

**Walking speed and the risk of type 2 diabetes: a systematic review and meta-analysis**

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**eText 1.** Instructions to rate the certainty of evidence using the GRADE approach.

We evaluated the certainty of evidence for each association using the updated Grading of Recommendations Assessment, Development and Evaluations (GRADE) tools [1]. We used the updated GRADE tool, which integrates the application of ROBINS-I [2, 3]. GRADE rates the certainty of evidence as high, moderate, low, or very low. [4] Randomized controlled trials start as high certainty evidence that can then be downgraded based on pre-specified criteria. In the updated GRADE tool, observational studies also start at a high certainty of evidence level. The criteria to upgrade evidence include large effect size and dose-response gradient. The criteria used to downgrade evidence include:

Study limitations- as assessed by ROBINS-I tool [5] for cohort studies.

Inconsistency- substantial between-study heterogeneity,  $I^2 \geq 50\%$  and  $P_{\text{heterogeneity}} < 0.10$ ), which remained unexplained in pre-specified subgroup and sensitivity analyses [6].

Indirectness- presence of population, intervention or comparator factors that limit the generalizability of the results [7].

Imprecision- the 95% CIs are wide, the optimal information size was not met, or the point estimate does not surpass the minimally important difference [8]. To determine the presence of imprecision, we considered the optimal information size (the number of cases included in the review compared with the number required by a conventional sample size calculation for a single adequately powered trial). On the basis of a 5% event rate in the control group and a 25 % relative risk reduction, we calculated the optional information size to be 400 cases [8]. We considered a 2% absolute risk reduction, proposed by the GRADE working group for nonfatal outcomes [9], as minimally important difference threshold. We adapted a recently published GRADE minimally contextualized approach to rate for imprecision based on minimally important difference [10, 11]. Accordingly, we considered whether the point estimate of effect size was greater than or less than the minimally important difference, and whether the 95% confidence interval overlapped that threshold. To calculate absolute effect, we estimated risk difference and its 95%CI using the pooled relative risk. We calculated pooled relative risk and then converted the pooled relative risk to risk difference using baseline risk [12]. Baseline risk was estimated using the average event rate across included cohort studies.

Publication bias- compelling evidence of publication bias [13].

**eTable 1.** Literature search and study selection process.

<b>PubMed</b> (305)
1. "Walking speed" [all fields] OR "walking pace" [all fields] OR "gait speed" [all fields] OR "gait pace" [all fields] or "step intensity" [all fields]
2. Diabetes Mellitus [Mesh] OR Diabetes Mellitus, Type 2 [Mesh] OR diabetes [ti/ab] OR diabetic [ti/ab]
3. Prospective [all fields] OR retrospective [all fields] OR cohort* [all fields] OR follow-up [all fields] OR longitudinal [all fields] OR observational [all fields] OR nested [all fields] OR case-control [all fields] OR case-cohort [all fields] OR "relative risk" [all fields] OR "risk ratio" [all fields] OR "rate ratio" [all fields] OR "hazard ratio" [all fields] OR "odds ratio" [all fields]
4. #1 AND #2 AND #3
<b>Scopus</b> (1203)
<b>CENTRAL</b> (542)
<b>Web of Science</b> (356)
<b>Total:</b> 2406

**eTable 2.** Description of the ICEMAN domains and how to judge each domain.

<b>1: Is the analysis of effect modification based on comparison within rather than between trials?</b>			
Completely between	Mostly between or unclear	Mostly within	Completely within
Subgroup analysis or meta-regression comparing overall effects of each individual trial. This is typical for aggregate data meta-analysis.	Subgroup analysis or meta-regression with most information coming from overall effects, but some trials providing within-trial subgroup information	Most trials providing within-trial subgroup information; or individual participant data analysis that combines within and between trial information	All trials providing within-trial subgroup information or individual participant data; and the analysis separates within from between trial information, e.g. meta-analysis of interactions
<b>2: For within-trial comparisons, is the effect modification similar from trial to trial?</b> Not applicable: no or one within-RCT comparison			
Definitely not similar	Probably not similar or unclear	Mostly similar	Definitely similar
Effect modification reported for two or more trials and clearly different directions	Effect modification not reported for individual trials or too imprecise to tell	Effect modification reported for two or more trials, mostly similar in direction, but considerable differences in magnitude	Effect modification reported for two or more trials, similar in direction, only some differences in magnitude
<b>3: For between-trial comparisons, is the number of trials large?</b> [ ] Not applicable: no between RCT comparison			
Very small	Rather small or unclear	Rather large	Large
1 or 2 or in smallest subgroup; 5 or less in continuous meta-regression	3-4 in smallest subgroup; 6-10 in continuous meta-regression	5-9 in smallest subgroup; 11 to 15 in continuous meta-regression	10 or more in smallest subgroup; more than 15 in continuous meta-regression
<b>4: Was the direction of effect modification correctly hypothesized a priori?</b>			
Definitely no	Probably no or unclear	Probably yes	Definitely yes
Clearly post-hoc or results inconsistent with hypothesized direction or biologically very implausible	Vague hypothesis or hypothesized direction unclear	No prior protocol available but unequivocal statement of a priori hypothesis with correct direction of effect modification	Prior protocol available and includes correct specification of direction of effect modification, e.g. based on a biologic rationale
<b>5: Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification?</b> (consider irrespective of number of effect modifiers)			
Chance a very likely explanation	Chance a likely explanation or unclear	Chance may not explain	Chance an unlikely explanation
Interaction or meta-regression p-value >0.05	Interaction or meta-regression p-value ≤0.05 and >0.01, or no test of interaction reported and not computable	Interaction or meta-regression p-value ≤0.01 and >0.005	Interaction or meta-regression p-value ≤0.005
<b>6: Did the authors test only a small number of effect modifiers or consider the number in their statistical analysis?</b>			
Definitely no	Probably no or unclear	Probably yes	Definitely yes
Explicitly exploratory analysis or large number of effect modifiers tested (e.g. greater than 10) and multiplicity not considered in analysis	No mention of number or 4-10 effect modifiers tested and number not considered in analysis	No protocol available but unequivocal statement of 3 or fewer effect modifiers tested	Protocol available and 3 or fewer effect modifiers tested or number considered in analysis
<b>7: Did the authors use a random effects model?</b>			
Definitely no	Probably no or unclear	Probably yes	Definitely yes
Fixed (or common) effect or	Probably fixed effect(s) model	Probably random (or mixed)	Random (or mixed) effects

fixed effects model explicitly stated		effects	explicitly stated
<b>8: If the effect modifier is a continuous variable, were arbitrary cut points avoided?</b> [ ] not applicable: not continuous			
Definitely no	Probably no or unclear	Probably yes	Definitely yes
Analysis based on exploratory cut point(s), e.g. picking cut point associated with highest interaction p-value	Analysis based on cut point(s) of unclear origin	Analysis based on pre-specified cut point(s), e.g. suggested by prior RCT	Analysis based on the full continuum, e.g. assuming a linear or logarithmic relationship
<b>9 Optional: Are there any additional considerations that may increase or decrease credibility?</b> (manual section 3.9) [ ] not applicable			
yes, probably decrease		yes, probably increase	
<b>10. How would you rate the overall credibility of the proposed effect modification?</b> Overall rating: The overall rating should be derived by the items that decrease credibility: <b>Very low:</b> All responses definitely or probably decrease credibility or unclear <b>Maximum usually low:</b> Two or more responses definitely decrease credibility even if all other responses satisfy credibility criteria <b>Maximum usually moderate:</b> One response definitely decreases credibility even if all other responses satisfy credibility criteria <b>Maximum usually moderate:</b> Two responses probably decrease credibility even if all other responses satisfy credibility criteria <b>High very likely:</b> No response options definitely or probably decrease credibility			
<b>11. How would you interpret the overall credibility of the proposed effect modification?</b> <b>Very low:</b> Very likely no effect modification. Use overall effect for each subgroup. <b>Maximum usually low:</b> Likely no effect modification. Use overall effect for each subgroup but note remaining uncertainty. <b>Maximum usually moderate:</b> Likely effect modification. Use separate effect for each subgroup but note remaining uncertainty. <b>High very likely:</b> Very likely effect modification. Use separate effect for each subgroup.			

**eTable 3.** List of studies which were excluded based on full text assessment.

1. Not relevant exposure (n=61) [14-74]
2. Review study (n=8) [75-82]
3. Not relevant outcome (n=2) [83, 84]
4. Duplicate publication (n=1) [85]
5. Cross-sectional (n=1) [86]
6. Patient-based cohort (n=1) [87]

**eTable 4.** ROBINS-I judgement for each domain and overall for studies included in meta-analysis of walking speed and the risk of type 2 diabetes.

Study	Bias due to confounding	Bias due to selection of participants	Bias due to exposure assessment	Bias due to misclassification during follow-up	Bias due to missing data	Bias due to measurement of the outcome	Bias due to selective reporting of the results	Overall judgement
Boonpor, 2022	Serious	Low	Serious	Low	Low	Low	Low	Serious
Cuthbertson, 2022	Serious	Low	Low	Low	Low	Low	Low	Serious
Hu, 1999	Moderate	Moderate	Serious	Low	Low	Moderate	Low	Serious
Hu, 2001	Moderate	Moderate	Serious	Low	Low	Moderate	Low	Serious
Iwasaki, 2021	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Joseph, 2016	Serious	Low	Serious	Low	Low	Low	Low	Serious
Kaplan, 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Krishnan, 2008	Serious	Low	Serious	Low	Low	Serious	Low	Serious
Master, 2022	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Nakanishi, 2004	Serious	Low	Low	Low	Low	Low	Low	Serious

**eTable 5.** Assessment of credibility of subgroup difference for the association of average/normal walking and the risk of type 2 diabetes based on ICEMAN.

Variable	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall credibility
Walking speed assessment	Completely between	Mostly similar	Rather large	Definitely yes	Chance a likely explanation	Definitely yes	Definitely yes	Not applicable	Moderate
Diagnosis of type 2 diabetes	Completely between	Mostly similar	Rather small	Definitely yes	Chance a likely explanation	Definitely yes	Definitely yes	Not applicable	Moderate
Risk of bias	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Region	Completely between	Mostly similar	Very small	Definitely no	Chance an unlikely explanation	Probably no	Definitely yes	Not applicable	Low
Number of cases	Completely between	Mostly similar	Rather large	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Definitely yes	Low
Follow-up duration	Completely between	Mostly similar	Rather large	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Definitely yes	Low
Sex	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Definitely yes	Low
Adjustments									
Total physical activity	Completely between	Mostly similar	Rather large	Definitely yes	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Time spent walking per day or step count per day	Completely between	Mostly similar	Rather small	Definitely yes	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Smoking status	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Definitely yes	Definitely yes	Not applicable	Low
Alcohol drinking	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Blood pressure	Completely between	Mostly similar	Rather large	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Body mass index	Completely between	Mostly similar	Rather large	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Family history of diabetes	Completely between	Mostly similar	Rather small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low

Q, question; Q1, Is the analysis of effect modification based on comparison within rather than between trials? Q2, For within-trial comparisons, is the effect modification similar from trial to trial? Q3, For between-trial comparisons, is the number of trials large? Q4, Was the direction of the effect modification



correctly hypothesized priori? Q5, Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? Q6, Did the authors test only a small number of effect modifiers? Q7, Did the authors use a random effects model? Q8, If the effect modifier is a continuous variable, were arbitrary cut points avoided?

**eTable 6.** Subgroup analyses of the association between brisk/striding walking and the risk of type 2 diabetes.

Variables	Number of cohorts	Relative risk (95%CI)	I <sup>2</sup> , P heterogeneity	P subgroup difference
All cohorts	6	0.61 (0.49, 0.73)	81%, <0.001	-
<b>Risk of bias</b>				
Moderate	1	1.05 (0.69, 1.41)	-	0.01
Serious	5	0.57 (0.46, 0.69)	81%, <0.001	
<b>Region</b>				
US	5	0.64 (0.46, 0.83)	85%, <0.001	0.35
Europe	1	0.55 (0.49, 0.61)	-	
<b>Sex</b>				
Male	2	0.46 (0.33, 0.59)	73%, 0.05	<0.001
Female	2	0.75 (0.70, 0.80)	0%, 0.44	
Both	3	0.72 (0.50, 0.94)	57%, 0.10	
<b>Follow-up duration</b>				
<8 years	2	0.55 (0.49, 0.61)	0%, 0.94	0.74
≥8 years	4	0.66 (0.44, 0.88)	89%, <0.001	
<b>Number of cases</b>				
<1000	2	0.82 (0.46, 1.19)	72%, 0.06	0.08
≥1000	4	0.55 (0.42, 0.68)	82%, <0.001	
<b>Walking speed assessment</b>				
Measured	2	0.79 (0.31, 1.27)	78%, 0.03	0.40
Self-reported	4	0.57 (0.45, 0.70)	85%, <0.001	
<b>Type 2 diabetes assessment</b>				
Medical records or measured	4	0.65 (0.50, 0.80)	66%, 0.03	0.58
Self-reported	2	0.55 (0.24, 0.86)	94%, <0.001	
<b>Adjustments</b>				
<b>Body mass index</b>				
Yes	2	0.48 (0.32, 0.63)	87%, 0.01	0.08
No	5	0.66 (0.52, 0.79)	76%, <0.001	
<b>Total physical activity</b>				
Yes	3	0.53 (0.33, 0.73)	79%, 0.01	0.24
No	3	0.70 (0.51, 0.88)	83%, <0.001	
<b>Time spent walking or step count per day</b>				
Yes	2	0.62 (0.47, 0.78)	83%, 0.02	0.97
No	4	0.63 (0.39, 0.86)	83%, <0.001	
<b>Smoking status</b>				
Yes	6	0.61 (0.49, 0.73)	81%, <0.001	-
No	-	-	-	
<b>Alcohol drinking</b>				
Yes	5	0.60 (0.46, 0.74)	84%, <0.001	0.51
No	1	0.67 (0.52, 0.82)	-	
<b>Blood pressure</b>				
Yes	2	0.82 (0.46, 1.19)	72%, 0.06	0.17
No	4	0.55 (0.42, 0.68)	83%, <0.001	
<b>Family history of diabetes</b>				
Yes	2	0.55 (0.24, 0.86)	94%, <0.001	0.58

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No	4	0.65 (0.50, 0.80)	66%, 0.03	
<b>Studies that reported relative risk both before and after adjustment for body mass index</b>				0.49
Yes	1	0.52 (0.46, 0.58)	-	
No	1	0.55 (0.49, 0.61)	-	

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**eTable 7.** Assessment of credibility of subgroup difference for the association of brisk/striding walking and the risk of type 2 diabetes based on ICEMAN.

Variable	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Overall credibility
Walking speed assessment	Completely between	Mostly similar	Very small	Definitely yes	Chance a very likely explanation	Definitely yes	Definitely yes	Not applicable	Low
Diagnosis of type 2 diabetes	Completely between	Mostly similar	Very small	Definitely yes	Chance a very likely explanation	Definitely yes	Definitely yes	Not applicable	Low
Risk of bias	Completely between	Mostly similar	Very small	Definitely no	Chance a likely explanation	Probably no	Definitely yes	Not applicable	Low
Region	Completely between	Mostly similar	Very small	Definitely no	Chance an unlikely explanation	Probably no	Definitely yes	Not applicable	Low
Number of cases	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Definitely yes	Low
Follow-up duration	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Definitely yes	Low
Sex	Completely between	Mostly similar	Very small	Definitely no	Chance an unlikely explanation	Probably no	Definitely yes	Definitely yes	Low
Adjustments									
Total physical activity	Completely between	Mostly similar	Very small	Definitely yes	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Time spent walking or step count per day	Completely between	Mostly similar	Very small	Definitely yes	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Smoking status	-	-	-	-	-	-	-	-	-
Alcohol drinking	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Blood pressure	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Body mass index	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low
Family history of diabetes	Completely between	Mostly similar	Very small	Definitely no	Chance a very likely explanation	Probably no	Definitely yes	Not applicable	Low

Q, question; Q1, Is the analysis of effect modification based on comparison within rather than between trials? Q2, For within-trial comparisons, is the effect modification similar from trial to trial? Q3, For between-trial comparisons, is the number of trials large? Q4, Was the direction of the

effect modification correctly hypothesized priori? Q5, Does a test for interaction suggest that chance is an unlikely explanation of the apparent effect modification? Q6, Did the authors test only a small number of effect modifiers? Q7, Did the authors use a random effects model? Q8, If the effect modifier is a continuous variable, were arbitrary cut points avoided?

**eTable 8 .** GRADE evidence table for the association between walking speed and the risk of type 2 diabetes.

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants	Cases (%)	Relative (95% CI)	Absolute (95% CI)		

**Average or normal walking**

4	observational studies	very serious <sup>a</sup>	serious <sup>b</sup>	not serious	serious <sup>c</sup>	Dose-response gradient	160,321	6520 (4.07%)	<b>RR 0.85</b> (0.70 to 1.00)	<b>0.86 fewer per 100</b> (from 1.72 fewer to 0 fewer)	⊕⊕○○ Low	CRITICAL
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**Fairly brisk walking**

10	observational studies	very serious <sup>d</sup>	not serious <sup>e</sup>	not serious	serious <sup>f</sup>	Dose-response gradient	539,793	18,117 (3.4%)	<b>RR 0.76</b> (0.65 to 0.87)	<b>1.38 fewer per 100</b> (from 2.01 fewer to 0.75 fewer)	⊕⊕○○ Low	CRITICAL
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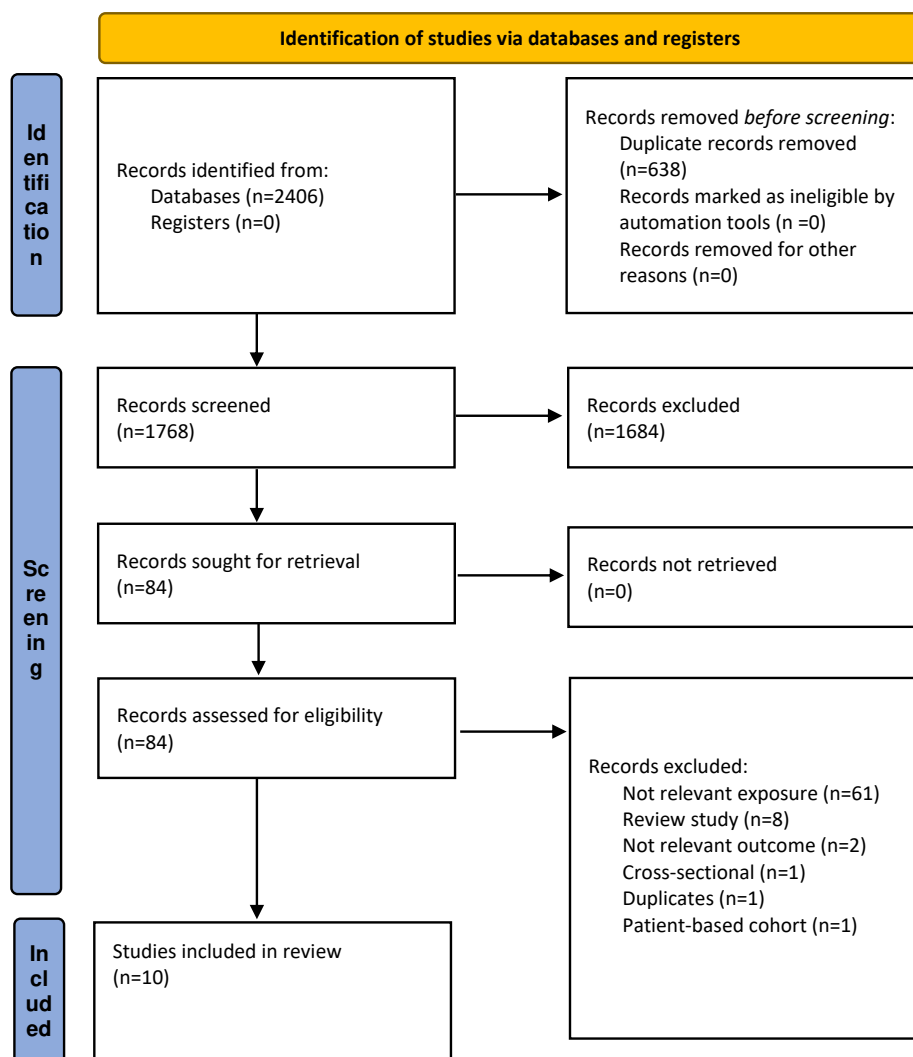
**Brisk/striding walking**

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Participants	Cases (%)	Relative (95% CI)	Absolute (95% CI)		
6	observational studies	very serious <sup>g</sup>	not serious <sup>h</sup>	not serious	not serious <sup>i</sup>	Dose-response gradient	202,223	10,438 (5.16%)	<b>RR 0.61</b> (0.49 to 0.73)	<b>2.24 fewer per 100</b> (from 2.93 fewer to 1.55 fewer)	⊕⊕⊕○ Moderate	CRITICAL

CI: confidence interval; RR: relative risk,

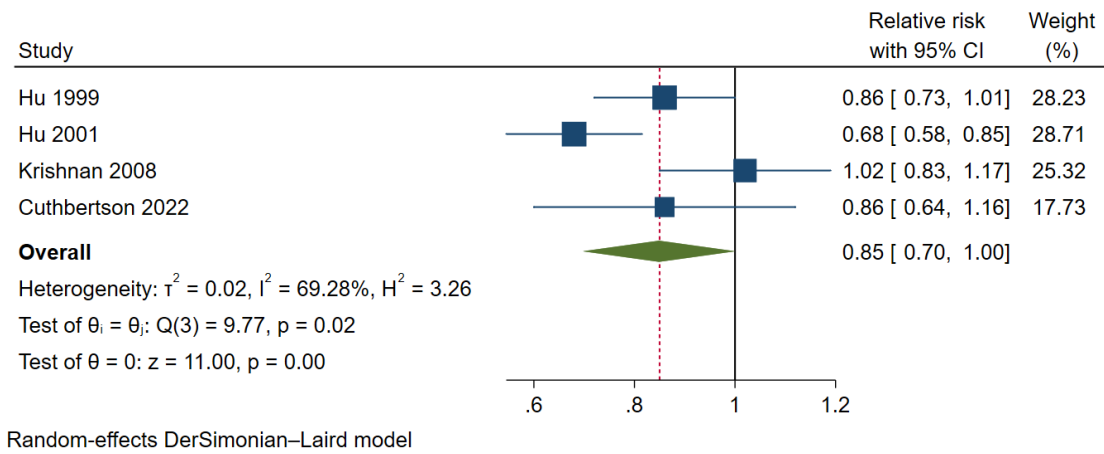
### Explanations

- a. Downgraded twice since all studies judged as serious risk of bias based on ROBINS-I were included in the meta-analysis and residual confounding cannot be ruled out.
- b. Serious inconsistency since  $I^2 = 70\%$ . Downgraded.
- c. Serious imprecision since the point estimate of the absolute effect was lower than 2%, and 95%CI included null value. Downgraded.
- d. Downgraded twice since 8 studies with high weighting (81%) judged as serious risk of bias based on ROBINS-I were included in the meta-analysis and residual confounding cannot be ruled out.
- e. Serious inconsistency since  $I^2=88\%$ ; however, a pre-specified subgroup analysis by method of walking speed assessment explained the observed heterogeneity. Not downgraded.
- f. Serious imprecision since the point estimate of the absolute effect was lower than 2%. Downgraded.
- g. Downgraded twice since 5 studies with high weighting (89%) judged as serious risk of bias based on ROBINS-I were included in the meta-analysis and residual confounding cannot be ruled out.
- h. Serious inconsistency since  $I^2=81\%$ ; however, 6 out of 7 studies were in the same direction and reported consistent inverse association, and a pre-specified influence analysis explained most of the observed heterogeneity (RR after exclusion of the Kaplan et al. was 0.57, 95%CI: 0.46, 0.69;  $I^2=12\%$ ). Not downgraded.
- i. Not serious since the point estimate in the absolute effect surpassed the MID threshold. Not downgraded.

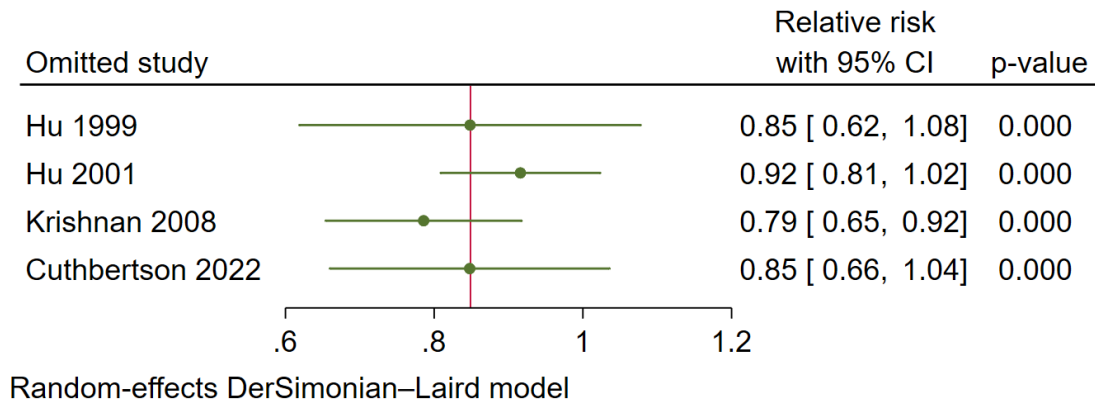


**eFigure 1.** Literature search and study selection process.

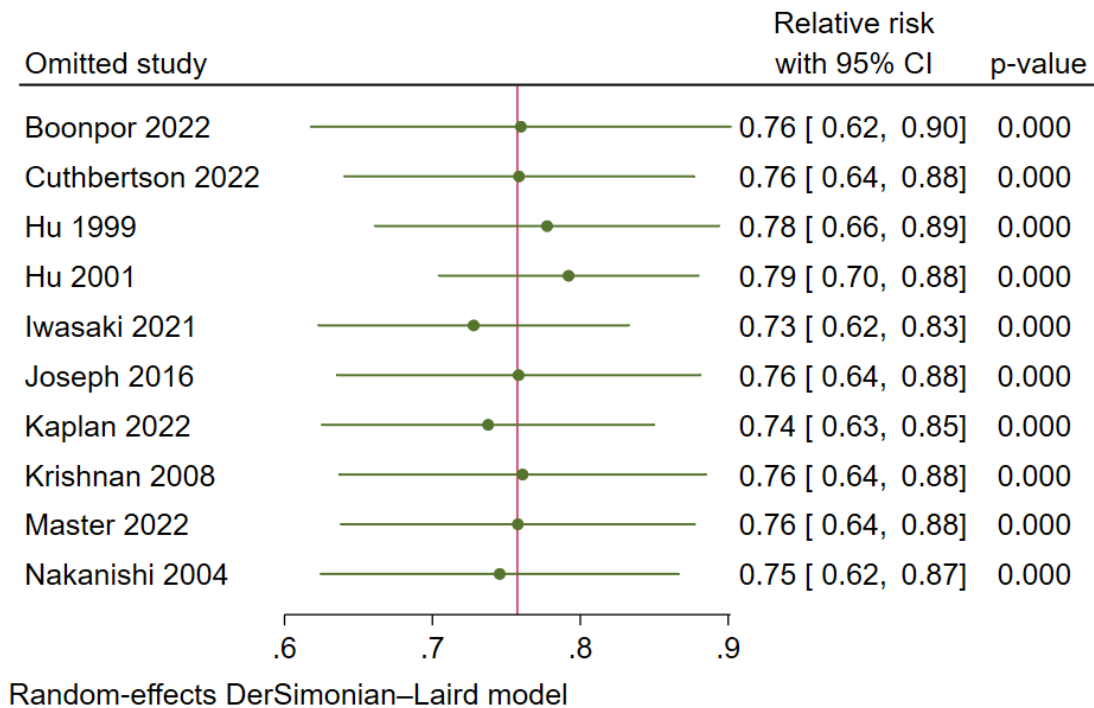




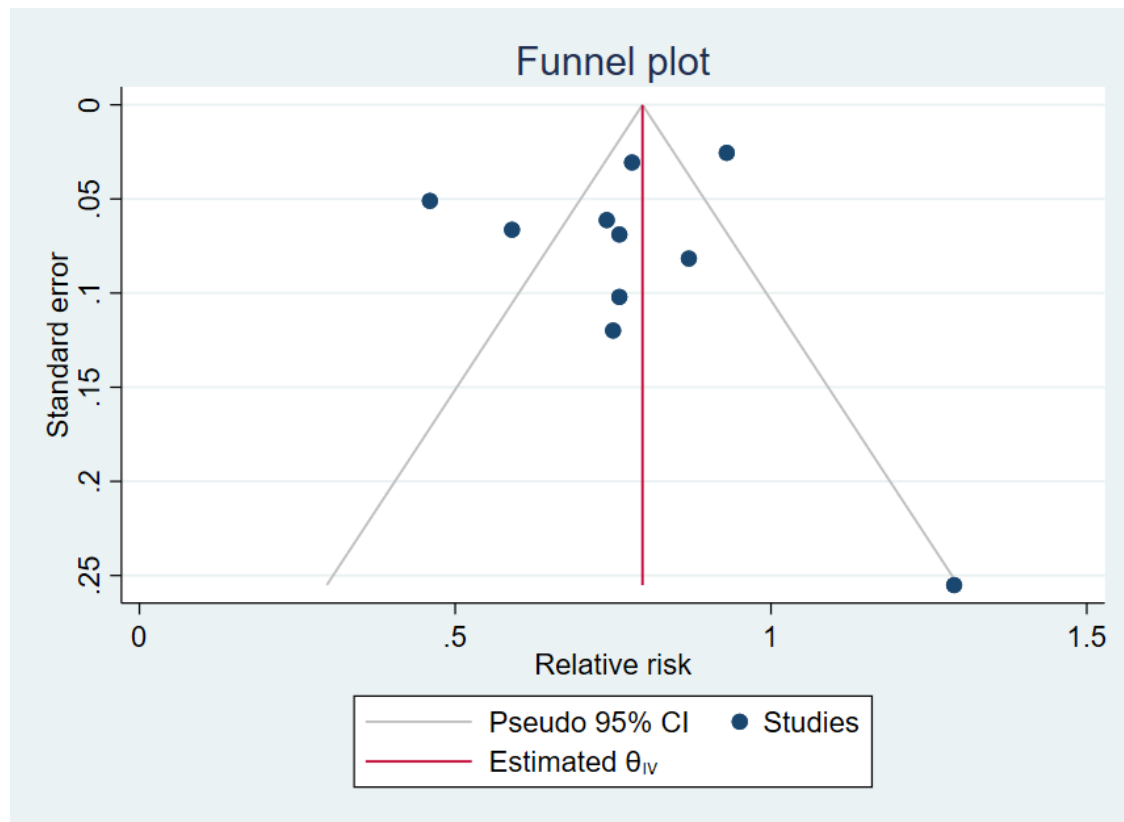
**eFigure 2.** Relative risk of type 2 diabetes for average/normal walking.



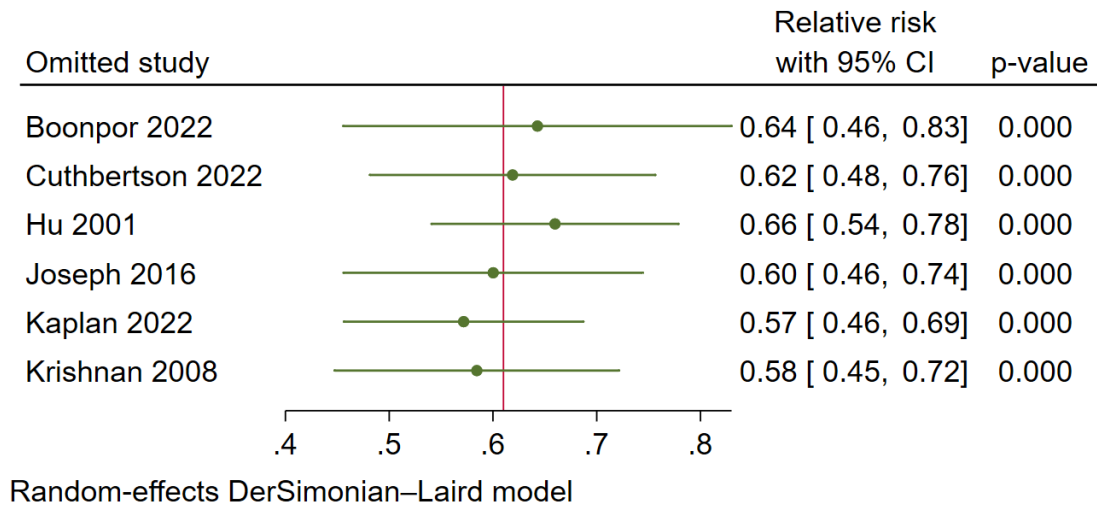
**eFigure 3.** Influence analysis showing the relative risk of type 2 diabetes for average/normal walking after exclusion of every single study at a time.



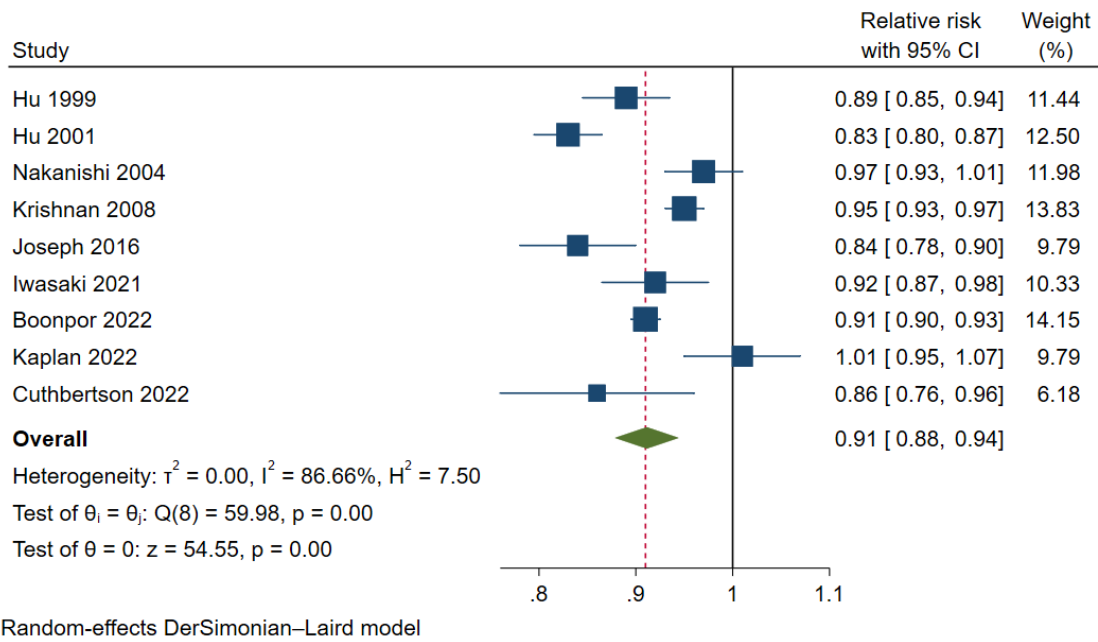
**eFigure 4.** Influence analysis showing the relative risk of type 2 diabetes for fairly brisk walking after exclusion of every single study at a time.



**eFigure 5.** Funnel plot of 10 cohort studies of the association between fairly brisk walking and the risk of type 2 diabetes.



**eFigure 6.** Influence analysis showing the relative risk of type 2 diabetes for brisk/striding walking after exclusion of every single study at a time.



**eFigure 7.** Relative risk of type 2 diabetes for each 1 km/hour increase in walking speed.

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