INPLASY PROTOCOL

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Review Stage at time of this submission: **Risk of bias assessment.**

Conflicts of interest:
None declared.

Role of physical activity and sedentary behavior in venous thromboembolism: A systematic review and dose-response meta-analysis

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Condition being studied: **Venous thromboembolism will be studied.**
Eligibility criteria: **The following criteria will beused to determine if a study is eligible for inclusion: (1) the study design is cohort, case control or cross-section studies to assess the relationship between PA or sedentary behavior and VTE; (2) reported effect estimates as hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) with 95% confidence intervals (CIs); (3) The exposures of interest were physical activity or sedentary behavior. If the data of multiple articles come from the same study, we chose the articles which reported the most informative PA level or the largest sample size.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 15 May 2023 and was last updated on 15 May 2023 (registration number INPLASY202350059).

INTRODUCTION

Review question / Objective: **Among the modifiable factors, physical activity (PA) is one of the main lifestyle related factors for VTE that individuals are exposed to daily. Accumulating studies focus on the potential role of PA in the development of VTE, however, the benefits of PA for VTE is an ongoing debate. One meta-analysis of prospective studies have suggested that compared with people with the lower levels of PA, those with higher PA level had 13% (95% CI 5%-21%) lower odd of developing VTE, while another review without the meta-analysis provides diverging results as to the association between high levels of PA and risk of VTE. Furthermore, several**

additional studies have since been published on the association, and the findings have been mixed in the absence of an update and comprehensive systematic review and meta-analysis. Accurate estimates of the dose-response association between PA and VTE risk may be useful to promote awareness of VET and guide decisions at policy level. Nevertheless, existing reviews estimated PA exposure by using binary categorization, but this approach results in loss of information on PA doses and does not provide the variation in VTE risk across a range of PA doses.

Sedentary behavior is a highly prevalent behavior in our daily lives, which is related but distinct from physical inactivity, considering that someone can meet the PA recommendations despite being highly sedentary throughout the remaining waking hours. Some previous studies found that the associations between sedentary behavior and clinical health outcomes are independent of PA. Available literature that prolonged sitting may cause vein compression, which reduces blood flow and thereby increases the risk of VTE. There are public health PA recommendations internationally, while there was insufficient evidence to quantify a sedentary behavior threshold. And it remains unclear if increasing PA alone is sufficient for prevention of VTE or whether reductions in sedentary behavior are also required. It is noteworthy that the association between sedentary behavior and VTE have not reported systematically yet, which is required to inform public health guidelines.

To bridge the knowledge gap, we conducted an update and comprehensive systematic review and meta-analysis to investigate the shape of dose-response associations between PA and sedentary behavior with VTE. We also further explore whether the relationships of these two exposures with VTE are independent after mutually adjustment.

Condition being studied: Venous thromboembolism will be studied.

METHODS

Participant or population: The exposures of interestVenous Thromboembolism.

Intervention: Higher level of physical activity and sedentary behavior.

Comparator: Lower level of physical activity and sedentary behavior.

Study designs to be included: The study design is cohort, case control or cross-section studies to assess the relationship between PA or sedentary behavior and VTE.

Eligibility criteria: The following criteria will beused to determine if a study is eligible for inclusion: (1) the study design is cohort, case control or cross-section studies to assess the relationship between PA or sedentary behavior and VTE; (2) reported effect estimates as hazard ratios (HRs), odds ratios (ORs), or relative risks (RRs) with 95% confidence intervals (CIs); (3) The exposures of interest were physical activity or sedentary behavior. If the data of multiple articles come from the same study, we chose the articles which reported the most informative PA level or the largest sample size.

Information sources: A comprehensive search was conducted from electronic databases including PubMed, Web of Science and Embase from inception to February 28, 2023. Besides, the references list of relevant articles and reviews were also searched manually.

Main outcome(s): The exposures of outcome is venous thromboembolism.

Quality assessment / Risk of bias analysis: New-castle-Ottawa scale was used to evaluate the study quality of cohort and case-control study.

Strategy of data synthesis: All statistical analyses will be executed by STATA version 12 (Stata Corp, College Station, Texas, USA). For categorical meta-analysis, the ORs and 95%CIs will be pooled for highest vs. lowest category of PA and sedentary behavior. Cochran Q test and I2 are used to

test the heterogeneity. P<0.1 is considered as statistical significantly for Q statistic. The value of I2 ranged from 0% to 25% is considered as no heterogeneity, I275% are considered as low, moderate and high heterogeneity, respectively. Fixed effects model wis used if I2<50%, or else, the random effects model is employed. Potential publication bias is tested by Begg's test, Egger's test and funnel plots, the results are considered to indicate publication bias when P<0.1 for tests or the existence of asymmetry in the funnel plot. Studies with at least three exposure categories will be included in dose-response analyses. Dose-response relationship are estimated by using the Greenland and Longnecker and Orsini. Generalized least-squares (GLS) regression will be used to evaluate the linear dose-response relationship between MET or sedentary time and VTE.

Subgroup analysis: Subgroup analyses by potential factors will be performed.

Sensitivity analysis: Sensitivity analyses will be adopted to assess the stability of results by excluding one study at a time.

Country(ies) involved: China.

Keywords: physical activity, sedentary behavior, venous thromboembolism.

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