Physical activity and the risk of frailty among community-dwelling healthy older adults
A protocol for systematic review and meta-analysis

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Abstract
Background: Frailty has become one of the biggest challenges in facilitating healthy aging. Our study aims to investigate the association between physical activity and the risk of frailty, meanwhile, conduct a dose–response to observe the relationship between physical activity volume and frailty.

Method: We will systematically search six databases to identify cohort studies assessing the association between physical activity and risk of frailty. Risk of bias of individual study will be assessed using the Newcastle–Ottawa Scale. Data will be analyzed by using STATA V.12.0.

Results: The results of this study will be published in a peer-reviewed journal.

Conclusion: We will first investigate whether specific-physical activity reduce the risk to onset frailty in healthy older adults. However, predictable heterogeneity may exist in our study because of the inconsistent definitions of frailty.

Keywords: community-dwelling older adults, dose-response, frailty, meta-analysis, physical activity, protocol

1. Introduction

Population is continually growing older at an unprecedented rate throughout the world in recent centuries. According to a new report, this percentage is projected to jump to nearly 17% of the world’s population by 2050 (1.6 billion).[1] Although aging means prolongation of life expectancy, some problems have been raised at the same time, including the increase of social security costs and healthcare costs, decrease of labors, and how to keep older adults’ capacity to function well and live independently. Healthy aging has become an extremely challenging public health issue.

Frailty is defined as a geriatric syndrome resulted from the declines of multiple physiological systems, has become one of the biggest challenges in facilitating healthy aging.[2,3,4] It is often characterized by marked vulnerability to adverse health outcomes, including falls, fractures, disability, hospitalization, long-term care, and death.[3,5] The prevalence of frailty among population aged over 65 years old has been reported to range from 4% to 16% in the United States, and the prevalence is higher in patients with cancer (42%) and in nursing homes (52.3%).[6–10]

Exercise is believed to be the most effective management in older adults to improve quality of life and functionality.[11] Regular physical activity has been estimated to reduce and postpone several adverse health outcomes in older adults with frailty, which include functional performance, cognitive impairment, sarcopenia, and depression.[12,13] Recently, several systematic reviews focusing on frailty topic have been published, most of them aim to assess the effectiveness of physical activity/exercise training on adverse health consequences for older adults with frailty, or on the level or progression of frailty.[14–18] For example, Puts’s review focused on different interventions to prevent or reduce the level of frailty.[16] Apostolo’s review investigated the prevention of interventions on pre-frailty and frailty progression,[18] and Jadczak’s meta-analysis aimed to assess the effectiveness of interventions on physical function in frail older people.[17] Obviously, none of them focused on the physical activity and the risk to onset frailty in healthy older adults. An epidemiological study showed that physical activity (walking, jogging, hiking or dancing) could reduce the risk of disability in older adults compared to sedentary.[19] Cross-sectional studies showed that physical activity was associated...
with lower incidence of frailty.\textsuperscript{[20,21]} Savela’s cohort study showed that high-intensity physical activity was associated with a decreased risk of both frailty and pre-frailty in initially healthy people.\textsuperscript{[22]}

Our systematic review and meta-analysis will synthesis all available evidence, aims to investigate the association between specific types and intensity of physical activity and the risk of frailty in health older adults, and then to explore the possible dose-response relationship between physical activity volume and frailty.

2. Method

Our study protocol has been registered on the international prospective register of a systematic review (PROSPERO). The registration number was CRD42018090277. The systematic review protocol was planned and performed adherence to Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) statement.\textsuperscript{[23]}

2.1. Ethic statement

Ethics approval and patient consent are not required because this study is a meta-analysis based on the published cohort studies.

2.2. Search strategy

We will systematically search PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, Web of science, CBM (Chinese Biological Medical Database), and CNKI (Chinese National Knowledge Infrastructure). There will be no restrictions on publication date and publication language. We have conducted a comprehensive search strategy with the help of a search specialist and will update the search in July 2019. A detailed search strategy can be found in Supplemental Digital Content (Appendix 1), http://links.lww.com/MD/D197.

2.3. Inclusion and exclusion criteria

We will include studies met the following criteria:

1. study design: longitudinal cohort studies (retrospective or prospective), a secondary analysis of randomized control trials;
2. participants: community-dwelling older adult (aged ≥ 65);
3. exposures: specific-types of physical activity (include leisure-time, transportation, occupational, household, sports, daily/family/community activities, and exercise), intensity and volume of physical activity;
4. outcomes: reporting at least one variable adjusted results of odds ratios (OR), or hazard ratios (HR), or risk ratios (RR) with the 95% confidence intervals (CI);
5. others: reporting any quantitative measures of physical activity. We will exclude abstract without detailed data, and reviews.

2.4. Physical activity intensity and volume

Intensity of physical activity will be classified as (1.6–2.9 metabolic equivalents (METs), <40% maximum heart rate (HRmax), or <40% maximum oxygen uptake (VO2max)); moderate (3–5 METs, 50–60% HRmax or 50–60% VO2max); vigorous (≥6 METs, 70–80% HRmax, or 70–80% VO2max). The volume of physical activity usually was measured in inconsistent methods, including METs × minutes / hours per week, kcal of energy expenditure, hours per week, and other methods. All of those measures will be included in our study.

2.5. Study selection

Our search records will be imported into “Rayyan”\textsuperscript{[24]} which is an online literature management platform. In order to ensure high inter-rater reliability among the reviewers, a pilot-test will be performed firstly. If the agreement among reviewers is not acceptable (Kappa <80%), we will perform multiple rounds calibration exercises. Then paired reviewers (SM, HLL, YHW, HC) will independently screen the title and abstract of all the records according to eligibility criteria. Any potentially relevant records will move to full-text screening. Any conflict will be resolved by discussing. In order to illustrate the study selection process, we will also adherence to PRISMA guidelines to form a flow diagram.\textsuperscript{[25]}

2.6. Data extraction

We will use Microsoft Excel 2010 to conduct a standard data abstraction sheet to collect data of interest. Paired reviewers (SM and HLL, YHW and HC) will extract the following data: the first author, year of publication, study name, country in which study were conducted, sample size, follow up period, mean age, exposures, physical intensity (reported as MET, HRmax, VO2max), physical activity volume (reported as either MET-hours/minutes per week or kcal of energy expenditure), frailty assessment scales, physical activity assessment scales, relative risk estimates (hazard ratio (HR), risk ratio (RR), and odds ratio (OR)) with the 95% CI, and variables adjusted for in the study. Any conflict will be resolved by discussing.

2.7. Risk of bias assessment

Risk of bias of included studies will be assessed according to the Newcastle–Ottawa Scale (NOS)\textsuperscript{[24]} including 3 subscales as follows:

Selection
1. representativeness of the exposed cohort;
2. selection of the non-exposed cohort;
3. ascertainment of exposure;
4. demonstration that outcome of interest was not present at start of study.

Comparability
1. comparability of cohorts on the basis of the design or analysis
2. adjustment of confounders in the analysis.

Outcome
1. assessment of outcome;
2. was follow-up long enough for outcomes to occur;
3. adequacy of follow up of cohorts.

We will consider studies with scores of less than 4 to have a high risk of bias, those with scores of 4 to 6 a medium risk of bias, and those with scores of 7 or more a low risk of bias.\textsuperscript{[25]} The risk of bias assessment will be assessed by paired reviewers (BP and HLL), and conflict will be resolved by a third reviewer (JCW).
We will use STATA V.12.0 software (Stata Corporation, College Station, TX) to conduct our meta-analysis. We will consider unadjusted and adjusted measures of effect separately. We will first pool ratio measures of effect including HR, RR, and OR using random effects model. Then, we plan to perform a sensitivity analysis using only studies that reported time-to-event data (HR) to observe the robustness of the results.\(^{27}\) Dose-response analysis will be conducted to investigate the relationship between physical activity volume and frailty risk by using generalized least squares trend estimation to computing regression slopes (trends) across different physical activity levels.\(^{28}\) Heterogeneity of treatment effects across trials will be assessed using the Q test with the DerSimonian-Laird method, and quantify heterogeneity using I\(^2\) statistics. We will consider 25%, 50%, and 75% as low, moderate and high 25%, 50%, and 75% heterogeneity, respectively.\(^{29}\)

### 2.9. Subgroup analysis

In order to examine the effect of study-level variables on the association between physical activity and frailty, we will perform a priori subgroup analysis if there are more than 2 studies for each subgroup factor.\(^{30}\) We will consider the following effect modified factors: age, gender, adjustment for confounding factors, risk of bias, and types of physical activity. In addition, we will classify the definition of frailty into stricter and less strict based on the reporting of included studies.

#### 2.10. Publication bias

We will draw a funnel plot to identify the possibility of publication bias using STATA V.12.0 software (Stata Corporation, College Station, TX).

### Author contributions

Conceptualization: Bei Pan, Jiancheng Wang. Investigation: Bei Pan, Hong Li Li, Yun Hua Wang, Min Sun, Hui Cai. Methodology: Bei Pan, Hong Li Li. Project administration: Hong Li Li, Yun Hua Wang, Min Sun. Writing – original draft: Bei Pan. Writing – review & editing: Bei Pan, Hong Li Li, Yun Hua Wang, Min Sun, Hui Cai, Jiancheng Wang.

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