucial with respect to major NCDs and longevity is very strong. Thus, what could be possible reasons for the general lack of effect in RCTs? One explanation could be a lack of studies with adequate statistical power. However, the meta-analyses and individual RCTs that have shown a lack of effect of exercise on all-cause mortality include more than 36,000 participants and 3300 deaths from a variety of populations including general older adults, older adults with dementia, middle-aged individuals with coronary heart disease, heart failure and prediabetes. The results appear similar for CVD and cardiovascular mortality based on studies including more than 20,000 participants and 2500 events. Thus, altogether the results indicate that lack of studies is unlikely to be the primary reason for the lack of effects, at least not if discussing clinically relevant effects of more than 15% for the different exercise interventions tested with respect to the outcomes discussed above. Yet, in some selected studies, lack of statistical power remains a possible explanation for the lack of effect.

On the other hand, one contributing explanation for the strong associations found in observational studies could be reverse-causality bias, where the outcome affects the exposure rather than the opposite. This bias could be introduced when follow-up duration is short, in the presence of pre-existing disease, and when events occur shortly after baseline. Thus, low physical activity at baseline in some participants is caused by the pre-existing disease, or early onset of disease when an event occurs shortly after baseline, consequently leading to overestimated associations. Indeed, studies have shown that the associations between higher physical activity and lower all-cause mortality become weaker in conjunction with longer follow-up durations and when accounting for pre-existing disease through statistical adjustment or exclusion of these participants [72, 73]. Whilst these methods likely improve the potential to move closer to causal inference, there may be important residual or unmeasured confounding.

In light of the above, an even more plausible explanation for the strong associations found in observational studies is confounding through genetic pleiotropy, meaning that the same genes that influence physical activity in the individual also impact the outcome studied. In twin studies, about half of the individual differences in physical activity have been attributed to hereditary factors and the heritability of exercise participation has been estimated from 48 to 71% [74–76], with even higher estimates of 78% for objective measures of physical fitness [77]. Likewise, studies have shown a high heritability also for susceptibility to disease and longevity [78–80]. The lack of established causality between physical activity and CVD is further shown by mendelian randomization (MR) studies that have not been able to establish an association between genetically predicted accelerometer-measured physical activity and the risk of heart failure, coronary heart disease, myocardial infarction, and stroke [81, 82]. Another MR study found that whereas genetic predisposition to a variety of metabolic risk factors and smoking were associated with lower odds of longevity, there was no such association for genetically predicted self-reported physical activity [83]. Furthermore, although one twin study has found a single estimate of self-reported physical activity to be associated with reduced risk of all-cause and cardiovascular mortality in monozygotic twin pairs with discordant levels of physical activity [84], several other twin studies have shown other results. For instance, studies that have used either repeated estimates of self-reported physical activity or a single measure of objectively measured physical fitness have found no beneficial associations in relation to major NCDs or mortality in twin pairs with discordant levels of physical activity/fitness [85–87], further suggesting that genetic pleiotropy may influence the strong associations of physical activity with various diseases and mortality found in observational studies.

How does exercise affect risk factors for disease compared to medications?

The effects of drugs on incident CVD have been evaluated in detail in meta-analyses of RCTs. Specifically, one of the most important risk

factors for CVD is hypertension, and a meta-analysis of 123 trials comprising >613,000 participants showed that lowering systolic blood pressure by 10 mmHg reduces the risk of various CVD outcomes by 20 to 30%, whereas the overall risk of mortality is reduced by 13%, with even smaller effects in individuals with diabetes [88]. In this context, it is relevant that a network meta-analysis has shown that exercise lowers systolic blood pressure by 4.84 mmHg, whereas antihypertensive medication lowers systolic blood pressure by 8.80 mmHg [89]. Thus, from this comparison, the lack of detected effect of exercise on especially mortality seems reasonable. However, as the meta-analysis found that the interventions produced similar effects amongst hypertensive patients [89], it may be argued that exercise could reduce CVD and mortality in those with hypertension by lowering systolic blood pressure. Yet, the current RCT evidence presented in this review contradicts this hypothesis, as it shows no effect of exercise on CVD and mortality in populations where hypertension is highly prevalent, including older adults and people with coronary heart disease or heart failure. It remains possible that insufficient long-term compliance may have contributed to the lack of effects of exercise. It should also be noted that when the study population includes older individuals or people with chronic conditions who are at higher risk of disease, exercise needs to result in additive effects besides that of drugs used in the prevention of disease in routine medical care in order to become visible. Otherwise, the exercise-induced effect may become masked. Accordingly, in the Look AHEAD Study, an intensive lifestyle intervention including exercise failed to reduce the risk of CVD, despite effects on weight loss amongst overweight or obese individuals with T2D [49]. One of the explanations for this lack of effect included increased use of statins and effective routine medical management in individuals with T2D amongst general practitioners. The prevention of fractures using exercise is more complex as exercise interventions could increase balance and reduce the risk of falls [90], in addition to drugs that increase bone strength by increasing bone density [91]. It is therefore also of interest that small RCTs included in the meta-analyses, that have likely included more intensive interventions and with better compliance compared to the larger pragmatic RCTs, showed effects on the risk of fractures, which would be valuable even in the short-term for selected populations such as older hospitalized patients. However, part of this evidence could not rule out publication bias and was predominantly based on studies with fracture as a secondary outcome or observation. Thus, the null findings from large pragmatic RCTs in representative samples of older adults with longer follow-up and with fracture as a primary outcome indicate that the potentiality of exercise to reduce fractures on a population level is more uncertain and could relate to lack of compliance.

Summary and implications

In general, most people, whether experts or laymen, consider physical activity and exercise to be fundamental to overall health and longevity. Indeed, the strong associations shown in observational studies ubiquitously point in the same direction, seem biologically plausible and fulfill several of the criteria traditionally used when attempting to determine causality in epidemiological studies. However, based on current RCT evidence presented in this review, some of the commonly ascribed preventive effects of physical activity seem unsupported. Specifically, although exercise can prevent T2D assuming it is combined with dietary intervention, the current evidence shows that exercise does not prevent premature mortality or CVD, with inconsistent evidence for fractures. The shortcomings of the evidence include risks of publication bias, lack of high-quality studies in certain high-risk populations, and inadequate power in some separate studies. Therefore, additional large RCTs are warranted, especially with the primary outcome of fracture. These conclusions, which are based on the current evidence, do not stand in opposition with the fact that many people practice exercise for other reasons, such as for pure enjoyment, perceived well-being, or social interaction. Nevertheless, in the context of advancing the field, creating deeper knowledge and meaningful public health impact, continuous critical appraisal of the evidence is important. The opposing alternative, namely presuming observational evidence to be causal without considering its limitations as well as the RCT evidence, might endanger timely development and implementation of effective preventive measures of disease and premature mortality aimed at populations at the highest risk.

Conflict of interest

The authors declare that they have no conflict of interest.

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