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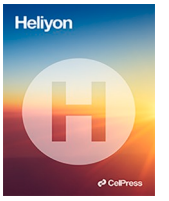

Research article

# Dose-response relationship between physical activity and frailty: A systematic review and meta-analysis

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A R T I C L E I N F O

*Keywords:*
Physical activity
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A B S T R A C T

*Objective:* Frailty is a significant public health issue facing aging societies and can be reduced by physical activity (PA), but the dose-response relationship between PA and frailty is not clear. This systematic review and dose-response meta-analysis aimed to assess the effect of PA on frailty in adults by aggregating data from observational studies.

*Methods:* PubMed, Embase, Web of Science, Cochrane Library, Scopus, SAGE Reference Online, SinoMed, CINAHL and CNKI were retrieved for articles published before May 2024. After quality evaluation, data on PA and the risk of frailty were extracted. Stata/MP 17.0 was used for dose-response meta-analysis.

*Results:* A total of 15 articles were included, involving 34,754 participants, including 4250 subjects with frailty or pre-frailty. The consequence of the dose-response meta-analysis revealed that compared with those who were not active at all, a 22 % (95 % CI, 16 %-28 %) reduction in the risk of frailty in individuals with 11.25 MET h/week of cumulative activity and a 55 % (95 % CI, 44 %-63 %) reduction in the risk of frailty in those with 22.5 MET h/week of cumulative activity; for higher activity levels (36.75 MET h/week), the risk of frailty was reduced by 68 % (95 % CI, 58 %-76 %) and continued to be reduced as PA volum increased.

*Conclusions:* There is a non-linear dose-response relationship between PA and frailty risk. Even small amounts of PA could reduce the risk of frailty. Meeting the minimum recommended PA target could reduce some risks, and doubling the recommended PA volumes could reduce most risks, which continue to increase as the volum of PA accumulates.

## 1. Introduction

Physical activity is defined as body movements generated by skeletal muscles that significantly increase energy consumption [1]. Regular physical activity improves physical function and bone health, reduces the risk of hypertension, coronary heart disease, diabetes, stroke, diabetes, various types of cancer and falls [2]. Physical inactivity is defined as failure to meet the World Health Organization's recommended threshold of moderate to vigorous physical activity lasting more than 10 min [3], Currently, approximately

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23 % of adults over the age of 18 are physically inactive globally [1], and the prevalence increases dramatically with age. Physical inactivity is also a vital risk factor for non-communicable diseases, for instance, cardiovascular disease (NCDs), cancer, diabetes and depression [4]. Frailty is a transitional state from healthy aging to disability. It is also a state of age-related decline in physiologic reserve function and stress adaptation, which in turn leads to increased vulnerability of the body [3]. The global prevalence of frailty is estimated to be between 12 % and 24 %, with more than 10 % of people aged 65 years or older suffering from frailty [4–6]. Studies have shown that frailty is a predictor of a variety of negative clinical events [7–12] and it is also associated with adverse outcomes, such as depression [13],loneliness [14],and sleep disorders [15]. Therefore, it is a crucial task to prevent and treat frailty under the background of aging society [16].

Several reviews [17–19] found that exercise training reduces frailty and enhancements the prognosis for frail older adults. There was a study showed that higher levels of PA were significantly associated with a reduced risk of frailty [20]. And a prospective cohort study showed a dose-response relationship between PA and of frailty, higher levels of physical are linked to a lower risk of frailty [21].

Due to the diversity of PA assessments and inconsistency in reporting, there is variability in the calculation of PA volumes. Harmonization of exposure estimates for PA is usually achieved by dichotomizing them [22,23,], but this approach leads to low efficacy of information utilization and fails to tell us about the dynamics of the risk of outcomes over a range of physical activity doses. However, previous studies have quantified PA through the use of more detailed exposure coordination and examined the relationship between physical activity and type 2 diabetes using dose-response meta-analysis techniques [24], which could clarify the risk of frailty at different PA doses.

As no study has synthesized the evidence by performing a dose-response meta-analysis using harmonized exposure estimates to characterize the strength or trend of the association. The present study demonstrated the effect of PA on frailty risk based on a dose-response meta-analysis, so as to provide new clues for implementing positive exercise strategies to prevent frailty.

## 2. Methods

### 2.1. Search strategy

Computer search:PubMed, Cochrane, Embase, Web of Science, Scopus, SAGE Reference Online, SinoMed, CINAHL and CNKI were retrieved. The search strategy consisted of words relating to PA (e.g., “physical activit* “,“exercise”, “resistance training”, “PA”) and Frailty (e.g., Frailty, Frailties, Frailness,” Frailty Syndrome”, Debility, Debilities, frail*, Faint, fragile, delicate). Specific search terms are provided in the supplementary information **(Supplementary Material, eMethod 1)**

### 2.2. Inclusion and exclusion criteria

Inclusion criteria:(1) study participants were adults; (2) reported 3 or more exposure levels; (3) reported RR, OR, or HR for prevalence of frailty.

Exclusion criteria: (1) studies reporting PA assessments with insufficient detail to estimate PA volume (measured as task metabolic equivalent (MET) h/week); (2) Missing important data did not support data transformation; (3) studies reporting PA as a binary variable; (4) duplicate data.

Two reviewers independently examined titles and abstracts based on the inclusion and exclusion criteria, performed an initial screening of the literature, and then independently assessed the full text of the studies to validate articles eligible for inclusion. A third reviewer was consulted if there was a difference in opinion about the articles included in the study. Any final disagreements encountered were resolved through discussion.

### 2.3. Data extraction and exposure coordination

Data extraction using a standardized extraction form, with 2 researchers working independently and a third researcher resolving disagreements. The content we extracted includes: general information (first author, year of publication, location, study name, sex, and age), study content (type of study design, sample size, follow-up years, method of frailty assessment, method and units of PA assessment, reported levels of PA exposure(PA type, frequency, intensity and duration), number of cases of frailty, and total number of individuals), and outcome indicators (effect sizes, 95 % CI, and analysis-adjusted covariates). For effect sizes, the outcome that controlled for the most confounders was extracted whenever possible. Outcomes from multiple cohorts in an original study will be treated as independent study results extraction. When the original article does not report data needed for exposure harmonization or meta-analysis, we used information already available in the original article for estimation and transformation of missing values (Supplementary Material, eMethods 2). When articles reporting HR or OR for PA and frailty, we assumed that HR approximates RR [25], and OR was converted to RR by calculating [26]. Cohort studies were evaluated using the Newcastle-Ottawa Scale (NOS) [27,28,], and cross-sectional studies were evaluated using The Agency for Healthcare Research and Quality (AHRQ) scale, the detailed grading rules are provided in the supplementary information **(Supplementary Material, eMethod 1)**.

At first, we harmonized group-level exposure estimates with a harmonized unit of MET h/week, permitting for the integration of PA accumulations of lasting longer than one week and PA of varying intensities. For specific intensity assignments of PA exposure categories, the mean intensities of MVPA and VPA were respectively defined as 4.5(or 3.5 marginal METs [mMETs]) and 8 METs (or 7 marginal METs [mMETs]) [29]. Studies reporting results for men only [30] were considered as separate findings. For studies reporting risk estimates using the highest dose group as the reference group, the reference group was transformed, and the risk estimates and 95

**Table 1**
Study characteristics and exposure harmonization.

| study | Country; study name | Participants (cases), No.[a] | sex | Age at baseline (years) | Follow-up (years) | Outcome subtype | study design | frailty assesment | Exposure harmonization (PA dose in MET h/week)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Peterson et al., 2009 | America | 2964(323) | both | 68–80 | 5 | frailty | cohort study | Gill frailty measure | Assume the frequency and duration of the activity content for each category reported in the article, using the midpoint of each category duration multiplied by intensity (mMET). |
| Savela et al., 2013 | Finland | 514(48) | male | 47.5(4.1) | 26 | frailty | cohort study | RAND-36 | Intensity is assigned according to the type of PA described in each category: light (3), moderate (4), and vigorous (8), multiplied by the midpoint of the duration category, and resting metabolic capacity is removed to obtain marginal metabolic capacity. |
| Graciani et al., 2016 | America | 1745(117) | both | 68.5(6.3) | 3.5 | frailty | cohort study | FP | Using the midpoint of each category duration multiplied by intensity (mMET). |
| Poli et al., 2016 | Italy | 542(82) | both | 75.2(6.3) | N/A | frailty | cross-sectional study | FRAIL scale | Assume the frequency and duration of the activity content for each category reported in the article, using the midpoint of each category duration multiplied by intensity (mMET). |
| Gil-Salcedo et al., 2020 | England | 6357(445) | both | 50(5) | 20 | frailty | cohort study | FP | Use the midpoint of the duration category multiplied by intensity (mMET). |
| Watanabe et al., 2020 | Japan | 3616(409) | both | 72.3(5.4) | N/A | frailty | cross-sectional study | FP | Using the midpoint of each category duration multiplied by intensity (mMET). |
| Kolehmainen et al., 2021 | Finland | 1041(227) | both | 56 (10.9) | 13.5 | frailty/ pre-frailty | cohort study | FP | Intensity is assigned according to the type of PA described in each category: light (3), moderate (4), and vigorous (8), multiplied by the midpoint of the duration category, and resting metabolic capacity is removed to obtain marginal metabolic capacity. |
| Zhao et al., 2021 | Japan | 482(45) | both | 70–74 | 3 | frailty | cohort study | Kaigo-Yobo Checklist | Assume the frequency and duration of the activity content for each category reported in the article, using the midpoint of each category duration multiplied by intensity (mMET). |
| Lefferts et al., 2021 | America | 427(36) | both | 72(6) | N/A | frailty | cross-sectional study | FP | Using the midpoint of each category duration multiplied by intensity (mMET). |

(*continued on next page*)

**Table 1** (*continued*)

| study | Country; study name | Participants (cases), No.[a] | sex | Age at baseline (years) | Follow-up (years) | Outcome subtype | study design | frailty assesment | Exposure harmonization (PA dose in MET h/week)[b] |
|---|---|---|---|---|---|---|---|---|---|
| Li et al., 2022 | China | 1458(295) | both | 72.38(7.28) | N/A | frailty | cross-sectional study | FI | Using the midpoint of each category duration multiplied by intensity (mMET). |
| Wang et al., 2022 | China | 6300(48) | both | 57.8 (9.2) | 10 | frailty | cohort study | FI | Assume the frequency and duration of the activity content for each category reported in the article, using the midpoint of each category duration multiplied by intensity (mMET). |
| Kheifets et al., 2022 | Israel | 601(82) | both | 74.6(6.2) | 12–14 | frailty | cohort study | FP | Using the midpoint of each category duration multiplied by intensity (mMET). |
| Saeki et al., 2023 | Japan | 255(52) | both | ≥65 | N/A | frailty | cross-sectional study | Kihon Checklist (KCL) | Assuming the duration of the activity content for each category, multiply the midpoint of each category duration by the intensity and frequency reported in the article (mMET). |
| Ding et al., 2023 | China | 436(84) | both | 60–85 | N/A | frailty | cross-sectional study | FP | Assume the frequency and duration of the activity content for each category reported in the article, using the midpoint of each category duration multiplied by intensity (mMET). |
| Saito et al., 2024 | Japan | 1218(430) | both | 74.0 (68.0–81.0) | N/A | frailty | cross-sectional study | Rockwood cumulative deficit approach | Assume the intensity and duration of the activity content for each category reported in the article, using the midpoint of each category duration multiplied by intensity (mMET). |

Abbreviations: Fried's phenotype, FP; frailty index, FI.
MET-h/week. Duration category refers to the description of physical activity duration in the article.
[a] :Cases of incident frailty/pre-frailty.
[b] :Volume category refers to the description of physical activity volume in the article, eg, <10, 10–20, and >20.

% confidence intervals was recalculated using the lowest PA category as the reference group. When the PA volume was not reported directly, the PA volume was calculated by multiplying the median or midpoint of the duration of the reporting category by its assigned classical MET value (MET h/week). When the duration of the highest exposure category was open-ended, the median of the category was assumed to be equidistant from the lower category boundary and half the width of the interval in the adjacent category [31]. For a study in which PA was reported as PA level (PAL, multiples of basal energy consumption represent relative values of physical activity intensity), an approximation of PA MET h/week was estimated using classical PA intensity for each category [32]. If only reported weekly treatment frequency, a single treatment duration of 45 min was assumed, and 30 min was assumed in the sensitivity analysis. Marginal PA volume (mMET h/week) was obtained by quantifying PA intensity minus resting metabolic volume. Dose allocation calculations are summarized in supplementary document (Supplementary Material,eTable 1). For pooled data, we subtracted 1 MET h from the total PA volume for each additional hour of reported time.

### *2.4. Statistical analysis*

Generalized least squares regression (GLS) was used to estimate study-specific dose-response association. Der Simonian-Laird squares regression model was used to combine study-specific dose-effect coefficients in the random effects model [33]. First, linear correlation was assumed; study-specific RR estimates were calculated separately for each 5 MET h/week PA increment and each 10 MET h/week PA increment and then combined. Restricted cubic spline for modeling the dose-response relationship between physical activity and incidence of frailty, and calculating the nonlinear *P* value by testing whether the second spline coefficient met the null

hypothesis($P < 0.05$ indicates that there is a nonlinear relationship). The nonlinear coefficients was estimated by the method-of-moments(MM). Four of the nodes were located at the 15th, 35th, 65th and 85th percentiles of physical activity volume [34]. All included studies that reported frailty risk estimates for at least three PA exposure categories were included in this model.

Heterogeneity was tested by the chi-square heterogeneity statistic $Q$ and the $I^2$ statistic [35]. For the $Q$ test, $P < 0.05$ was considered statistically significant; for the $I^2$ statistic, 25 %, 50 %, and 75 % $I^2$ values respectively reflected low, moderate, and high heterogeneity. Subgroup analyses involved study type, nationality, duration of follow-up, study quality, number of cases, and PA reporting method. Sensitivity analyses were performed with the leave-one-out method to assess the reliability and stability of the pooled results. Egger's test [36] was used to assess potential publication bias. $P < 0.05$ indicates publication bias in this study. All analyses were completed using Stata 17.0.

## 3. Results

### 3.1. Literature search

The flowchart of the literature screening is provided in supplemental document(eFig. 1). We retrieved 6069 independent studies, of which 5846 were excluded after title and abstract screening, leaving 223 studies for full-text evaluation. Based on the full-text evaluation, we additionally excluded 208 studies, ultimately identifying a total of 15 [30,37–50] eligible observational studies.

### 3.2. Characterization of included studies and evaluation of methodological quality

There were 7 cross-sectional studies and 8 cohort studies, and all included studies provided the required information (Table 1). The quality evaluation form can be found in the supplementary materials(eTable 2; eTable 3).

### 3.3. Non-liner dose-response analysis

A total of 15 data sets were included in the restricted triple spline analysis. The pooled RR for frailty was 89 % (95 % CI, 88%–91 %) with each 5 MET h/week increasement of PA, with significant heterogeneity ($I^2 = 80.6$ %; $P < 0.001$; Fig. 2); and the pooled RR for frailty was 80 % (95 % CI, 77%–82 %) with each 10 MET h/week increasement of PA, with significant heterogeneity ($I^2 = 77.2$ %; $P < 0.001$; Fig. 3). Dose-response meta-analysis plots (Fig. 1, Table 3) showed a notable nonlinear dose-response relationship, with greater risk reductions for moderate and high exposures compared to mild exposures. Overall, the frailty risk decreased with the accumulation of PA, but the rate of decline was first fast and then slow. The results of the cubic spline modeling indicated that characters who accumulated 11.25 MET h/week (equal to achieving the guideline recommendation of 150 min/week of activity at 4.5 MET) had a 22 % (95 % CI, 16 %-28 %) lower risk of frailty, relative to individuals who were completely inactive. Individuals who accumulated 22.5 MET h/week (equal to achieving the guideline recommendation of 150 min/week of activity at 4.5 MET twice as much) had a 55 % (95 % CI, 44 %- 63 %) lower risk of frailty. The reduction in the risk of frailty was most pronounced at increased activity levels of 11.25–22.5 MET h/week. For higher activity levels (more than 32.55 MET h/week), the risk of frailty continued to decline even after a 68 % (95 % CI, 58 %-76 %) reduction. Point risk estimates for the combined dose-response relationship of PA (MET h/week) and frailty are presented in Fig. 1.

### 3.4. Linear association between PA and frailty

We analyzed the results of the studies with longitudinal follow-up separately. Nonlinear tests of the six cohort studies using

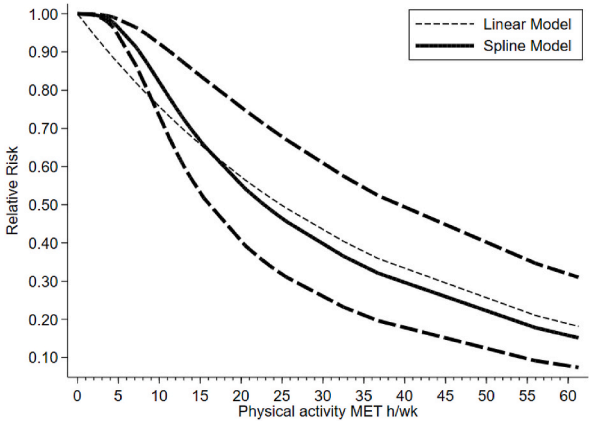


**Fig. 1.** Nonlinear dose–response association between physical activity and frailty modeled by using restricted cubic splines. MET indicates metabolic equivalent of task.

**Table 2**
Dose–Response Subgroup Analysis of Risk of Frailty With per 10 MET h/week of PA.

| Characteristics | PA MET h/wk (high vs low) | | | |
|---|---|---|---|---|
| | n | RR (95 % CI) | $I^2$ | *P* Value |
| All studies | 15 | 0.80(0.77–0.82) | 77.2 | 0.000 |
| Study type | | | | |
| Cohort | 6 | 0.74(0.71–0.78) | 0 | 0.000 |
| Cross sectional | 9 | 0.87(0.83-0.91) | 77.0 | 0.000 |
| Nationality | | | | |
| American | 3 | 0.89(0.83–0.96) | 74.5 | 0.002 |
| Finland | 3 | 0.74(0.65–0.84) | 0 | 0.460 |
| Japanese | 4 | 0.76(0.68–0.84) | 84.5 | 0.000 |
| China | 3 | 0.79(0.76–0.82) | 87.2 | 0.000 |
| Other | 3 | 0.66(0.56–0.97) | 0 | 0.588 |
| Follow-up | | | | |
| <10 y | 3 | 0.91(0.85–0.97) | 60.0 | 0.082 |
| ≥10 y | 5 | 0.75(0.71–0.78) | 0 | 0.641 |
| Study quality | | | | |
| High | 12 | 0.81(0.78–0.83) | 76.6 | 0.000 |
| Medium or low | 3 | 0.65(0.58–0.73) | 32.4 | 0.228 |
| Cases | | | | |
| <1000 | 7 | 0.79(0.71–0.88) | 65.7 | 0.008 |
| ≥1000 | 8 | 0.80(0.77-0.82) | 84.1 | 0.000 |
| PA MET h/wk | | | | |
| Reported | 6 | 0.81(0.78–0.83) | 85.4 | 0.000 |
| Assigned | 9 | 0.75(0.70–0.81) | 61.1 | 0.012 |
| Frailty assesment | | | | |
| Freid | 2 | 0.68(0.57–0.81) | 68.1 | 0.529 |
| FI | 2 | 0.79(0.76–0.82) | 93.6 | 0.000 |
| FP | 5 | 0.69(0.62–0.76) | 48.8 | 0.099 |
| Other | 6 | 0.88(0.83–0.93) | 68.1 | 0.008 |

PA, physical activity; RR, relative risk; MET, metabolic equivalent of task; FP Fried's phenotype; FI frailty index.

**Table 3**
Comparison of predicted relative risk (RR) point estimates for frailty in nonlinear outcomes.

| PA MET h/week | RR | 95%CI |
|---|---|---|
| 4.5 | 0.98 | 0.96–0.99 |
| 7.5 | 0.9 | 0.85–0.96 |
| 11.25 | 0.78 | 0.67–0.90 |
| 15.5 | 0.66 | 0.52–0.83 |
| 22.5 | 0.50 | 0.36–0.72 |
| 32.5 | 0.37 | 0.23–0.57 |
| 36.75 | 0.32 | 0.20–0.52 |
| 56 | 0.18 | 0.09–0.35 |

restricted cubic spline resulted in a linear association ($P = 0.08$), so both linear and nonlinear dose-response association analyses were performed for the six cohort studies included. The linear results (Fig. 4, Table 4) showed a 26 % (95 % CI, 22 %-29 %) reduction in the risk of frailty for per 10 MET h/week increase in PA and a 14 % (95 % CI, 12 %-16 %) reduction in the risk of frailty for per 5 MET h/week increase in PA. The results of the nonlinear analysis approached the linear results.

### *3.5. Subgroups, sensitivity analysis, and publication bias*

To investigate the origins of heterogeneity, we conducted subgroup analyses by study type, nationality, follow-up years, study quality, number of cases, PA reporting method and frailty assessment method (Table 2). Overall, this correlation was consistent across most subgroups. There was no heterogeneity between the subgroups in China and the other regions (Israel, UK, and Italy). Heterogeneity did not change significantly in other subgroup analyses.

Since some information was not directly available, assumptions related to the PA intensity or duration of were used in the dose allocation process, and sensitivity analyses were performed to assess the impact of these assumptions on this study. The activity duration was assumed to be 0.5 h/session, and the mean intensity of MVPA and VPA were respectively defined as 3.5 and 7 marginal MET [mMET]. If the intensity or duration were assumed to be larger in the original study, the benefit for a given exposure would be smaller, so these assumptions are necessary. Leave-one-out sensitivity analyses did not reveal any outliers (Supplementary Material, eFig. 3, eFig. 4). Egger's test did not identify publication bias (Supplementary Material, eFig. 2).

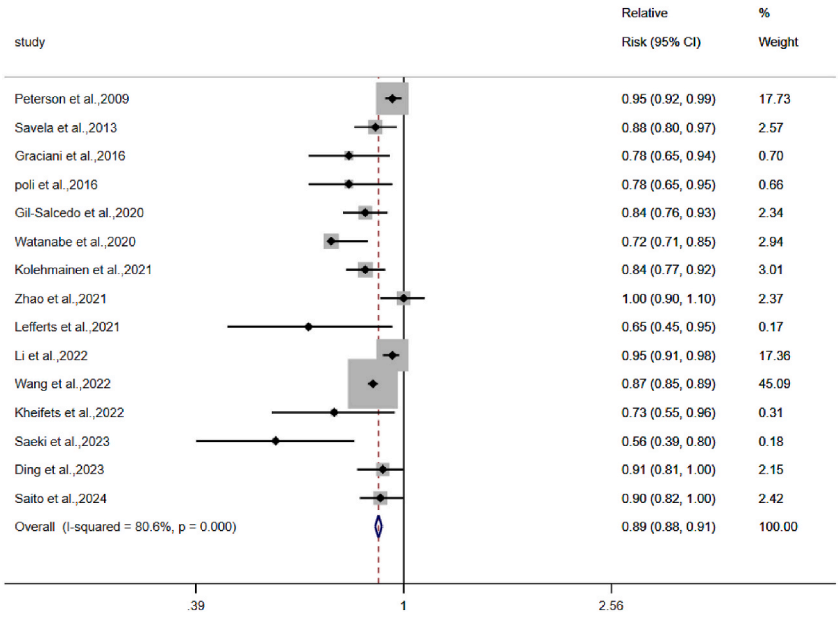


**Fig. 2.** Forest plot of study-specific relative risk statistics for frailty per 5 metabolic equivalent of task (MET) h/week increment of physical activity (PA).

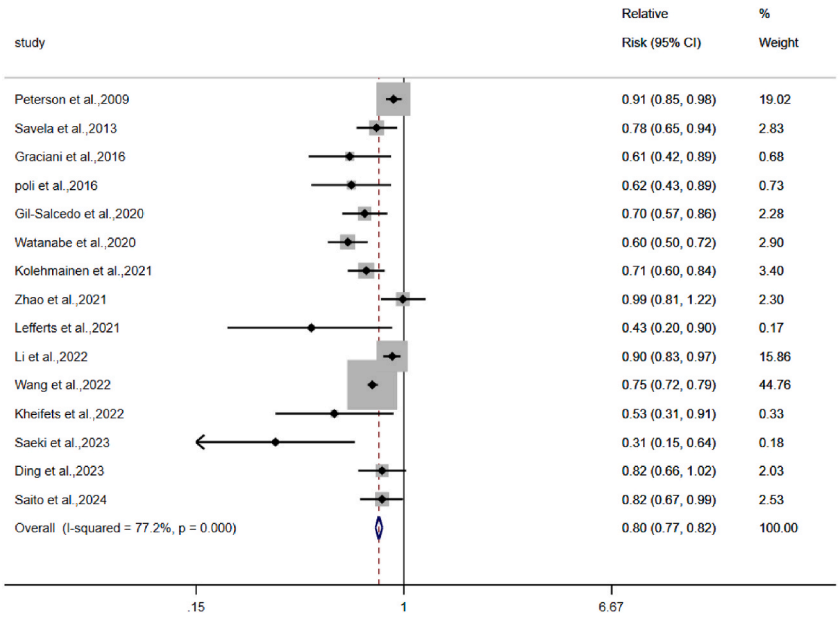


**Fig. 3.** Forest plot of study-specific relative risk statistics for frailty per 10 metabolic equivalent of task (MET) h/week increment of physical activity (PA).

## 4. Discussion

Currently, numerous studies have investigated the correlation between different forms of physical activity and frailty, and a cross-sectional study have also analyzed the dose-response relationship between physical activity and sedentary time and the risk of frailty. The World Health Organization recommends 150–300 min of moderate physical activity or 75–150 min of vigorous physical activity per week [51]. Our findings indicated that the greatest change in risk was achieved at the recommended physical activity doses, suggesting that most of the effects can be realized when individuals move from inactivity to regular physical activity. Our results found that individuals who accumulated 11.25 MET h/week (1time the recommended dose) had a 22 % lower risk of frailty. Individuals who accumulated 22.5 MET h/week (twice the recommended dose) had a 55 % reduced risk of frailty. And, as physical activity volum

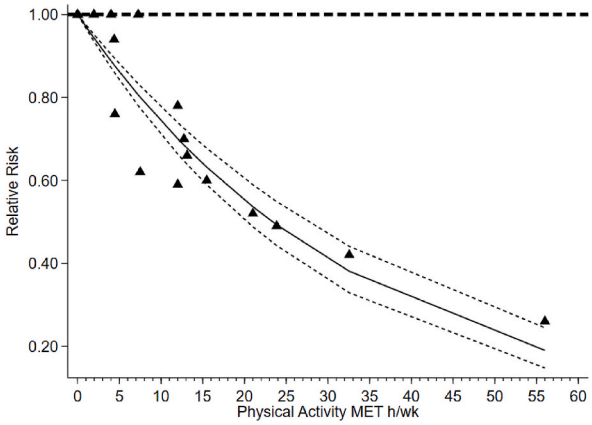


**Fig. 4.** Linear dose–response association between physical activity and frailty modeled by using restricted cubic splines. MET indicates metabolic equivalent of task.

**Table 4**
Comparison of predicted relative risk (RR) point estimates for frailty in linear outcomes.

| PA MET h/week | RR | 95%CI |
|---|---|---|
| 7.5 | 0.80 | 0.77–0.83 |
| 12.5 | 0.69 | 0.65–0.73 |
| 21 | 0.54 | 0.49–0.59 |
| 32.5 | 0.38 | 0.33–0.44 |
| 56 | 0.19 | 0.15–0.24 |
| RR per 1 MET h/week | 0.97 | 0.97–0.98 |
| RR per 5 MET h/week | 0.86 | 0.84–0.88 |
| RR per 10 MET h/week | 0.74 | 0.71–0.78 |

increases, the risk of frailty continues to decline at a slightly slower rate. However, a separate analysis of the longitudinal follow-up results extracted from the six cohort studies revealed that the risk of frailty gradually decreased with increasing physical activity. The two dose-response meta-analyses showed inconsistent results, with the nonlinear results showing a higher risk of frailty than the linear results when individuals had less than the recommended amount of PA (less than 11.25 MET h/week) and a slightly lower risk of frailty than the linear results when individuals met the recommended amount of 2 times the recommended amount of PA.

Previous systematic reviews have sought to assess the effectiveness of physical activity/exercise training interventions in improving frailty levels or progression in middle-aged and older adults, or the association between sedentary behavior and frailty [52,53]. Due to the difficulty of achieving structured exercise and the fact that life-based physical activity is easier for most people to achieve, our study does not adhere to a fixed form of PA, but rather quantifies various types of physical activity. Previous meta-analysis have shown that higher levels of PA are significantly associated with a reduced risk of frailty demonstrating a dose-response relationship [20]. However, this connection is only reflected at the PA level, and PA has not been quantified. So unlike existing studies, we synthesized observational studies on PA and frailty to observe trends in the risk of frailty with the amount of PA. We directly modeled the dynamics of frailty risk over a range of physical activity volumes, using a continuous variable rather than a crude categorization. We also found that even less amounts of exercise were effect, and we further quantified the discrepancy in risk at these doses, providing a new basis for more people to choose the appropriate volume of physical activity.

Our findings suggest a lower risk of frailty at moderate or high physical activity volume compared to low physical activity volume, which is consistent with the findings of a 10.5-year long follow-up study [22]. Similarly, another andomized controlled trial found that moderate-intensity exercise had the best effect on improving frailty [54]. However, the efficacy of interventions with different intensities of exercise for frail elderly adults is controversial. A 2-year follow-up study of community-dwelling frail elderly adults found that moderate-intensity physical activity reduced sedentary time oof elderly people, it did not significantly improve their frailty status [55]. This may be relevant to the diversity of assessments of physical activity.

In recent studies, decreased step counts and increased sedentary behavior have been demonstrated in frail populations [56,57], while physical inactivity may lead to increased metabolic resistance to muscle synthesis, which in turn causes muscle atrophy and impaired muscle mass [57]. From a genetic point-view, regular exercise can lead to characteristic changes in the epigenetics of skeletal muscle, especially genes related to muscle growth and metabolism [58]. According to the Cycle of Frailty model, sarcopenia is the central pathological basis for the onset and progression of frailty; therefore, management of frailty through physical activity is a priority. In addition, physical inactivity may also contribute to cardiovascular dysfunction in frailty , and it has been found that low left ventricular ejection function in frail populations is associated with PA [59], possibly due to myocardial atrophy induced by the reduction in PA [60], and myocardial atrophy, in turn, adversely affects left ventricular function, which is a bidirectional relationship.

And sedentary behavior is associated with atherosclerosis in the frail population, which may also result from reduced PA [61], with blood flow slowing down during sedentary times and further impairment of endothelial function in hardened vessels [62]. One more point, meta-analysis and a large number of observational studies have shown a positive effect of regular physical activity in reducing inflammation [63–65]. The underlying mechanism is that physical activity accelerates fatty acid oxidation in skeletal muscle and reduces fat mass [66]. A systematic review revealed a strong association between obesity and the incidence of frailty [67], with the underlying mechanism being that physical inactivity leads to an accumulation of visceral fat [68] and a higher uptake of hepatic free fatty acids[69], which reduces an individual's endurance and vitality, but this is a finding in non-frail populations, and the mechanism of occurrence in frail populations needs to be further explored. Overall, physical activity can have a multifaceted effect on ameliorating frailty, however most current exercise interventions have focused on the effects of different exercise modes, intensities, durations and frequencies on frail older adults, and the optimal exercise modes are yet to be fully determined. The results of our study may inform the selection of appropriate activity volum.

Subgroup and sensitivity analyses showed that the protective effect of PA on frailty was similar whether the method of PA assessment, and that PA was significantly protective against frailty regardless of the method of frailty assessment. PA and frailty also has reciprocal relationships. Previous studies have shown that the risk of reverse causality affecting outcomes is limited by longer follow-up times, but may also bring in regression dilution bias, as true changes in physical activity during follow-up can lead to exposure measurement error [70]. However, in our subgroup analyses, the association of PA with frailty was not found to be reduced in studies reporting longer follow-up time, possibly because we did not include results using two and more PA measures.

The following strengths exist in our meta-analysis. First, this study quantified physical activity and transformed categorical data from the original study into continuous data. PA exposure dose expressed as MET h/week, which is a method that allows for the aggregation of exposures characterized by different intensities and durations, and it is a suitable method for achieving data harmonization. Second, we simultaneously analyzed the possible linear and nonlinear dose-response relationships between PA and frailty to refine the risk of frailty at different doses as much as possible.

## 5. Limitations

Our study also has some potential limitations. With the exception of two studies that used three-axis accelerometer to measure step counts, almost all PA exposures were measured by self-report questionnaires. Because questionnaires have inherent measurement error and recall bias, PA levels of some study participants may be misclassified. In the 15 included studies, low, medium and high levels of PA were defined differently, PA frequency, intensity and duration were measured differently, and in most cases we categorised the different types of PA reported (total physical activity, leisure time physical activity, physical activity level, walking, gardening) as total physical activity. In addition, the MET is assigned at the study level but no at the individual level, so it is not possible to accurately assess the PA dose that should be achieved to reduce the risk of frailty. Thus the results we obtained may have led us to underestimate the effect of PA on reducing the risk of frailty. In most individuals, especially in the frail population, it is difficult to achieve structured physical activity, which poses an obstacle to the implementation of interventions and measurements. Therefore, the use of cumulative activity that incorporates more than one type of physical activity would be more representative of the actual activity of the majority of individuals. In future studies, emphasis should be placed on the measurement of total physical activity. In addition, our study had relatively limited data at higher doses, it is necessary to objectively measure PA volume by more advanced equipment and obtain a wider range of exposure in the future.

## 6. Conclusions

As demonstrated in this article, physical activity is protective against frailty. Suggesting that partial benefits can be realized even when individual physical activity levels or physical activity volume are lower than recommended for public health. Additional benefits can be achieved by meeting minimum recommended targets, which continue to increase as the amount of PA accumulates. In the nursing practice of the frailer population, it is still the most simple, economical and effective measure to encourage the increase of physical activity. It is of great significance to improve the health status of the frail elderly, reduce the occurrence of adverse outcomes and the cost of health care, and promote healthy aging. In future studies, the assessment of PA should be diversified to assess the activity level of individuals as comprehensively and objectively as possible. And dose response meta-analysis can be carried out for different populations to improve the pertinence and accuracy of the conclusions.

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## Data availability statement

No data was used for the research described in the article.

## Ethics statement

Informed consent is not required for this study because this article is a systematic review and meta-analysis, which is a review and analysis of data from published observational studies.

## CRediT authorship contribution statement

**Hui Chen:** Writing – review & editing, Writing – original draft, Software, Methodology, Data curation. **Meng-Cheng Cheng:** Data curation. **You Sun:** Data curation. **Yan-Qin Zhu:** Methodology. **Li-Xin Sun:** Methodology. **Yu-Xuan Zhang:** Software. **Bin-Bin Feng:** Software. **Guo-Cui Wu:** Writing – review & editing, Writing – original draft, Software, Methodology, Data curation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e33769.

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