Investigating the prognostic value of digital mobility outcomes in patients with chronic obstructive pulmonary disease: a systematic literature review and meta-analysis

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Shareable abstract (@ERSpublications)
In COPD, daily step count and gait speed, collected as digital mobility outcomes (DMOs), are associated with mortality risk and may have value as predictive digital biomarkers or outcome measures in clinical trials. https://bit.ly/3PES3k3

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Abstract

Background: Reduced mobility is a central feature of COPD. Assessment of mobility outcomes that can be measured digitally (digital mobility outcomes (DMOs)) in daily life such as gait speed and steps per day is increasingly possible using devices such as pedometers and accelerometers, but the predictive value of these measures remains unclear in relation to key outcomes such as hospital admission and survival.

Methods: We conducted a systematic review, nested within a larger scoping review by the MOBILISE-D consortium, addressing DMOs in a range of chronic conditions. Qualitative and quantitative analysis considering steps per day and gait speed and their association with clinical outcomes in COPD patients was performed.

Results: 21 studies (6076 participants) were included. Nine studies evaluated steps per day and 11 evaluated a measure reflecting gait speed in daily life. Negative associations were demonstrated between mortality risk and steps per day (per 1000 steps) (hazard ratio (HR) 0.81, 95% CI 0.75–0.88, p<0.001), gait speed (<0.80 $m \cdot s^{-1}$) (HR 3.55, 95% CI 1.72–7.36, p<0.001) and gait speed (per 1.0 $m \cdot s^{-1}$) (HR 7.55, 95% CI 1.11–51.3, p=0.04). Fewer steps per day (per 1000) and slow gait speed (<0.80 $m \cdot s^{-1}$) were also associated with increased healthcare utilisation (HR 0.80, 95% CI 0.72–0.88, p<0.001; OR 3.36, 95% CI 1.42–7.94, p=0.01, respectively). Available evidence was of low-moderate quality with few studies eligible for meta-analysis.

Conclusion: Daily step count and gait speed are negatively associated with mortality risk and other important outcomes in people with COPD and therefore may have value as prognostic indicators in clinical trials, but the quantity and quality of evidence is limited. Larger studies with consistent methodologies are called for.

Introduction

Reduced physical mobility is associated with poorer health outcomes in healthy individuals as well as those with chronic disease [1–5]. People with COPD regard mobility limitation as a key aspect of their health [6] and there is considerable evidence linking reduced mobility, especially walking ability, to lung function decline, quality of life, hospitalisation risk, falls, acute exacerbations and mortality [7–12].

Walking activity and gait parameters such as gait speed, step length and steps per day have been used to assess walking-related mobility, or as a measure for physical activity, including within clinical trials [13, 14]. Despite emphasis being placed on the importance of mobility for people with COPD and for COPD outcomes, it is not routinely assessed in clinical practice. Existing measures suffer from limitations with a lack of evidence to support their implementation [15, 16]. Traditionally, mobility has been measured using either subjective patient-reported outcomes or objective clinic-based or laboratory-based physical capacity tests such as the 6-min walk test (6MWT) [17] and incremental shuttle walk test [18]. These outcomes may not be representative of an individual's day-to-day walking performance in their own environment, limiting their validity [19]. The introduction of activity monitors such as accelerometers and pedometers offers a real-world objective quantification of walking activity and gait parameters that can be used to monitor, personalise and improve disease management [20, 21].

A recent meta-analysis recognising the importance of improving physical activity levels in chronic respiratory disease highlights the inconsistency in available end-points used to measure mobility [22], with most measuring what an individual can do (*i.e.* capacity), rather than what they actually do (*i.e.* habitual behaviour) [23]. Advances in wearable technology in recent years means that real-world daily walking can be measured and monitored more comprehensively and affordably [24]. Traditional laboratory-based measurements technologically developed as real-world digital measures of mobility (digital mobility outcomes (DMOs)), *e.g.* gait speed, steps per day and walking bouts, could also have value as conveniently collected prognostic indicators [25]. This may be through the use of a pedometer, accelerometer or a simple stopwatch to measure gait speed in a test such as the 4-m gait speed (4MGS) intended to reproduce normal walking. There is still uncertainty around outcomes measured in daily life (physical activity/DMOs) linked to subjective experience of intensity or amount [26, 27], including which ones can be used to accurately predict events and overall prognosis in COPD [28] as well as whether they perform better than tests of pure capacity [23, 29].

MOBILISE-D is a consortium project working towards validating DMOs for use in clinical research and healthcare settings across a range of long-term conditions. This aim of this review, focusing exclusively on DMOs in people with COPD, was to set out the current evidence base relating walking activity and gait parameters (that have the potential to be measured digitally) to outcomes over time. This is needed to establish their prognostic value regarding both survival and other important clinical outcomes, including acute exacerbations and hospitalisation.

Methods

This review was registered online (PROSPERO CRD42021240146) and reported in accordance with the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines [30]. Studies were originally extracted and obtained from a scoping review performed in November 2019 by members of the MOBILISE-D consortium, including authors of the present paper and an experienced research librarian [28]. An update was performed in July 2021 to reflect COPD literature published after the initial search.

Search strategy and eligibility criteria

The detailed methodology of the scoping review has been published previously [28, 31]. To be eligible, papers had to report an original analysis of longitudinal data assessing the relationship between a walking activity or gait parameter and a clinical outcome at follow-up. There was no restriction on the follow-up period, but cross-sectional studies were excluded. Walking activity and gait parameters were included from studies recording real-world measurements (*e.g.* using pedometers or accelerometers) or from laboratory/clinic settings where gait speed was measured using shorter tests instrumented with a stopwatch (*e.g.* 4MGS) where gait was deemed likely to be similar to during day-to-day activities. Longer duration tests were excluded (such as 6MWT) owing to the greater likelihood of subjects pausing or slowing down, making it difficult to measure normal gait speed (supplement: appendix 2). Studies observing both stable and hospitalised patients were included but separate analyses were conducted, where data were available. Study outcomes had to include either mortality or a measure known to be associated with increased mortality in COPD, such as healthcare utilisation (hospital admissions) or exacerbations. For the sake of feasibility, a limited list of all mobility parameters and clinical outcomes was prespecified (supplement:

appendix 2) and further details on inclusion criteria, search strategy and eligibility screening process can be accessed in the supplementary material.

Data extraction

To facilitate a standardised data-extraction process, a web-based software platform (www.covidence.org) was used. Data extraction was performed by two independent reviewers (S.C. Buttery and P.J. Williams: both part of the original scoping review team) and then checked for accuracy by a third reviewer (S.M. Alghamdi: previous experience in conducting systematic literature reviews and meta-analyses). Any discrepancies were discussed between the two initial reviewers, and where an agreement could not be reached the third reviewer was consulted. Details regarding information extracted from all articles can be viewed in the supplementary material.

Reporting of individual study quality and risk of bias

To evaluate the quality of the evidence included in this review we used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool [32]. This tool uses four categories (very low, low, moderate and high) and evidence can be either upgraded or downgraded based on key criteria: risk of bias, inconsistency, indirectness, imprecision and publication bias [33].

We assessed the presence of bias in the studies included in this review using the Quality in Prognostic Studies (QUIPS) tool, which has been used in other prognostic systematic reviews and meta-analyses [34, 35] and has been recommended by the Cochrane Prognosis Methods Group [36]. QUIPS assesses six areas of potential bias: participation, attrition, prognostic factor measurement, outcome measurement, analysis and reporting. Each of the six items were scored as either high, low or unclear risk of bias by two independent assessors (S.C. Buttery and P.J. Williams) and an overall risk of bias was then assigned based on the individual domain ratings [37]. Disagreements between the two initial assessors were addressed by a third reviewer (S.M. Alghamdi) and settled by mutual resolution.

Statistical analyses

Alongside the narrative review, a meta-analysis was performed estimating the pooled unadjusted hazard ratios (HRs) with 95% CIs and p-values (<0.05 significant) for walking activity and gait parameters to predict clinical outcomes. The meta-analysis was performed using Stata (version 17.0) (StataCorp LLC, College Station, TX, USA). An overall effect size was estimated using a restricted maximum likelihood random-effects model [38], which assumes common variance of the true effect of the DMO in the individual studies. Where necessary, HRs were transformed to the selected unit effect measure to allow comparisons.

Heterogeneity between studies (I^2 statistic >50% indicates substantial heterogeneity), publication bias (Funnel plots and trim and fill estimator) and small studies effect (Egger's test) were assessed. Sensitivity analyses were conducted to further explore heterogeneity in the effect estimates using stratified meta-analyses.

Results

The original search carried out in November 2019 and the update conducted in July 2021 yielded a collective 21 084 records. 21 studies addressing the prognostic value of DMOs for COPD were considered eligible and included in this review (n=14 from the original search and n=7 from the update). A scoping review of the literature carried out in March 2023 did not retrieve any further eligible studies. Further details are presented in the Preferred Reporting of Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram (figure 1) and reasons for exclusion are shown in supplementary table S2.

Characteristics of included studies

The 21 studies included were published between 2011 and 2021. Of these, 14 were prospective cohort studies [25, 39–51], three were retrospective [52–54] and three reported a secondary analysis of randomised controlled trials (RCTs) [55–57]. Most studies were carried out in the USA (n=5), the UK (n=6) or another European country (n=5) (table 1). In the 21 studies, two DMOs were investigated as predictors of longitudinal outcomes and are the focus of this review: 1) steps per day as a measure of volume of walking (n=9 studies) and 2) gait speed as a measure of pace (n=11 studies). Associated outcomes were mortality (n=14), acute exacerbations of COPD (AECOPD) (n=5), significant lung function deterioration (n=1) and healthcare utilisation/readmission rates (n=8). Additionally, one study looked at health-related quality of life (HRQoL) and functional status and activities of daily living [40]. Studies size ranged from 53 to 1218 participants with a collective sample size of 6076 (41% female), a mean±SD age of 67.5±3.3 years and a forced expiratory volume in 1 s of 42.8±9.1% predicted. Most studies investigated

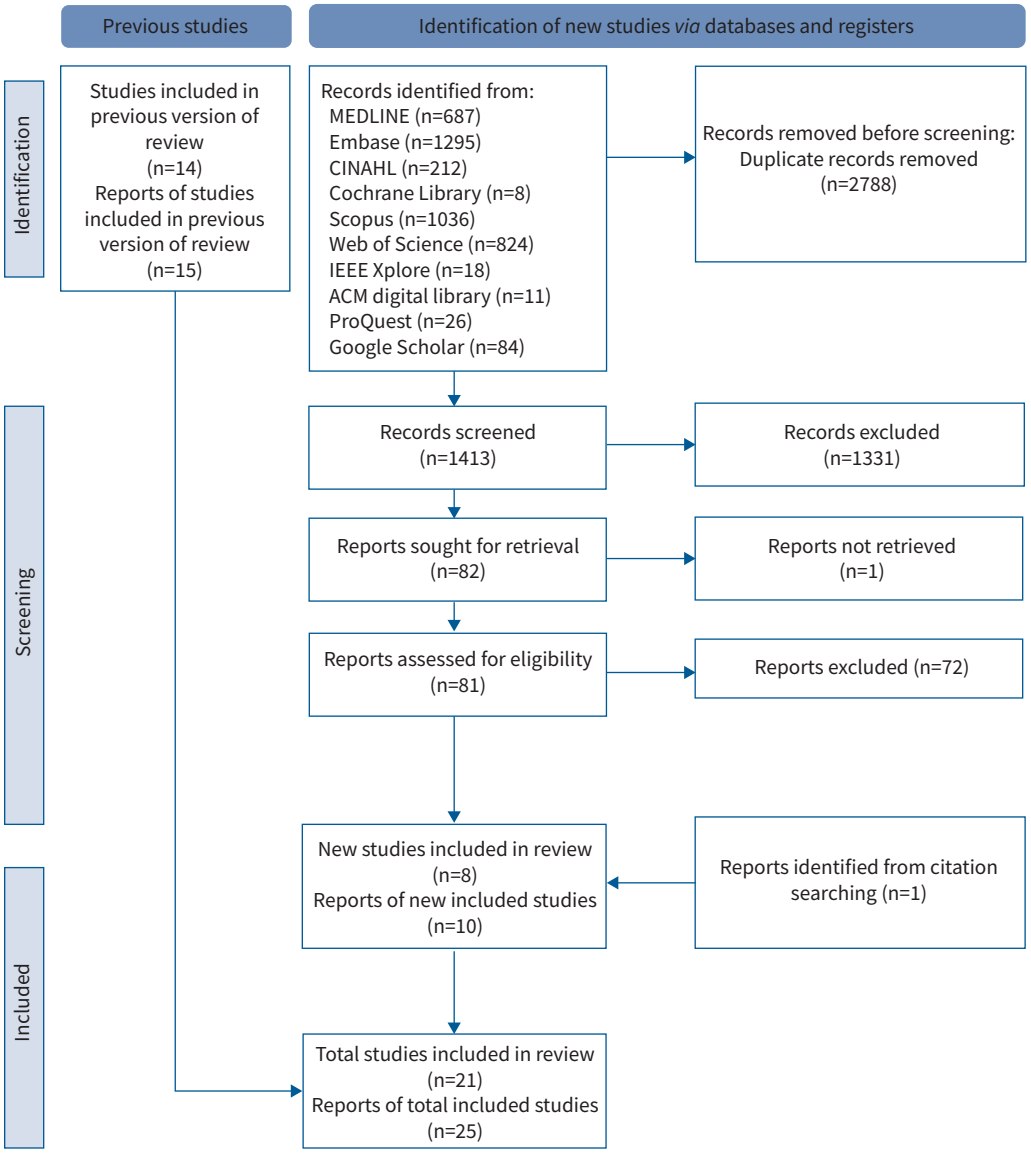

FIGURE 1 Preferred Reporting of Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for updated systematic reviews which included searches of databases, registers and other sources. Reasons for report exclusion are listed in supplementary table S2. One study had records in the original search and update, so there were 21 studies included in total.

stable COPD but two studies investigated hospitalised patients [39, 53]. Median study follow-up was 24 months (range 1–70 months, IQR 33.0 months).

All studies were included in the narrative analysis but only nine in the main quantitative data synthesis. 12 studies were excluded from the meta-analysis because of incomplete reporting of data or being unable to combine heterogenous study methodologies/data analysis. Of the included studies, five were conference abstracts [41, 45, 48, 52, 54]. Attempts to obtain unreported data from the authors of these abstracts were unsuccessful in all but two studies, where HRs [48] and clarification around unclear biases [52] were provided. Study characteristics per DMO are summarised in supplementary tables S4 and S5.

Gait speed was mostly investigated in laboratory-based assessments using 2-min walk distance (2MWD) [63] or 4MGS [64], which both involved the use of a stopwatch. Where a study described a "15-foot walk", this was taken to be equivalent to the 4MGS. In studies investigating steps per day, walking activity was assessed in a more real-world setting using a pedometer or accelerometer, most commonly the SenseWear (Bodymedia, Pittsburgh, PA) [65]. Wear time varied 10–22.5 $h \cdot day^{-1}$ for between two and

TABLE 1 Summary of included studies

First author, year(s) [reference(s)]	Study design	Country	Sample size (n)	Digital mobility outcome	Clinical outcome	Follow-up (months)	Plain text summary
Benzo, 2013 [56]	Secondary data analysis RCT	USA	1218	Gait speed	Mortality	24	Significant association
Cushen, 2016 [39]	Prospective cohort	Ireland	65	Steps·day^{-1}	Exacerbations	0.5	Significant association
Demeyer, 2017 [52]	Retrospective cohort	Europe (Belgium, Spain), UK and Brazil	758	Steps·day^{-1}	Mortality	48	Significant association
Demeyer, 2019 [40]	Prospective cohort	Europe (Spain, Belgium)	114	Steps·day^{-1}	Lung function, functional status and ADL, and HRQoL	31.2	Significant association in lung function and functional ADL but no association with HRQoL
Donaire-Gonzalez, 2015 [58]	Prospective cohort	Spain	177	Steps·day^{-1}	Healthcare utilisation	31.2	Significant association
Durheim, 2015 [57]	Secondary analysis part of RCT	USA	326	Steps·day^{-1}	Mortality and healthcare utilisation (time to first COPD-related hospitalisation)	4	Significant association for univariate analysis, nonsignificant trend for adjusted multivariable analysis
Fermont, 2020, 2021 [25, 59, 60]	Prospective cohort	UK	714	Gait speed	Exacerbations, healthcare utilisation	60	Significant association
Jones, 2019 [41]	Prospective cohort	UK	398	Gait speed	Mortality	12	Significant association
Kang, 2018 [55]	Secondary analysis part of RCT	USA	63	Steps·day^{-1}	Mortality	60	Significant association
Kon, 2015 [42, 61]	Prospective cohort	UK	213/402	Gait speed	Mortality [61], healthcare utilisation (risk of 90-day readmission to hospital) [42]	36	Significant association
Medina-Mirapeix, 2021 [43]	Prospective cohort	Spain	137	Gait speed	Exacerbations	12	Significant association for univariate analysis, no association for adjusted multivariable analysis
Nakano, 2021 [53]	Retrospective cohort	Japan	78	Gait speed	Mortality, healthcare utilisation, exacerbations	24	Significant association
Neo, 2017 [44]	Prospective cohort	Singapore	124	Gait speed	Mortality	18	Significant association
Neumannova, 2017 [45]	Prospective cohort	Czech Republic	174	Steps·day^{-1}	Mortality	36	Significant association
Pilsworth, 2018 [54]	Retrospective cohort	UK	448	Gait speed	Mortality	12	Significant association
Sievi, 2019 [46]	Prospective cohort	Switzerland	181	Steps·day^{-1}	Exacerbations	25.2	No association
Spacht, 2018 [62]#	Prospective cohort	USA	53	Gait speed	Healthcare utilisation (readmission at 30 days)	1	No association
Walsh, 2019 [48]	Prospective cohort	UK	472	Gait speed	Mortality	36	Significant association
Walsh, 2021 [47]	Prospective cohort	UK	213	Gait speed	Mortality, healthcare utilisation	12	Significant association
Wan, 2021 [51]	Prospective cohort	USA	176	Steps·day^{-1}	Mortality	69.6	Significant association
Waschki, 2011 [50]	Prospective cohort	Germany	170	Steps·day^{-1}	Mortality	48	Significant association
Witt, 2021 [49]#	Prospective cohort	USA	70	Gait speed	Healthcare utilisation (readmission at 30 days)	1	No association

RCT: randomised controlled trial; ADL: activities of daily living; HRQoL: health-related quality of life. #: studies had records in the original search and update, and reported the same findings.

14 consecutive days. Quantitative analysis of studies focused on mortality investigated in the linear association of steps per day expressed per 1000 steps difference. Gait speed was mostly analysed as a comparison of slow gait speed (<0.80 m·s^{-1}) *versus* normal gait speed (⩾0.80 m·s^{-1}), as well as incremental decline in gait speed (per 1.0 m·s^{-1}).

Walking activity (steps per day) and mortality

Six studies investigating the relationship between mortality risk and steps per day [45, 50–52, 55, 57] reported negative correlations which in all but one [57] were statistically significant. Two studies [45, 55] were excluded from meta-analysis (264 patients) because they did not report the effect estimate but found that walking between 3000 and 4000 steps·day^{-1} may be protective against mortality.

A meta-analysis of three observational studies [50–52] and one secondary analysis of an RCT [57] (n=1430 patients) demonstrated that a greater daily step count was associated with a reduced risk of mortality per 1000 steps (HR 0.81, 95% CI 0.75–0.88) (figure 2). Heterogeneity was reported to be low (I^2=37.10%, T^2=0.00) and funnel plots showed visual asymmetry (supplementary figure S1). Egger's test for small study effects did not indicate evidence of publication bias (p=0.077). A trim and fill estimator was used to verify this, and results supported our findings.

Sensitivity analysis excluding one study using an alternative cut-off to 1000 steps·day^{-1} did not show a substantial impact on the overall effect size (HR 0.84, 95% CI 0.79–0.89) (supplementary figure S2).

Gait parameters (gait speed) and mortality

Nine studies investigated gait speed and its relationship with mortality [25, 41, 44, 47, 48, 53, 54, 56, 61]. Papers by Kon *et al.* and Walsh *et al.* reported data from either the same cohort [42, 47, 61] or cohorts with significant cross-over [42, 48, 61]. Results from Kon *et al.* [42, 61] were included in the meta-analysis because statistical representation of data from solely these papers could be compared with other included studies (*e.g.* HRs).

Two studies, both abstracts with large sample sizes, were excluded from the meta-analysis; one (n=448) did not define how gait speed was measured or give an effect size [54] and the other (n=398) did not state a criterion to define a slow gait speed [41]. Nevertheless, both reported significant associations between gait speed and survival.

Meta-analysis of three studies (n=604) [44, 53, 61] showed that a slow baseline gait speed (<0.80 m·s^{-1}) (*versus* normal (⩾0.80 m·s^{-1})) had a significant impact on prognosis (HR 3.55, 95% CI 1.72–7.36) but with substantial heterogeneity (I^2=66.71) and publication bias (figure 3a and supplementary figure S7). Only one study in this model used 2MWD to measure gait speed and effect size was transformed for quantitative aggregation; all others used 4MGS. Removing this study caused a very slight reduction in effect size but with greater heterogeneity and considerable uncertainty (HR 3.62, 95% CI 1.19–11.03, I^2=76.12%) (supplementary figures S8a and S10a). Removing a study [53] investigating hospitalised

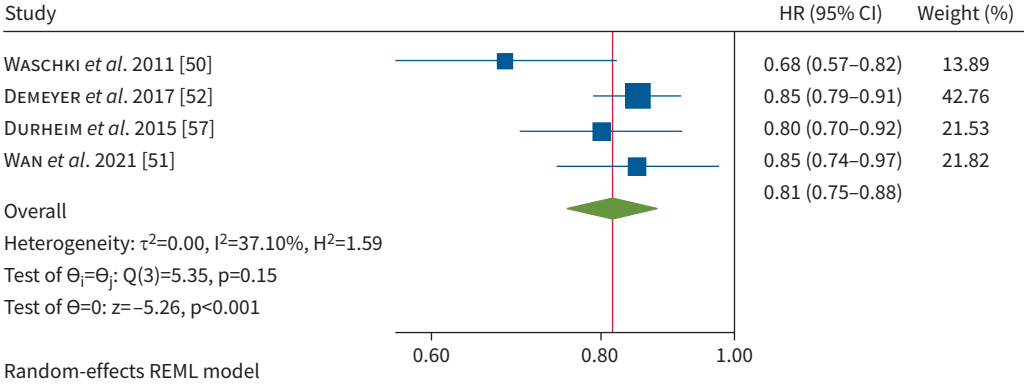

FIGURE 2 Association between daily step count and all-cause mortality in COPD. Hazard ratios (HRs) are presented with 95% confidence intervals. The red line is the average effect estimate. The black line shows no effect. REML: restricted maximum likelihood.

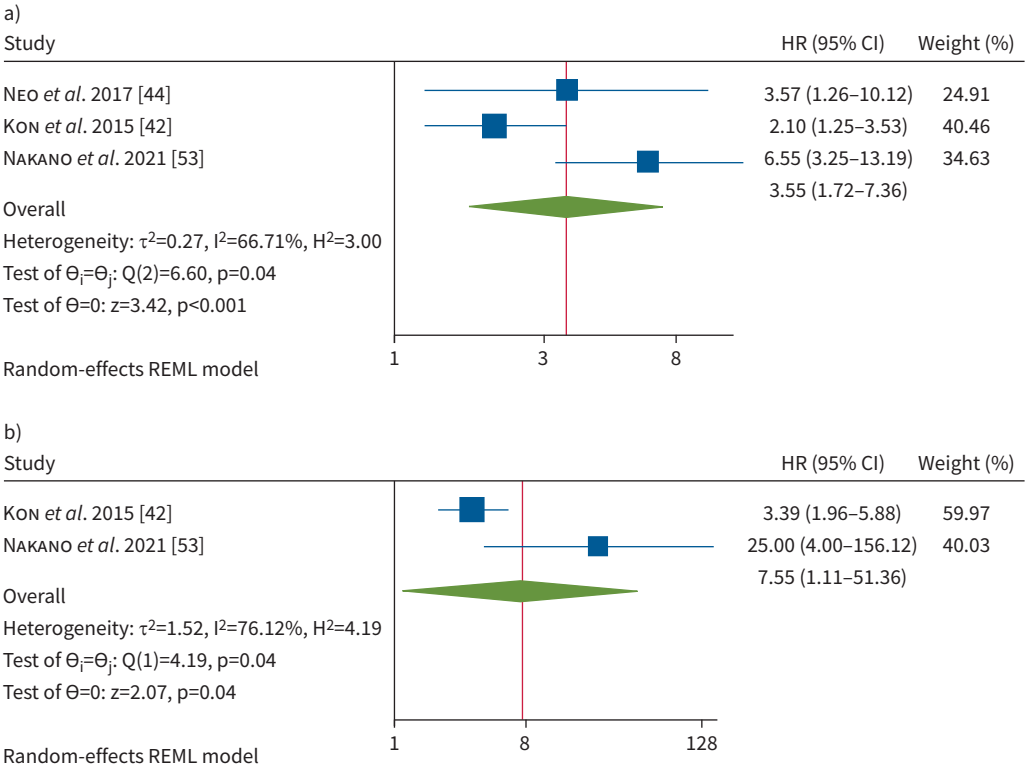

FIGURE 3 Association between a) low gait speed (<0.8 m·s^{-1}) and all-cause mortality in COPD. b) Decline in gait speed (per m·s^{-1}) and all-cause mortality in COPD. Hazard ratios (HRs) are presented with 95% confidence intervals. The red line is the average effect estimate. The black line shows no effect. REML: restricted maximum likelihood.

COPD patients increased the effect size and reduced heterogeneity (HR 2.33, 95% CI 1.47–3.71, I^2=0.00%) (supplementary figures S8b and S10b).

Two studies (n=480) [53, 61] showed strong association between declining gait speed and mortality risk (HR 7.55, 95% CI 1.11–51.3) (figure 3b and supplementary figure S8) but were highly heterogeneous (I^2=84.73%) and publication bias was likely (supplementary figure S10a, b). A further study [25] supported these findings but was excluded from meta-analysis because it reported short physical performance battery (SPPB) points change, rather than the actual pace (m·s^{-1}), as was reported in other studies.

Walking activity and gait parameters and exacerbations

Five studies reported data relating walking activity and gait parameters to AECOPDs. Two observed the relationship between steps per day and AECOPDs [39, 46]. Sievi *et al.* [46], in a cohort with stable but severe COPD, found no association between steps per day and occurrence of AECOPD over time (coefficient 58.4, 95% CI −189.3–72.5, p=0.38). Contrastingly, a study [39] observing inpatients admitted with an AECOPD showed that there was a relationship between those with increased steps per day (⩾396 steps) at 14 days post-discharge and absence of a further AECOPD in this time period (area under the receiver operating characteristic curve 0.66, 95% CI 0.46–0.82).

Significant associations were also reported in studies investigating gait speed and the risk of AECOPDs [43, 53, 59]. However, Medina-Mirapeix *et al.* [43] found that this association did not remain significant when adjusting for age and exacerbations in the previous year. Nakano *et al.* [53] concluded that having an AECOPD event and the time to first AECOPD during the observation period were both positively associated with a slower gait speed (p=0.0124 and R=0.47, p=0.0042, respectively), which was supported by similar associations in the study by Fermont *et al.* [59] but in the context of exacerbations requiring hospitalisation. Meta-analysis was not performed for AECOPD owing to differences in data analysis and reporting methodology.

Walking activity and gait parameters and healthcare utilisation/admissions to hospital

Both Kon *et al.* [42] and Fermont *et al.* [59, 60] reported findings showing that a slower gait speed was associated with a higher risk of admission, including both severe AECOPDs requiring hospitalisation and cardiovascular-related admissions. This was in contrast to Witt *et al.* [49] who found that there was no significant relationship between gait speed and healthcare utilisation but in a smaller sample and over a shorter observation period. Studies could not be combined in meta-analysis because relationships were reported in the context of different reporting methods (median 4MGS and point change in 4MGS as part of the SPPB, respectively). However, meta-analysis of two studies (n=283) [42, 49] suggested that patients with a slow gait speed (<0.80 $m \cdot s^{-1}$) were three times more likely to be readmitted to hospital in the short-term (90 days) (OR 3.36, 95% CI 1.42–7.94, I^2=0.00%) (supplementary figures S11 and S12) and healthcare utilisation also showed a negative correlation, with steps per day and time to first COPD-related hospitalisation being associated with a 20% greater risk per 1000 steps·day^{-1} decrease (HR 0.80, 95% CI 0.72–0.882) (supplementary figures S13 and S14).

Walking activity, gait parameters and lung function, HRQoL and functional activities of daily living

We identified one study which reported, in a largely male cohort, associations between baseline steps per day and subsequent decline in lung function parameters and St Georges Respiratory Questionnaire (SGRQ) symptoms score but no other SGRQ domains or functional status/activities of daily living [40].

Critical appraisal of studies, quality and risk of bias

Table 2 and supplementary figure S15 summarise the quality and risk of bias (QUIPS) of included studies. The quality of evidence was generally deemed low to moderate [32]. The majority of included studies were observational, which are considered lower grade evidence than other study designs, and a number were also conference abstracts, rather than full study manuscripts. However, the evidence supporting an association between steps per day and mortality and between gait speed and healthcare utilisation was upgraded from low to moderate and for between gait speed and mortality from very low to low owing to methodologically rigorous studies having a large magnitude of effect [66].

In total, 11 studies were graded as being at an overall high risk of bias and nine as having a low risk of bias. Participation, prognostic factor measurement and confounding were the most common reasons for bias being present in studies, but a large contributing factor was the unclear risk of bias mostly owing to the limited reporting in abstract papers.

Discussion

The findings from this systematic literature review and meta-analysis demonstrate important relationships between walking activity and gait parameters (steps per day, gait speed) and mortality risk, establishing the potential prognostic value of these parameters as DMOs. However, the number of studies was low and overall quality of evidence to support associations was affected by some limitations.

Significance of findings

Walking activity and gait parameters have previously been evaluated in a number of other reviews and meta-analyses but these largely appraised the psychometric properties of outcomes that could be collected digitally [22, 67] or as part of physical activity promotion interventions [68, 69]. Among a long list of potential DMOs considered, only two were found to be assessed longitudinally in COPD; steps per day and gait speed. Of note, we did not consider physical activity parameters that were not walking specific as DMOs and, therefore, studies evaluating total quantity or intensity of physical activity such as vector magnitude units or time in moderate to vigorous physical activity were not included. However, our findings support those presented by Gimeno-Santos *et al.* [10] in a review of determinants of physical activity that was not restricted to the *a priori* decided digital measures.

The 4MGS and 2MWD were taken to be representative of normal continuous walking in comparison to the 6MWT, which may include a greater number of pauses or changes in pace due to the longer duration. Measures such as 4MGS are quick and simple to administer, requiring only a small amount of space and resource. Likewise, daily step count can be measured routinely with relative ease using a small device without interruption to daily life. Owing to their practicability and potential to be collected digitally, measures such as these could be of greater clinical value in monitoring and identifying patients at high risk for significant events such as AECOPDs, admissions and mortality [19, 67].

Pooled effects analysis suggests that doing 1000 steps·day^{-1} more could be associated with a decrease in mortality of between 19% and 23%, and a reduction in healthcare utilisation. However, causality cannot be assumed given that many of the studies used a between-patient, rather than within-patient, design. Thus,

TABLE 2 GRADE certainty of evidence summary of findings table

Participants (n)/ studies	Quality assessment					
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence GRADE
Daily step count and mortality						
1629 Six cohorts	Moderate risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Strongly suspected	⊕⊕⊕⊙ Moderate
Gait speed and mortality						
3177 Seven cohorts	High risk of bias	Serious inconsistency	Serious indirectness	Serious imprecision	Strongly suspected	⊕⊕⊙⊙ Low
Daily step count and healthcare utilisation						
465 Two cohorts	Moderate risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊙ Moderate
Gait speed and healthcare utilisation						
1075 Four cohorts	Moderate risk of bias	Serious inconsistency	Serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊙ Moderate
Daily step count and exacerbations						
224 Two cohorts	High risk of bias	Serious inconsistency	Serious indirectness	No serious imprecision	Undetected	⊕⊕⊙⊙ Low
Gait speed and exacerbations						
929 Three cohorts	Moderate risk of bias	Serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊙⊙ Low
Daily step count and lung function, HRQoL, functional status/ADLs						
114 One cohort	High risk of bias	No serious inconsistency	Serious indirectness	No serious imprecision	Undetected	⊕⊕⊙⊙ Low
Gait speed and cardiovascular events						
714 One cohort	Low risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	⊕⊕⊕⊙ Moderate

All outcomes started with a baseline GRADE rating of low. Daily step count and mortality marked up due to large magnitude of effect; gait speed and healthcare utilisation marked up due to large magnitude of effect; gait speed and cardiovascular events marked up due to large magnitude of effect. GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; HRQoL: health-related quality of life; ADL: activities of daily living. ⊕: GRADE quality criteria met; ⊙: downgrading for decreased quality based on quality criteria.

suggested findings would need to be evaluated in prospective interventional trials. Furthermore, the sensitivity and specificity of this and other included associations has not been explored. Here we reviewed the available evidence, but evaluation of other characteristics will be important in confirming the value of DMOs as predictive digital biomarkers [19, 70]. Furthermore, we cannot rule out the impact of confounders that may not have been accounted for but could have played a role in the associations.

A low daily step count (between 3000 and 4000 steps·day^{-1}) appeared to be associated with increased mortality risk over time but a lack of information, including participant characteristics, methodology and reporting of statistics, meant that the studies could not be combined in a meta-analysis and all associations were based on low-quality evidence. Nevertheless, comparable recent work in healthy older people shows a link between more steps per day and increased survival, up to a threshold of 6000–8000 steps·day^{-1} [71]. A previous study showed correlation between greater steps per day in a group of COPD patients using a pedometer, compared to a control group, and fewer exacerbations [72]. Our findings may be useful reference points when monitoring steps per day as a measure of mobility or when discussing the importance of increasing and maintaining physical activity levels with a patient, but the large effect size of steps per day on mortality and the linearity of this association requires further investigation. Of note, although related, the impact of physical capacity (what people can do) and physical activity (what people actually do) may have different prognostic value [23].

There was low-quality evidence to support the significant association between gait speed and survival in terms of both having a slow gait speed and particularly with a declining gait speed. Digitally assessed gait speed is a reliable indicator of age-related decline associated with important health outcomes and other measures of function [64, 73–75]. Additionally, its utility as a gait parameter estimating real-world walking speed measured using an activity monitor has been demonstrated [73]. The large effect size we found between a reduction in gait speed and mortality suggests that it could be used to monitor and highlight deterioration over time, signalling when intervention is indicated. Additionally, a slow gait speed could

categorise hospitalised patients who are at higher risk for readmissions and therefore may be candidates for community care or services such as hospital at home. Interestingly, removing the only study that evaluated mortality risk and gait speed in hospitalised patients yielded the greatest effect size and therefore this association cannot be generalised to hospitalised COPD patients.

The relationship between mobility and admissions has been explored previously [76, 77] but in studies using subjective measures to quantify physical activity level, in which problems of overreporting are well-known [78]. Additionally, our findings in step count and gait speed are consistent with physical activity more broadly as presented by Garcia-Rio *et al.* [15], who concluded that amount and intensity (vector magnitude units) of daily activity was predictive of admission rate. We do acknowledge that walking makes up a substantial amount of physical activity.

The relationship between walking activity and gait parameters and other clinical outcomes (AECOPDs, lung function parameters, HRQoL and function) was unclear either because of the heterogeneity of studies or sparseness of available evidence according to our research criteria. However, recent findings from a pooled analysis found that increasing steps per day by as little as 750 steps may be associated with an improvement in quality of life in people with COPD [79]. This is supported by previous work suggesting a minimum importance difference of between 600 and 1100 steps·day^{-1} following pulmonary rehabilitation [80]. Greater research is required in more routinely used clinical outcomes such as AECOPD, lung function, HRQoL and functional status to provide clarity around the utility of steps per day, gait speed or other walking activity and gait parameters in predicting these outcomes.

Limitations

The results of this meta-analysis must be interpreted with some caution owing to the small number of studies, their quality and the heterogeneity of the assessment of DMOs in the studies that were included. This is largely due to the review being based on observational studies, which do suffer from shortcomings in trial design, partly because of the likelihood of publication bias due to preregistration and protocol preparation not being mandatory for observational studies; this therefore makes it difficult to identify unpublished studies or other reporting biases [81].

The quality and heterogeneity of the studies observing the relationship between gait speed and mortality meant that many could not be included in the meta-analysis and those that could were hampered by the differences in study design and participant characteristics. For example, the majority of studies investigated gait speed using the 4MGS, an instrument that has been extensively studied in a COPD population with its validity and reliability confirmed [64, 82]. However, a number of studies instead used the 2MWD, making comparison in a meta-analysis difficult. In addition, three of the largest studies could not be included in the quantitative analysis because of reporting limitations [41, 54, 56]; therefore, effect estimates may actually be underestimated. The wide confidence intervals that were reported in meta-analyses, particularly in those analysing gait speed, should also be noted because they indicate poorer precision of the effect estimate. The limitations associated with different methodologies for measuring gait speed have been described previously [75]. Differences were also evident in studies investigating walking activity. For example, the type of device used to measure daily step count, the location it was worn and the duration of time it was worn all introduce diversity and potential bias when pooling data. An international task force has published recommendations for working towards a common framework in objective measurement of physical activity [83].

A proportion of the included studies were conference abstracts and, in these abstracts, it was often difficult to report the presence of bias due to restricted methodology, and the small number of studies meant that subgroup analysis was not possible. The lack of studies exploring other measures of walking activity and gait parameters is also of note given the recent interest in sedentary behaviour on health outcomes. Alternative measures of volume of walking such as walking bouts (number, length, duration) are available and may also be of value as prognostic measures, but more research is needed.

The heterogeneity of included studies must also be considered. This heterogeneity was due to differences in study design, outcomes used, analysis methods and participant selection criteria, which is a significant source of inconsistency in relation to variables such as disease severity and stable *versus* hospitalised patients as well as lack of commonality in confounders. We aimed to address this in several ways, *i.e.* by transforming unit effects where necessary, using random-effects models and conducting sensitivity analyses.

Future research should focus on validating the prognostic ability of gait speed and other DMOs in larger studies and using standardised methodologies that can be compared across studies.

Questions for future research

- Future research should address methodological inconsistencies and increase the number and range of COPD patients enrolled to build understanding of the predictive value of walking activity and gait parameters that can be measured digitally across disease phenotypes.
- Interpretation of the literature is limited by bias, largely due to observational study designs, heterogeneous methodologies and conference abstracts that were not written up into full studies. Evaluation in prospective interventional trials is called for.
- Future research addressing the feasibility of implementing digital mobility outcomes into clinical practice should focus on which walking activity and gait parameters are superior predictive digital biomarkers and the sensitivity and specificity of such measures.

Conclusion

Although the evidence on the prognostic value of walking activity and gait parameters measured digitally in people with COPD is limited to a few studies, these studies do provide evidence that taking fewer steps per day and/or having a slower or decreasing gait speed is associated with a greater mortality risk. Therefore, these DMOs may have value as prognostic indicators and outcome measures in clinical trials.

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