**Device-measured light-intensity physical activity and mortality: A meta-analysis**


**Running Head:** Light physical activity and mortality

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1     **Device-measured light-intensity physical activity and mortality: A meta-analysis**

2                                                    **Abstract**

3     **Introduction:** The association of light-intensity physical activity (LPA) with mortality is poorly

4     understood. This meta-analysis of cohort studies aimed to examine the dose-response

5     relationships between daily device-measured LPA and mortality in adults aged 18 or older and to

6     explore whether the associations were independent of moderate-to-vigorous physical activity

7     (MVPA).

8     **Methods:** Searches for prospective cohort studies providing effect estimates of daily LPA

9     (exposure) on all-cause mortality (outcome) were systematically undertaken in electronic

10    databases up to 30 April 2019. Subgroup analyses and meta-regression analyses with

11    random-effects models were performed to quantify the dose-response relationships between

12    daily LPA and mortality. Sensitivity analyses were also conducted to assess the stability of the

13    results.

14    **Results:** A total of 11 studies were included in the meta-analysis. Analyses contained 49,239

15    individuals (mean age 60.7, SD = 13.6) who were followed up for a mean 6.2 years $(2.3-14.2$

16    years), during which 3,669 (7.5%) died. In comparison with the reference group (< 3 hours/day),

17    the pooled HRs (and 95% CIs) of mortality were 0.71 $(0.62-0.82)$, 0.68 $(0.59-0.79)$, 0.56

18    $(0.44-0.71)$ for groups $3-<5$ hours/day, $5-<7$ hours/day, and more than 7 hours a day LPA

19 respectively. Meta-regression models indicated that there was a log-cubic dose-response

20 relationship between daily LPA and mortality in adults and older people, independent of MVPA.

21 **Conclusions:** Time spent in daily LPA was associated with reduced risks of mortality in adults

22 and older people. These data support the inclusion of LPA in the future physical activity

23 guidelines.

24 **Keywords:** LIPA, Meta-regression, Review, Guideline, Recommendation

## 1 INTRODUCTION

International physical activity guidelines suggest that adults aged 18 or older should engage in at least 150 min of moderate-intensity aerobic physical activity, or at least 75 min of vigorous intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity [1-3]. Research has tended to focus on moderate-to-vigorous physical activity (MVPA) (i.e. approximately ≥ 3 metabolic equivalents [METS]), although there is a lack of evidence on health benefits of light physical activities (LPA) (i.e. activities ranging between 1.5 -< 3 METS) such as casual walking, lifting lightweight objects, light household chores or yard works, and stretching [4,5]. According to the estimates from the US National Health and Nutrition Examination Survey, time spent in device-measured LPA among adults (7.8 hours/day) is much higher than those spent in MVPA (0.2 hours/day) [6]. LPA appears to have potential to increase daily physical activity energy expenditure [7]. Therefore, it is important to explore the benefits of LPA for improving health.

To date, there have been three systematic reviews examining the relationships of LPA with mortality, revealing that LPA may confer health benefits in reducing risks of all-cause mortality [5,8,9]. Füzéki et al. [8] reported a statistically significant beneficial association between LPA and mortality based on longitudinal studies (n=3) by means of systematic review instead of meta-analysis. Although the included studies were conducted using objective measures of LPA, all the data were collected from a single source (i.e. accelerometer data of the US National Health

44 and Nutrition Examination Survey [NHANES]). This limits the generalizability of the findings

45 since the prevalence, patterns and contexts of LPA may vary across societies. Amagasa et al. [9]

46 provided additional evidence to support the benefits of LPA for reducing risks of mortality based

47 on several cohort studies (n=4) using device-measured LPA, even after adjusting for MVPA.

48 However, meta-analytic techniques were also not adopted and quantification of the dose-response

49 relationships between LPA and mortality was not undertaken. In contrast, Chastin et al. [5]

50 conducted meta-analysis to investigate the effect of LPA (i.e. highest vs. lowest level of LPA) on

51 mortality, demonstrating that a 29% reduction of all-cause mortality for longer time spent in LPA.

52 Notably, these findings were not completely based on studies with objectively-assessed LPA (8

53 studies; self-reported LPA: n=2, device-measured LPA: n=6) and few studies in this review had

54 further included the underlying confounding factor-MVPA for adjustment. Accelerometer wear

55 time (or standardizing wear time for each participant) [10,11] can also confound analyses of LPA and

56 mortality although this issue was not addressed in prior reviews. Therefore, it warrants the need to

57 conduct a well-designed systematic review and meta-analysis to address these methodological

58 weaknesses.

59     Our study adopted a systematic literature search, including contacting the authors of relevant

60 studies for re-analyzing data (i.e. adjusting for MVPA and accelerometer wear time), and

61 performed meta-analyses to explore the dose-response relationships between daily

62 device-measured LPA and all-cause mortality in adults aged 18 or older. We also tested the

63 robustness of the findings by conducting sensitivity analyses (e.g. excluding studies with potential

64 confounding bias and investigating underlying moderators of observed associations).

65 **2 METHODS**

66 **2.1 Search strategy**

67 This review aimed to pool the relevant prospective studies to examine the dose-response

68 associations of device-measured LPA with all-cause mortality in adults aged 18 or older. Data

69 searches were conducted in accordance with the Preferred Reporting Items for Systematic

70 Reviews and Meta-Analyses (PRISMA) guidelines [12], Data sources were obtained through

71 searching the following five electronic bibliographic databases, including PubMed, Medline,

72 Scopus, Web of Science, and Google Scholar, and manual searches. We performed the searches

73 up to 30 April, 2019, using the following keywords: ((physical activity OR light physical activity

74 OR light intensity physical activity OR LIPA OR LPA OR light activity OR MVPA) AND

75 (mortality OR mortalities OR death OR fatal)) AND (risk OR Cox OR hazard OR survival

76 analysis OR odds) AND (actigraph OR motion sensor OR activity monitor OR accelerometer OR

77 accelerometry OR objectively measured OR objectively assessed OR device-measured). These

78 search terms were utilized based on previous studies [5,9]. The reference lists of all selected articles

79 were also screened for eligible records.

**2.2 Inclusion criteria**

We included the following criterion: a) device-measured physical activity was adopted as an exposure variable; b) adult participants (age ≥ 18 years) or the mean age within this range; c) provided estimates of hazard ratio (HR) or odds ratio (OR) or relative risk (RR) with 95% confidence intervals (CIs) for all-cause mortality; d) published in English.

**2.3 Exclusion criteria**

Studies were excluded if they met the following criteria: a) did not provide cut-off points of LPA based on original data or after data re-analyses; b) a study sample was based on a clinical population with diseases; c) did not adjust for MVPA, since MVPA is a potential confounder for the relationships of death with LPA [9].

**2.4 Study selection**

After retrieving the relevant studies, titles and abstracts were screened for eligibility by two independent reviewers (MCH and YL). Studies were excluded if LPA the information of the title or the abstract did not meet the criteria. For all included studies, full texts were further retrieved and were assessed for inclusion by two randomly assigned reviewers to each study from a pool of four reviewers (PWK, MCH, LY, LJC) who read the studies independently. PWK collated all information and in the case of disagreement, consensus was reached via discussion between PWK and the reviewers. In addition, MCH contacted the corresponding authors of the potentially eligible studies to request them to re-analyze data for meeting the review criteria (e.g. adjusting

99    for MVPA), and we also requested them to include accelerometer wear time for further

100   adjustment, if participants wear time had not been normalized.

101   **2.5 Data extraction and study quality assessment**

102   Data extraction and study quality assessment was performed by two independent researchers

103   (MCH and YL), and differences in judgement between the two researchers were further discussed

104   with the third reviewer's (PWK) involvement until they reached a consensus. The extracted data

105   included the following information: author (s), year of publication, country, number of

106   participants, number of deaths from all-cause mortality, age at baseline, sex, length of follow-up,

107   LPA measurement (type of accelerometer, mean or median time of LPA duration), number of

108   covariates included in the multivariable adjusted models, cut-off points of LPA duration, the HR

109   estimates with corresponding 95% CIs for models.

110        The quality of the included studies was assessed using the quality criteria checklist [13]. This

111   assessment tool includes a 14-item checklist (e.g. 'Question/objective sufficiently described?' and

112   'Method of subject/comparison group selection of information/input variables described and

113   appropriate?'). However, three of them regarding intervention research were excluded from the

114   following evaluation. Thus, the 11-item checklist was used for quality assessment. Points were

115   assigned to each item based on the grading level (i.e. 'yes (2)' or 'partial (1)' or 'unclear (0)). The

116   sum of all points was divided by the possible highest score (22 points). Each study score ranged

117   from 0 (worst) to 1 (best), and a score $\geq$ 0.85 was classified as high [14]. Quality scores for each

118    study are shown in Appendix Table S1.

119    **2.6 Statistical analysis**

120    The maximally adjusted hazard ratios (HRs) from multivariable proportional hazards models

121    were utilized to alleviate the potential confounding bias in each study. All of the HRs and the

122    corresponding CIs were employed in subgroup analyses and were then transformed into the

123    natural logarithm of the HRs and their variances for subsequent meta-regression analyses.

124        The median or mean level of LPA in each category was assigned as the "dose of LPA" for

125    the corresponding relative risk for each study to investigate the dose-response relationships of

126    daily LPA with the risk of all-cause mortality. We computed the midpoint of the range in each

127    category when studies reporting LPA by ranges of time. If the lowest category was open-ended,

128    the lower boundary was regarded as zero. The length of the open ended category was assumed to

129    be the same as that of the neighboring category when the highest category was open-ended [15,16].

130        Heterogeneity between studies was evaluated using the $Q$ statistic (i.e. a measure of weighted

131    squared deviations) and the $I^2$ (i.e. the proportion of total variation explained by variation between

132    studies). We used Q and degree of freedom to check if the heterogeneity was statistically

133    significant [17]. The $I^2$ values of 25%, 50%, and 75% correspond to the low, moderate, and high

134    levels of heterogeneity [18]. To explore the shape of the associations of LPA with log-transformed

135    risk of all-cause mortality, we used pooled data extracted from the 11 prospective cohort studies.

136    We conducted subgroup analyses and meta-regression analyses by using the random-effects

137    models due to heterogeneity across studies.

138    Subgroup analyses were conducted first to assess the preliminary dose-response relationships

139    between LPA and mortality. The doses of LPA (e.g. median, mean or midpoint level of LPA in

140    each category) were classified into four categories (< 3 [reference], 3 − < 5, 5 − < 7 and 7+

141    hours/day). Rationales for the classification were as follows: (i) the reference group for LPA in

142    each study was mostly set at less than three hours a day; (ii) The total weighted mean of LPA in

143    the current review was 5.01 hours a day (see Table 1.). The first subgroup analysis was performed

144    based on all included studies (11 studies). Then, to investigate the effect of accelerometer wear

145    time on the relationships of LPA with mortality, another subgroup analysis was carried out to

146    compare the effect sizes for the subgroup with adjustment (8 studies) against the subgroup

147    without adjustment (3 studies) [19-21]. Third, we conducted the first subgroup analysis again after

148    excluding three studies without adjusting for accelerometer time (8 studies) since these was a

149    significant difference between the mean effects of subgroups.

150    Before conducting meta-regression, it is essential to evaluate the dose-response pattern

151    between dose of LPA (e.g. median, mean or midpoint level of LPA in each category) and

152    all-cause mortality. We investigated the first-order and second-order fractional polynomials

153    models by determining the model of best fit for the pooled dose-response data first [22,23]. These

154    included the linear, quadratic and cubic models and a range of possible functions such as

155    U-shaped and J-shaped patterns, which were comprehensively examined using the model - (log

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156    HR $|X)= \beta_1 X^{P1}+\beta_2 X^{P2}$, in which P1 and P2 were chosen from a predefined set P = [−2, −1, −0.5, 0,

157    0.5, 1, 2, 3], in which $X^{pi}$ denotes $X^{pi}$ if $p^i \neq 0$ and log X if $p^i = 0$ [24]. The results of goodness of

158    fit tests among the 45 models are shown in Appendix Table S2. The selection of the best fit model

159    was based on the $R^2$ analog. More variance between studies explained by the model is better [25,26].

160    The first-order cubic model possessed the highest value of the $R^2$ analog. (0.61), and explained

161    more variance between studies than the other 44 models.

162        In the following meta-regression analyses, we conducted three random-effects models with

163    restricted maximum likelihood estimations based on the first-order cubic equation. First of all, the

164    univariate meta-regression was utilized to examine the shape of the associations of LPA and

165    all-cause mortality (n= 11 studies, 39 effect sizes), (Model 1). Then, we conducted a first

166    sensitivity analysis to assess effects after excluding three studies with potential bias (since they

167    did not adjust for accelerometer wear time), and these results are presented in Model 2 (8 studies;

168    29 effect sizes). Based on the Model 2, a second sensitivity analysis was conducted to identify

169    study-level variables that could moderate the association of LPA with all-cause mortality and

170    contribute the heterogeneity across studies. Mean age, percentage of males, sample size at

171    baseline, number of covariates, study quality scores, and mean length of follow-up were

172    scrutinized in a univariate meta-regression model. The variables reaching the significance level

173    ($p< 0.05$) were then included in Model 3.

174        To assess publication bias, the Egger's test [27] is first employed to examine the funnel plot

175 asymmetry. The tests with a significant result indicate that the funnel plot is asymmetric. This

176 suggests that publication bias may occur because small studies with small effect sizes (i.e.,

177 insignificant findings) are not published and then not included in the meta-analysis. The Duval

178 and Tweedie's Trim and Fill test [28] were then conducted to provide a funnel plot that includes

179 both the included studies and the imputed studies for assessing effect size shift. One can be more

180 confident in the validity of the reported effect if the shift is trivial. The funnel plot asymmetry was

181 also visually assessed.

182 A two-sided *p*-value of less than 0.05 was considered statistically significant. All analyses

183 were carried out using Comprehensive Meta-Analysis Version 3.3.070 (Biostat, Englewood, New

184 Jersey, US) [25].


185 **3 RESULTS**

186 **3.1 Study selection**

187 A flow diagram of article inclusion is shown in Figure 1. A total of 1,167 potential studies were

188 identified through electronic database searching. After removing duplicate records (n = 134),

189 1,033 articles remained. Of these, 1,010 articles were excluded after title and abstract screening

190 and 23 full text articles were assessed for potential eligibility [10,11,19-21,29-46]. Of these 23 articles,

191 six studies met the criteria [10,11,19-21,33]. From the remaining 17 studies contacted via email, five of

192 them provided the requested results [29-32,34]. Eight studies did not provide cut-off point of LPA

193 because data re-analysis was not available [36-38,40-42,44,45], one study included participants with

194 chronic kidney disease [35], and the other three studies did not adjust for MVPA [39,43,46]. As a result,

195 11 articles were included in this review.

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197 Figure 1 Here

198 Figure 1 Flowchart of selection of studies for inclusion in meta-regression

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200 **3.2 Study characteristics and quality assessment**

201 The characteristics of the 11 articles included in the review are described in Table 1. Among the

202 11 eligible articles, eight originated from the United States, two from the United Kingdom, and

203 one from Sweden, which were published between 2012 and July 2018. These studies included

204 49,239 individuals who were followed up for $2.3 - 14.2$ years (mean time = 6.2 year), during

205 which 3,669 (7.5%) died. Overall, the baseline mean age across studies was 60.7 (SD 13.6) years.

206 One study involved females only [34] and one study involved males only [11]. All studies utilized the

207 ActiGraph accelerometer, with five studies defining LPA as $\geq 100 - \leq 2019$ counts/min [10,19,29,31,33],

208 two studies defined as $\geq 100 - \leq 1951$ counts/min [30,32], two studies defined as $\geq 100 - < 760$

209 counts/min [20,21], one used $\geq 200 - \leq 2689$ counts/min [34], one used $\geq 100 - \leq 1040$ counts/min [11].

210 According to the estimate of the include studies, LPA occupies a large amount of overall wake

211 time in daily life (total weighted average of LPA = 5.01 hr/d). All studies adjusted for multiple

212    potential confounding factors ranging from 7 − 17 covariates. Each study was adjusted for age,

213    sex, and MVPA, while eight studies included accelerometer wear time for adjustment [10,11,29-34] and

214    three did not report accelerometer wear time [19-21]. Other covariates varied across the studies (see

215    Table 1). Six studies found that time spent in LPA was significantly associated with a lower risk

216    of mortality [10,11,29,32]. Most of the studies were rated as high quality. The study appraisal criteria

217    and number of studies scoring a point for each item are presented in Appendix Table S1 (≥ 0.85 in

218    all studies). Low-to-moderate heterogeneity was apparent (Q-value = 57.02, df = 37, p = 0.019; $I^2$

219    = 35.11%).

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221    Table 1 here

222    Table 1. Characteristics of studies included in the meta-analysis

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224    **3.3 Light physical activity and mortality: Subgroup analyses**

225    The first random-effects subgroup analysis demonstrated that more time spent in daily LPA is

226    progressively associated with lower risks of all-cause mortality (n = 11 studies and 35 effect

227    sizes). In comparison with the reference group (< 3 hours/day), the pooled HRs (and 95% CIs) of

228    mortality were 0.71 (0.62-0.82) for the group (3 − < 5 hours/day), 0.68 (0.59 − 0.79) for the group

229    (5 − < 7 hours/day), and 0.56 (0.44 − 0.71) for those spent time in LPA equal or more than 7 hours

230    a day.

231        These was a significant difference between the mean effect of the subgroup (eight studies

232    adjusting for accelerometer wear time), as opposed to that of the other subgroup (three studies

233    without adjusting for accelerometer time) ($Q$-value = 4.04, df = 1, p = 0.044). After excluding

234    three studies without adjusting for accelerometer time, the second subgroup analysis indicated

235    that the dose-response relationships remained and became slightly stronger (n = 8 studies and 26

236    effect sizes) (See Table 2).

237    ---------------------------------------------

238    Table 2 here

239    Table 2 Dose-response relationships of time spent in objectively-measured light-intensity physical

240    activity with all-cause mortality assessed using random-effects subgroup analyses.

241    ---------------------------------------------

242    **3.4 Light physical activity and mortality: Meta-regression analyses**

243    We conducted three random-effects models with restricted maximum likelihood estimations

244    based on the first-order cubic equation. The first meta-regression based on all included studies (n

245    = 11 studies and 38 effect sizes) indicated a significant dose-response relationship between daily

246    LPA and log-transformed risk of all-cause mortality ($\beta$ = -0.78E-3, p = 0.012) (Model 1 in Table

247   3). Second, we performed the first sensitivity analyses after excluding the three studies that did

248   not adjust for accelerometer wear time (n = 8 studies and 29 effect sixes), which yielded a

249   stronger effect estimate (β = -0.97E-3, p = 0.025) (Model 2 in Table 3).

250       Finally, we performed simple meta-regression models to examine several study-level

251   variables including mean age, percentage of males, sample size at baseline, number of covariates,

252   study quality scores, and mean length of follow-up. Among them, only sample size reached

253   significance ($p < 0.05$), which was then included in Model 3. Although the dose-response

254   associations between LPA and death risks did not alter in Model 3, the results demonstrated that

255   studies with smaller sample sizes (median of sample sizes = 1000, n < 1000 [10 effect sizes] vs. n

256   ≥ 1000 [19 effect sizes, reference]) tended to have stronger relationships between daily LPA and

257   mortality risks (Model 3 in Table 3).

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259   Table 3 here

260   Table 3 Dose-response relationships of time spent in objectively-measured light-intensity physical

261   activity with all-cause mortality assessed using random-effects meta-regression models.

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264    **3.5 Evaluation of publication bias**

265    It appeared that the funnel plot was asymmetry, suggesting that a few studies may be missing near

266    the right side (Figure 2). The Egger's test also indicated that there was evidence of publication

267    bias (p = 0.001). Similarly, the observed point estimate in log unit (-0.38, 95% CI = -0.47 ～

268    -0.30) was larger than the adjusted estimate after imputing several studies (-0.28, 95% CI= -0.38

269    ～ -0.18) in the Trim and Fill adjustment (See Figure 2).

270    ---------------------------------------------

271    Figure 2 Here

272    Figure 2 Funnel plot with imputed studies

273    ---------------------------------------------

274    **4 DISCUSSION**

275    This is the first meta-analysis assessing the dose-response relationship of device-measured LPA

276    with all-cause mortality in adults aged 18 or older, which systematically adjusted the effect

277    estimates for MVPA and accelerometer time. Our meta-analyses found a significant log-cubic

278    association between time spent in daily LPA and all-cause mortality using objective

279    device-measured assessments. These findings were based on the 11 prospective studies adjusting

280    for multiple confounders (especially MVPA and accelerometer wear time), and the sensitivity

281    analyses provided further support for these results.

282    LPA occupies a large amount of overall wake time in daily life. The subgroup analyses and

283    meta-regression analyses both confirmed that more time spent in LPA was inversely associated

284    with mortality risks, supporting previous systematic reviews and meta-analysis for general

285    populations [5,8,9,47]. The present meta-analyses showed progressive decreases in mortality risk as

286    people spend more time in LPA. Compared with the lowest LPA group, the risk of death

287    decreased approximately 35% and 50% for participants spending between 5 and 7 hours/day and

288    more than 7 hours a day in LPA, respectively (Model 2 in Table 1). However, the meta-regression

289    indicated that the mean age of the sample (< 65 vs. 65+) was not a significant moderator of the

290    relationships between LPA and death risks, suggesting that LPA can confer health benefit for all

291    adults. This may provide implications for the current international physical activity guidelines [1,48],

292    which mainly focus on the effects of MVPA.

293    Although the most potent component of the 24-hour movement time-use using compositional

294    analysis after adjusting for its synergies with time spent in all other behaviors maybe is MVPA,

295    LPA could play a pivotal role in reducing death risks, especially in contexts where MVPA is less

296    feasible (e.g. older people or frail populations)[49]. Notably, the effect estimate of LPA in this

297    meta-analysis was independent of MVPA and other underlying covariates. There is a paucity of

298    research comparing the effect size of LPA and MVPA in the same regression analyses [5]. Fishman

299    et al. [46] conducted an isotemporal substitution model to examine the effects of replacing

300    10-minute sedentary time with LPA or MVPA on mortality, demonstrating the HRs for mortality

301 of 0.91 for LPA and 0.70 for MVPA. Schmid et al. [45] utilized the same analytical approach to

302 estimate the effect of substituting a 30-minute sedentary time with another activity behavior,

303 revealing the HRs for mortality of 0.88 for LPA and 0.51 for MVPA. Similarly, another study

304 using this analytical model substituting 30 min/day of sedentary time with LPA or MVPA

305 exhibited mortality risk reductions by 13 % and 81 % respectively[50]. A recent meta-analysis

306 pooled these relevant studies suggested that the effects reported for MVPA on mortality risk

307 reduction may be two times larger than the same amount of time spent in LPA (approximately

308 40% vs. 20%)[51]. There is no clear explanation for this. It is possibly related to energy expenditure

309 because the same time spent in MVPA may expend two times or higher the energy of that spent in

310 LPA.

311      There was a significant difference between the mean effect of the studies adjusting for

312 accelerometer wear time, as opposed to those without adjusting for accelerometer time. Both

313 subgroup analyses and meta-regression analyses demonstrated that the effect of LPA on

314 subsequent risks of mortality became stronger after excluding the studies without adjusting for

315 accelerometer wear time. Estimates of LPA may vary according to the duration of objective

316 recordings if a study fails to consider absolute wear time. This effect may have implications for

317 future systematic reviews or meta-analyses based on device-measured assessment of LPA.

318      The funnel plot asymmetry was observed in this meta-analysis, which has been frequently

319 seen as a sign of potential publication bias. However, previous evidence suggests that funnel plots

320  should be appropriately regarded as a tool for examining "small study effects" instead of a mean

321  of screening other types of bias [52,53]. Exaggeration of effects in small studies may also cause

322  asymmetrical funnel plots, which was further supported by the sensitivity analysis of the present

323  meta-regression. Studies with a smaller sample size tended to demonstrate stronger relationships

324  between daily LPA and death.


325  Illnesses before death may limit physical activity, which may lead to the possibility of

326  reverse causation, especially in studies with short periods of follow-up. However, several studies

327  in this review have found similar results after excluding those with mobility limitations and

328  cardiovascular diseases [11] or excluding early deaths in the first one or two year of follow-up [11,20,21],

329  indicating that the reverse causality is not supported.


330  This study has several strengths worth mentioning. First, it is the first meta-analysis

331  examining the dose-response associations of LPA with mortality risks in adults based on

332  prospective cohort studies with device-based measures, which systematically adjusted the effect

333  estimates for MVPA and accelerometer time. Second, we contacted the authors of potentially

334  eligible studies to request data re-analyses (i.e. providing cut-off points of LPA duration and

335  adjusting for MVPA or accelerometer wear time) for meeting the inclusion criteria and statistical

336  analysis, which makes this review more inclusive than the previous systematic reviews or

337  meta-analysis (n ranging between 2 and 6). Finally, official death registry records provided high

338    quality data for mortality ascertainment.

339    The main limitation of this meta-analysis is that we cannot rule out the influences of

340    unmeasured confounding [54,55], although we utilized the maximally adjusted hazard risks that took

341    into account the underlying confounders, including age, sex, educational attainment, health

342    behaviors, health status, MVPA and accelerometer wear time. Second, differential criteria for

343    defining LPA across studies may result in misclassification. Third, most of the included studies

344    adopted uniaxial accelerometers for assessing LPA. Only one study utilized tri-axial

345    accelerometer. Although this may induce misclassification bias, previous study demonstrated that

346    the differences in estimation between the tri-axial and uni-axial devices found for sedentary

347    behaviours, LPA and MVPA were small [56]. Fourth, the included studies involved a wide range of

348    ages. However, most of them were based on participants aged 40 or above. It should be cautious

349    when interpreting these findings. Finally, the present analyses were based on all-cause mortality

350    as the outcome and there were insufficient events to perform analyses on sub-types of death. The

351    association patterns of LPA with other health outcomes such as non-fatal illness or adiposity may

352    be differential.

353    **5. CONCLUSIONS**

354    Our meta-analysis suggests that there is a log-cubic dose-response relationship between daily

355    LPA and all-cause mortality in adults and older people. Although the current international

356 physical activity guidelines mainly focus on MVPA, LPA engagement may provide additional

357 health benefits, which is independent of MVPA. The health effects for MVPA on death risk

358 reduction may be larger than the same amount of time spent in LPA. However, LPA offers

359 another pathway to replace sedentary behaviors and to accumulate daily energy expenditure,

360 especially for inactive or insufficiently active adults, older people or frail populations [3]. These

361 findings provide additional evidence to support the inclusion of LPA in the future physical

362 activity guideline.


363 **6 PERSPECTIVE**

364 To the best of our knowledge, this is the first meta-analysis assessing the dose-response

365 relationship of device-measured LPA with all-cause mortality in adults aged 18 or older. Unlike

366 previous work, we systematically adjusted the effect estimates for MVPA and accelerometer time.

367 Our meta-analyses found a significant log-cubic association between time spent in daily LPA and

368 all-cause mortality using objective device-measured assessments. These findings were based on

369 the 11 prospective studies adjusting for multiple confounders (especially MVPA and

370 accelerometer wear time), and the sensitivity analyses provided further support for these results.

371 Although the current international physical activity guidelines mainly focus on MVPA, LPA may

372 provide additional health benefits, which is independent of MVPA. The health effects for MVPA

373 on death risk reduction may be larger than the same amount of time spent in LPA. LPA offers

374 another pathway to replace sedentary behaviors and to accumulate daily energy expenditure,

375 especially for inactive or insufficiently active adults, older people or frail populations. These

376 findings provide additional evidence to support the inclusion of LPA in the future physical

377 activity guideline.

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380 **ACKNOWLEDGEMENTS**

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384 **CONFLICTS OF INTEREST**

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**TABLE 1** Characteristics of studies included in the meta-analysis

| Author (year), Country | Study population N (death) | age | Male % | Follow-up (mean year) | LPA measure (mean or median time, h/d) | Covariates (number of covariates) | Cut-off (h/d) | Cox regression HR (95% CI) | Quality assessment |
|---|---|---|---|---|---|---|---|---|---|
| Koster et al. (2012)[29], US | 1906 (145) | ≥ 50 $M = 63.8$ (± 10.5) | 49.3% | 2.8y | objectively measured LPA ≥ 100 – ≤ 2019 counts/1min [AM-7164 uniaxial ActiGraph] ($M = 5.2$) | Age, gender, race/ethnicity, education, BMI, diabetes, coronary heart disease, congestive heart failure, cancer, stroke, mobility limitation, smoking, alcohol, MVPA, accelerometer wear time (15) | Quartile: male/ female | | 0.95 |
| | | | | | | | 0.25 – 3.63/ 0.33 – 3.9 | 1.00 | |
| | | | | | | | 3.65 – 4.8/ 3.9 – 5.18 | 0.81 (0.52 – 1.26) | |
| | | | | | | | 4.85 – 6.18/ 5.2 – 6.28 | **0.41 (0.21 – 0.81)**[*] | |
| | | | | | | | 6.2 – 12.0/ 6.28 – 10.82 | **0.15 (0.05 – 0.50)**[*] | |
| Fox et al. (2015)[30], UK | 208 (32) | ≥ 70 $M = 78.0$ (± 5.7) | 51.2% | 4.3y | objectively measured LAP ≥ 100 – ≤ 1951 counts/1min [uniaxial Actigraph GT1Ms,] ($M = 2.8$) | Age, gender, educational, index of multiple deprivation, weight status, general practitioner management system, number of self-reported chronic illnesses at baseline, lower limb function, MVPA, accelerometer wear time (10) | < 2.33 (ref.) | 1.00 | 0.95 |
| | | | | | | | 2.33 – < 3.25 | 0.57 (0.19 – 1.72) | |
| | | | | | | | ≥ 3.25 | 0.60 (0.19 – 1.88) | |
| Edwards et al.(2016)[31], US | 2295 (101) | 20 – 85 $M = 39.7$ | 49.3% | 6.8y | objectively measured LAP ≥ 100 – ≤ 2019 counts/1min [AM-7164 uniaxial ActiGraph,] ($M = 6.1$) | Age, gender, race/ethnicity, income, Cardiorespiratory fitness, MVPA, accelerometer wear time (7) | Quartile | | 0.91 |
| | | | | | | | < 4.94 (ref.) | 1.00 | |
| | | | | | | | 4.94 – 6.02 | 0.70 (0.34 – 1.42) | |
| | | | | | | | 6.03 – 7.19 | 0.85 (0.41 – 1.76) | |
| | | | | | | | ≥ 7.20 | 0.73 (0.32 – 1.63) | |

| | | | | | | Quartile | | |
|---|---|---|---|---|---|---|---|---|
| Evenson et al. (2016)[19], US | 3809 (325) | $\geq 40$ $M = 55.3$ | 45.4% | 6.7y | objectively measured LAP $\geq 100 - \leq 2019$ counts/1min [AM-7164 uniaxial ActiGraph] (weighted $M = 5.6$) | Age, sex, race/ethnicity, education, married, interaction between current, employment, follow-up time, need special equipment to walk, arthritis, cancer, BMI, interaction between BMI categories and follow-up time, hypertension, diabetes, smoking, MVPA (16) | $\leq 4.29$ (ref.) | 1.00 | 0.95 |
| | | | | | | | $\geq 4.30 - <$ 5.41 | 0.89 (0.22 – 3.60) | |
| | | | | | | | $\geq 5.41 - <$ 5.49 | 0.70 (0.35 – 1.47) | |
| | | | | | | | $\geq 5.49$ | 0.73 (0.48 – 1.08) | |
| Lee, (2016)[32], US | 5193 (145) | $18 - 64$ $M = 39.5^{b}$ | 46.9% | 6.8y | objectively measured LAP $\geq 100 - \leq 1951$ counts/1min [AM-7164 uniaxial ActiGraph] ($M = 5.7$) | Age, sex, education, income, BMI, self-reported general health condition, high blood pressure, high cholesterol, type 2 diabetes, history of heart attack, stroke, cancer, energy intake by 24-h dietary recall, binge drinking, smoking, MVPA, accelerometer wear time (17) | < 4.17 (ref.) | 1.00 | 1.0 |
| | | | | | | | 4.17 – < 5.30 | 0.68 (0.45 – 1.02) | |
| | | | | | | | 5.30 – < 6.50 | **0.42 (0.26 – 0.68)**[*] | |
| | | | | | | | $\geq 6.50$ | **0.47 (0.29 – 0.77)**[*] | |
| | 1813 (463) | $\geq 65$ $M = 72.3^{b}$ | 53.2% | 6.3y | objectively measured LAP $\geq 100 - \leq 1951$ counts/1min [AM-7164 uniaxial ActiGraph] ($M = 4.4$) | Age, sex, education, income, BMI, self-reported general health condition, high blood pressure, high cholesterol, type 2 diabetes, history of heart attack, stroke, cancer, energy intake by 24-h dietary recall, binge drinking, smoking, MVPA, accelerometer wear time (17) | < 4.17 (ref.) | 1.00 | |
| | | | | | | | 4.17 – < 5.30 | **0.68 (0.53 – 0.86)**[*] | |
| | | | | | | | 5.30 – < 6.50 | **0.61 (0.44 – 0.83)**[*] | |
| | | | | | | | $\geq 6.50$ | **0.51 (0.34 – 0.79)**[*] | |
| Matthews et al. (2016)[20], US | 4840 (700) | $\geq 40$ $M = 56.8$ | 49.7% | 6.6y | objectively measured LAP $\geq 100 - < 760$ counts/1min [AM-7164 uniaxial ActiGraph] ($M = 4.2$) | Age, race, education, sex, smoking, alcohol, diabetes, coronary artery disease, cancer, stroke, mobility limitations, BMI, MVPA (13) | 3 (ref.) | 1.00 | 0.95 |
| | | | | | | | 4 | **0.79 (0.7 – 0.9)**[*] | |
| | | | | | | | 5 | 0.77 (0.6 – 1.0) | |
| | | | | | | | 6 | 0.89 (0.6 – 1.3) | |

| Study | N (cases) | Age | % female | Follow-up | LAP measurement | Covariates | Category | HR (95% CI) | Score |
|---|---|---|---|---|---|---|---|---|---|
| Borgundvaag et al. (2017)[33], US | 5562 (578) | ≥ 20 $M$ = 48.4 (± 30) | 49.2% | 6.7y | objectively measured LAP ≥ 100 – ≤ 2019 counts/1min [AM-7164 uniaxial ActiGraph] ($M$ = 2.8) | Age, sex, race/ethnicity, poverty-to-income ratio, education, smoking, alcohol, dietary fat, dietary saturated fat, dietary sodium, MVPA, accelerometer wear time (12) | 1.86 (ref.) | 1.00 | 1.0 |
| | | | | | | | 2.76 | 0.72 (0.51 − 1.03) | |
| | | | | | | | 3.34 | **0.64 (0.42 − 0.98)**[*] | |
| | | | | | | | 3.93 | 0.75 (0.51 − 1.11) | |
| | | | | | | | 4.86 | 0.90 (0.62 − 1.29) | |
| Dohrn et al. (2018)[10], Sweden | 851 (79) | ≥ 35 $M$ = 66.7 | 44.1% | 14.2y | objectively measured LAP ≥ 100 – ≤ 2019 counts/1min [AM-7164 uniaxial ActiGraph] ($M$ = 5.7) | Age, sex, education, hypertension, heart disease, cancer, diabetes, BMI, smoking, MVPA, accelerometer wear time (11) | Tertile | | 0.95 |
| | | | | | | | 4.09 (ref.) | 1.00[a] | |
| | | | | | | | 5.7 | **0.46 (0.27 − 0.78)**[*] | |
| | | | | | | | 7.43 | **0.34 (0.17 − 0.67)**[*] | |
| Lee et al. (2018)[34], US | 16741 (207) | $M$ = 72.0 | 0% | 2.3y | objectively measured LAP ≥ 200 – ≤ 2689 counts/1min [triaxial ActiGraph Corp] ($M$ = 5.9) | Age, hormone therapy, parental history of myocardial infarction, family history of cancer, general health, cardiovascular disease, cancer, cancer screening, smoking, alcohol, intakes of saturated fat, fiber, fruits, and vegetables, MVPA, accelerometer wear time (15) | Quartile | | 1.0 |
| | | | | | | | ≤ 4.87 (ref.) | 1.00 | |
| | | | | | | | ≥ 4.87 − < 5.85 | 0.97 (0.67 − 1.39) | |
| | | | | | | | ≥ 5.85 − < 6.84 | 0.79 (0.52 − 1.21) | |
| | | | | | | | ≥ 6.84 | 1.06 (0.69 − 1.64) | |
| Jefferis et al. (2018)[11], UK | 1181 (194) | 71 − 92 $M$ = 78.4 | 100 % | 5.0y | objectively measured LAP ≥ 100 – ≤ 1040 counts/1min [triaxial ActiGraph GT3x] ($M$ = 3.3) | Age, region of residence, living alone, season of wear, social class, BMI, mobility disability, alcohol, smoking, sleep time, MVPA, accelerometer wear time (12) | Quartile | | 0.95 |
| | | | | | | | 0.08 − 2.57 (ref.) | 1.00 | |
| | | | | | | | 2.58 − 3.28 | 0.76 (0.53 − 1.10) | |
| | | | | | | | 3.3 − 3.97 | **0.42 (0.27 − 0.68)**[*] | |
| | | | | | | | 3.98 − 7.97 | **0.57 (0.34 − 0.95)**[*] | |

| Study | n (death) | Age | Female | Follow-up | Measure | Adjustments | | HR | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | 2.72 (ref.) | 1.00[a] | |
| Saint-Mauric e et al. (2018)[21,] US | 4840 (700) | ≥ 40 $M = 57.0$ | 49.7 % | 6.6y | objectively measured LAP ≥ 100 – < 760 counts/1min [AM-7164 uniaxial ActiGraph] ($M = 4.1$) | Age, sex. ethnicity, education, BMI, diabetes mellitus, stroke, chronic heart failure, reduced mobility, cancer/malignancy, alcohol, MVPA (12) | 3.74 | **0.72 (0.56 – 0.91)**[*] | 0.95 |
| | | | | | | | 4.51 | 0.77 (0.59 – 1.02) | |
| | | | | | | | 5.61 | 0.69 (0.47–1.00) | |

Average of total n (death) = 4,108 (306)

Median of study sample = 3,052

Total n = 49,239

Deceased n = 3,669

Total weighted sample $M$ (± SD) age= 60.7 (± 13.6) y

Total weighted follow-up $M$ year = 6.2 y

Total weighted average of LPA= 5.01 (± 1.15) h/d

$M = 0.96$

[*]$p= <.05.$

a = Tests for linear trend ($p < 0.05$)

b = One studies did not report mean age of the study samples. The mean age of the study were recalculated as follows: ∑(median age of a age group)× (sample size of a age group)] divided by the total sample size.

Abbreviations: $M$: mean, HR: hazard ratios, MVPA: moderate to vigorous physical activity.

**TABLE 2** Dose-response relationships of time spent in objectively-measured light-intensity physical activity with all-cause mortality assessed using random-effects subgroup analyses.

| LPA (hours/day) | Number of ES | HR (95%CI) |
|---|---|---|
| Model 1 | 35[b] | |
| < 3 (ref.) | | 1.00 |
| 3 − < 5 | 12 | 0.71(0.62-0.82) |
| 5 − < 7 | 15 | 0.68(0.59-0.79) |
| 7+ | 8 | 0.56(0.44-0.71) |
| Model 2[a] | 26[b] | |
| < 3 (ref.) | | 1.00 |
| 3 − < 5 | 8 | 0.67(0.54-0.84) |
| 5 − < 7 | 11 | 0.64(0.52-0.78) |
| 7+ | 7 | 0.51(0.38-0.68) |

LPA: light-intensity physical activity; ES: effect size; HR: hazard ratio.

[a]Excluding the three studies without adjusting for accelerometer time.

[b]Three effect sizes were excluded from the subgroup analyses because they not the reference group but its doses were less than 3 hours a day in the original studies.

**TABLE 3** Dose-response relationships of time spent in objectively-measured light-intensity physical activity with all-cause mortality assessed using random-effects meta-regression models.

| Models | Number of ES | Coefficients (SE) | $p$-values |
|---|---|---|---|
| Model 1 | 38 | | |
| Light physical activity | | -0.78E-3 (0.31E-3) | 0.012 |
| Model 2 (sensitivity analysis 1) [a] | 29 | | |
| Light physical activity | | -0.97E-3 (0.43E-3) | 0.025 |
| Model 3 (sensitivity analysis 2)[a] | 29 | | |
| Light physical activity | | -0.89E-3 (0.43E-3) | 0.039 |
| Sample size (< 1000 vs. ≥1000 [ref]) | | -0.28 (0.14) | 0.049 |

ES: effect size; SE: standard error; E: exponential.

[a]Excluding the studies without adjusting for accelerometer wear time
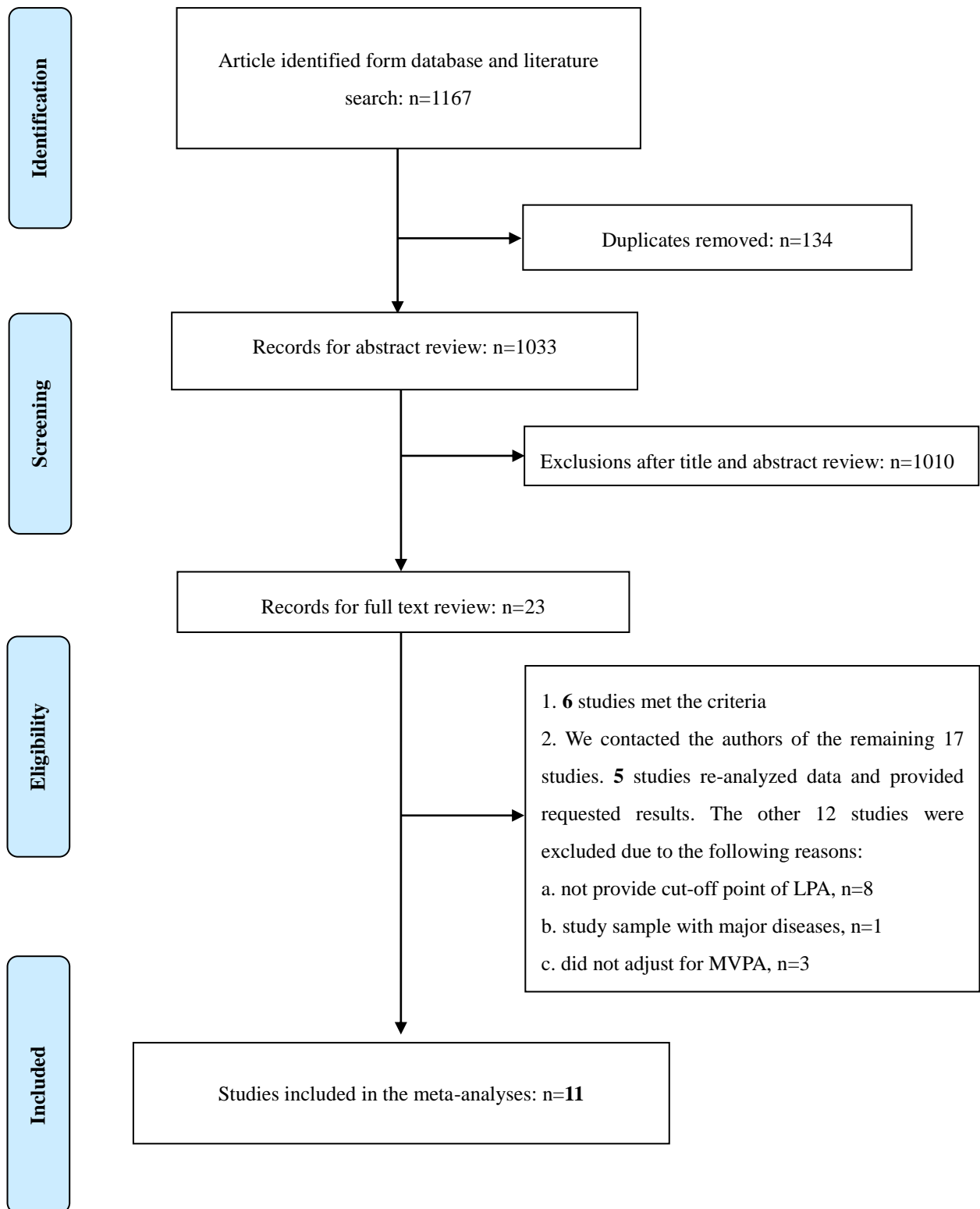
Figure legends
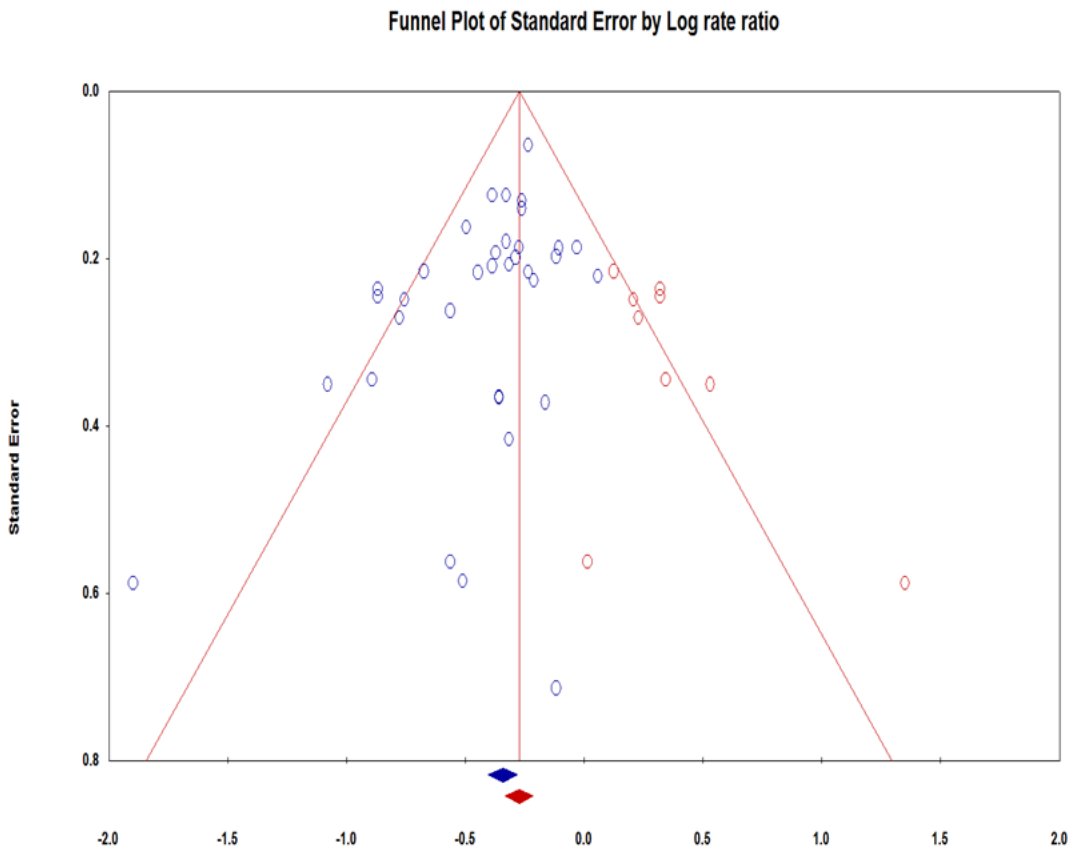


FIGURE 1 Flowchart of selection of studies for inclusion in meta-regression.

FIGURE 2 Funnel plot with imputed studies.