



Association of preserved ratio impaired spirometry with mortality: a systematic review and meta-analysis

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Individuals with PRISm have a significantly increased risk of all-cause, cardiovascular and respiratory-related mortality compared with those with normal spirometry. These findings highlight the importance of recognising PRISm in clinical settings. <https://bit.ly/3qWGIHZ>

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Abstract

Background: Preserved ratio impaired spirometry (PRISm) is prevalent within the general population. Increased mortality has been reported among subjects with PRISm, but the evidence has never been summarised. This systematic review aims to synthesise evidence on the association between PRISm and the risk of all-cause, cardiovascular and respiratory-related mortality.

Methods: We systematically searched MEDLINE, Embase and Web of Science for population-based cohort studies from inception to April 2023 using the terms related to impaired spirometry and mortality. Titles and abstracts were screened to identify eligible studies that reported mortality estimates for individuals with PRISm. We excluded studies that adopted other definitions of impaired spirometry, had a specific study setting (e.g. HIV patients), had an insufficient follow-up period (<1 year) or reported duplicated data. Random-effects meta-analysis was used to produce pooled hazard ratio (HR) with 95% confidence intervals. Between-study heterogeneity was assessed with I^2 .

Results: Eight studies met the inclusion criteria involving 40 699 individuals with PRISm. All included studies reported increased risk of all-cause mortality among adults with PRISm. Meta-analysis showed that PRISm was associated with an increased risk of all-cause mortality (pooled HR 1.71, 95% CI 1.51–1.93; $I^2=64%$), cardiovascular mortality (pooled HR 1.57, 95% CI 1.44–1.72; $I^2=35%$) and respiratory-related mortality (pooled HR 1.97, 95% CI 1.55–2.49; $I^2=0%$).

Conclusions: Individuals with PRISm have a significantly increased risk of mortality compared with those with normal spirometry.

Introduction

There is significant heterogeneity in the definitions of impaired lung function characterised by the proportionate reductions in forced expired volume in 1 s (FEV_1) and forced vital capacity (FVC). The widely used phenotype in previous studies was “restrictive spirometry pattern”, which is defined by a nonobstructive ratio of FEV_1/FVC and reduced FVC [1]. Preserved ratio impaired spirometry (PRISm), a nonobstructive spirometry phenotype defined as the presence of low FEV_1 with a preserved ratio of FEV_1 in FVC, was subsequently introduced to distinguish the pattern from “nonspecific abnormality” and “restriction” that require the assessment of total lung capacity [2, 3]. PRISm has been described as a transitory state with increased rates of transitions to both normal and obstructive spirometry [4, 5] and is linked to the progression to COPD [4]. It is also associated with increased respiratory symptoms [2], poor quality of life [6] and an elevated risk of cardiovascular events [7] and all-cause mortality [4, 8–14]. Currently, there are no clinical guidelines for the diagnostic evaluation and management of PRISm despite the high prevalence rate of this phenotype globally, in a range between 7.1% and 25.9% [9, 10].

Given the limited understanding in the functional and structural pathophysiology of PRISm, there is an urgent need to summarise the current evidence systematically on the mortality impact of this spirometry phenotype so that the targeted interventions and rehabilitation therapies can be more objectively developed.



However, although several studies on the association between PRISm and health outcomes have been carried out in different populations since the concept of PRISm was introduced in 2014 [4, 8–14], the implications from individual studies are limited by many influential factors such as the regional differences in healthcare resources, local protocols and lifestyle factors. Furthermore, with a substantially increased body of data on PRISm now becoming available, a detailed and up-to-date synthesis of current evidence on the impact of PRISm on mortality is required to better understand the natural history of PRISm and guide ongoing healthcare provision. To inform these deliberations, we conducted a systematic review and meta-analysis to comprehensively evaluate the mortality impact of PRISm, focusing on the specific endpoints of all-cause mortality, cardiovascular mortality and respiratory-related mortality.

Methods

Search strategy

We systematically reviewed MEDLINE, Embase and Web of Science databases to identify the studies reporting data on risk of mortality in people with PRISm from inception to 14 April 2023. The studies were identified using terms related to impaired spirometry and mortality. A complete list of search strategies is available in the supplementary material. The citations of the eligible papers were also searched to identify the potentially relevant studies. Search strategies were pre-defined and agreed by all authors.

Study review

In this systematic review, PRISm was defined as a pre- or post-bronchodilator FEV₁/FVC ratio ≥ 0.7 with FEV₁ <80% predicted. Population-based cohort studies reporting the risk of all-cause, cardiovascular and respiratory-related mortality among individuals with PRISm were eligible for inclusion. We excluded studies if they 1) adopted other criteria for impaired spirometry; 2) had a specific study setting (*e.g.* HIV patients); 3) had a follow-up period <1 year; or 4) reported duplicated data. Two reviewers (S. Yang and G. Liao) independently screened the titles and abstracts of each record, and the potentially relevant records were further assessed for full-text review. The discrepancies were resolved by the consensus of two reviewers or the involvement of the third reviewer (L.A. Tse). The publications identified *via* manual searching of the references from eligible papers were subject to the same inclusion and exclusion criteria.

Quality assessment

The quality of the included studies was evaluated based on the Newcastle–Ottawa scale [15]. This scale scores the quality of a cohort study uses a star rating system based on the selection of study cohort (0–4 stars), comparability of adjustment for the confounding factors (0–2 stars) and the ascertainment of the outcome of interest (0–3 stars). For cohort selection, stars were awarded if the exposed cohort was truly representative of the exposed individuals in the community (1 star), the control cohort was drawn from the same community as the exposed cohort (1 star), the spirometry was post-bronchodilator and with assured quality (1 star) and the outcome of interest was not present at the start of study (1 star). For cohort comparability, one star was assigned if studies adjusted for at least age, sex and smoking status, and an additional star was given for the other confounding factors that were controlled for. For outcome assessment, stars were given if studies used record linkage to assess the outcome (1 star), had adequate follow-up period for the outcome to occur (1 star) and had a loss to follow-up rate <10% (1 star). Two researchers (S. Yang and G. Liao) independently assessed the quality of studies and came to consensus over discrepancies through discussion or in consultation with a third researcher (L.A. Tse).

Data extraction

The information extracted from the eligible studies were the name of the first author, year of publication, name of study, country of study, characteristics of study population, sample size, number of cases with PRISm, mean/median age of participants, criteria of PRISm definition (fixed ratio/lower limits of normal), whether post-bronchodilator test (yes/no), causes of death and measure of mortality estimates (*e.g.* hazard ratio (HR)) with 95% confidence interval. Two researchers (S. Yang and G. Liao) independently extracted data from eligible studies and came to consensus over discrepancies through discussion or in consultation with a third researcher (L.A. Tse).

Data analysis and synthesis

The random-effects meta-analysis was carried out to estimate the pooled HR of mortality among individuals with PRISm. The mortality estimates extracted from individual study were log-transformed and the 95% confidence intervals were used to calculate the corresponding standard errors. The pooled HR was then estimated based on log mortality estimates and standard errors using generic inverse variance method. Between-study heterogeneity was assessed by the I² statistic and Q-test and classified as low (I²=0–24%), moderate (I²=25–49%), substantial (I²=50–74%) and high (I²=75–100%). In cases of substantial or high heterogeneity, subset analyses with the removal of one or more individual studies and univariate

meta-regression were conducted to explore the source of heterogeneity. Study-specific effect size of the moderator of interest from meta regression was presented using meta-analytic scatter plot (bubble plot). Influential studies were assessed using Baujat plots. The publication bias was tested using Egger’s test and visualised using a funnel plot. All statistical analyses were carried out using R (version 4.3.0), and a two-sided p-value <0.05 was considered statistically significant.

Registration and reporting

The protocol of this study is registered at www.crd.york.ac.uk/prospero (registration number CRD42023408252). The present study is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis reporting guideline [16].

Results

Search results and study characteristics

The literature search yielded 6261 records. After the screening of titles and abstracts, 94 studies qualified for the full-text review, of which eight were eligible for the systematic review (figure 1) [4, 8–14]. Among

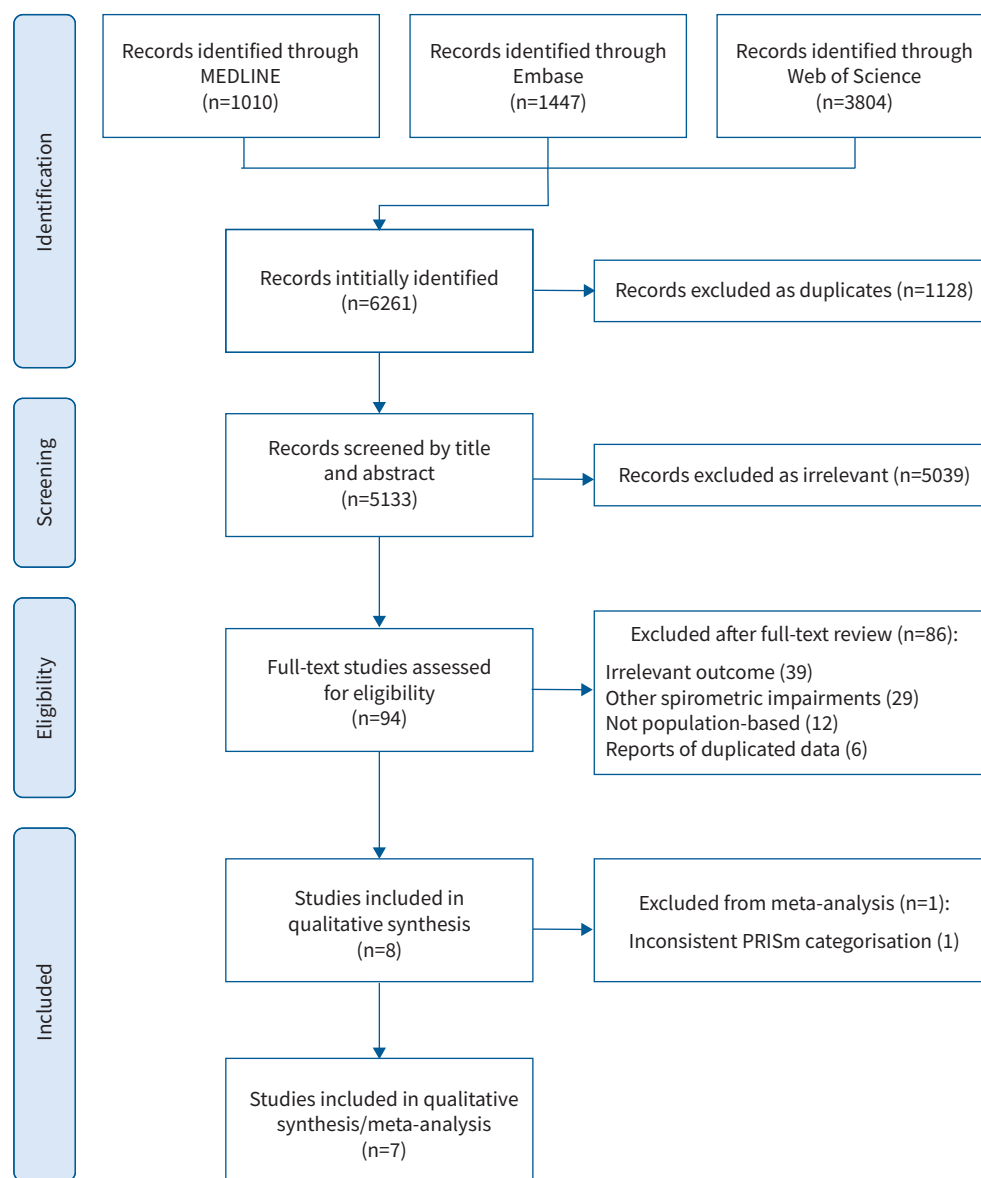


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analysis flowchart for the systematic review and meta-analysis.

TABLE 1 Summary of included studies

Author, year [reference]	Study	Country	Population notes	Subjects	PRISm cases	Prevalence of PRISm	Age years	Criteria	Post-BD?	Outcome	HR (95% CI)
WAN, 2018 [8]	COPDGene Study	USA	Non-Hispanic white and African American smokers aged 45–80 years	10 133	1260	12.40%	59.6	Fixed ratio	Yes	All-cause death	2.02 (1.60–2.54)
WIJNANT, 2020 [9]	Rotterdam Study	The Netherlands	Residents of Ommoord district in the city of Rotterdam aged ≥45 years	5487	387	7.1%	69.1	Fixed ratio	No	All-cause death; cardiovascular death	1.6 (1.2–2.0) for all-cause death; 2.8 (1.5–5.1) for cardiovascular death
MAROTT, 2021 [10] [#]	Copenhagen City Heart Study	Denmark	Individuals living in the inner city of Copenhagen aged 20–40 years	2387 (initial survey); 1208 (last survey)	619 (initial survey); 166 (last survey)	25.9% (initial survey); 13.7% (last survey)	NA (initial survey); 59.1 (last survey)	Fixed ratio	No	All-cause death	PRISm to normal 1.16 (0.70–1.92); normal to PRISm 2.84 (1.86–4.33); persistent PRISm 3.50 (2.29–5.34)
WAN, 2021 [11]	National Heart, Lung, and Blood Institute Pooled Cohorts Study	USA	Nine USA cohorts of community-dwelling adults aged 18–102 years	53 701	4582	8.50%	53.2	Fixed ratio	No	All-cause death; cardiovascular death; respiratory-related death	1.50 (1.42–1.59) for all-cause death; 1.55 (1.36–1.77) for cardiovascular death; 1.95 (1.54–2.48) for respiratory-related death
HIGBEE, 2022 [12]	UK Biobank	UK	Residents of the UK aged 40–69 years	351 874	38 639	11.0%	56.1	Fixed ratio	No	All-cause death	1.61 (1.53–1.69)
KAACKS, 2022 [13]	German Lung Cancer Screening Intervention Study	Germany	Population registers aged 50–69 years with a history of smoking	1987	311	15.70%	56.4	Fixed ratio	No	All-cause death	2.29 (1.65–3.19)
WASHIO, 2022 [4]	Hisayama Study	Japan	Residents of Hisayama aged ≥40 years	3032	301	10.0%	63.0	Fixed ratio	No	All-cause death; cardiovascular death; respiratory-related death	2.00 (1.22–3.30) for all-cause death; 3.20 (0.84–12.27) for cardiovascular death; 3.39 (0.53–21.52) for respiratory-related death
ZHENG, 2023 [14]	UK Biobank	UK	Residents of the UK aged 40–69 years	329 954	37 897	11.50%	55.9	Fixed ratio	No	Cardiovascular death	1.55 (1.37–1.76) for cardiovascular death

Data are presented as n, unless otherwise stated. PRISm: preserved ratio impaired spirometry; BD: bronchodilation; HR: hazard ratio; NA: not available. [#]: not included in the meta-analysis.

TABLE 2 Comparison of smoking statistics between individuals with and without preserved ratio impaired spirometry (PRISm)

Author, year [reference]	Current smokers %		Pack-years n	
	PRISm	Control	PRISm	Control
WAN, 2018 [8]	63.7	59.7	42.6	37.2
WIJNANT, 2020 [9]	14.0	9.2	8.5	3.0
WAN, 2021 [11]	46.3	38.1	21.0	10.4
HIGBEE, 2022 [12]	12.4	7.9	23.0	16.0
KAAKS, 2022 [13]	64.6	59.5	43.2	40.9
WASHIO, 2022 [4]	16.9	15.1	36.0	25.0
ZHENG, 2023 [14]	12.0	7.9	22.0	16.0

the eligible studies, seven reported the mortality risk of individuals with baseline PRISm and were included in the meta-analyses [4, 8, 9, 11–14], while one study [10] presented the mortality estimates of subsets of PRISm with distinct trajectories, *e.g.* PRISm-to-normal, normal-to-PRISm and persistent PRISm [10]. The characteristics of the eligible studies included in the systematic review are presented in table 1. Most of the studies were carried out in the Europe (United Kingdom n=2, Germany n=1, Denmark n=1, Netherlands n=1) [9, 10, 12–14] or the USA (n=2) [8, 11], except one that was conducted in Japan [4]. All studies were population-based, of which six were conducted in the general population [4, 9–12, 14], and two focused on individuals with a history of smoking [8, 13]. Although the prevalence of PRISm varies from 7.1% in the Rotterdam Study [9] to 25.9% in the Copenhagen City Heart Study [10], all studies reported higher percentage of current smokers and more pack-years among individuals with PRISm than in people with normal spirometry (table 2). Of the eight eligible studies included in the systematic review, seven reported the estimate of all-cause mortality [4, 8–13], four reported the estimate of cardiovascular mortality [4, 9, 11, 14] and two reported the estimate of respiratory-related mortality [4, 11]. The quality of included studies was high in all three categories assessed (table 3).

Association of PRISm with all-cause mortality

All included studies reported a significant association between baseline PRISm and increased risk of all-cause mortality, with the HR ranging from 1.50 to 2.29 (figure 2a) [4, 8, 9, 11–13]. The pooled HR of all-cause mortality among individuals with baseline PRISm was 1.71 (95% CI 1.51–1.93). MAROTT *et al.* [10] reported differentiated risk of all-cause mortality among individuals with distinct trajectory of PRISm: the risk was significantly increased among individuals with new or persistent PRISm (normal to PRISm HR 2.84, 95% CI 1.86–4.33; persistent PRISm HR 3.50, 95% CI 2.29–5.34) but the increase in risk was not significant among those who transitioned out of PRISm (HR 1.16, 95% CI 0.70–1.92) [10]. Substantial heterogeneity across the included studies were observed in the meta-analysis ($I^2=64%$, $p=0.02$). The Baujat plot identified two studies [8, 13] overly contributing to heterogeneity, in which the study populations were individuals with a history of smoking (supplementary figure S1). Random-effects univariate meta-regression indicated that percentage female ($p<0.001$), percentage current smokers ($p=0.03$) and mean/median pack-years ($p<0.001$) were significantly associated with all-cause mortality (table 4, supplementary figures S2–S4). Subgroup meta-analysis was carried out to differentiate between the smokers and general population for the included studies and demonstrated a higher risk of all-cause mortality among PRISm individuals with a history of smoking (pooled HR 2.11, 95% CI 1.74–2.54) as compared to the general population (pooled HR 1.56, 95% CI 1.47–1.66) (figure 3). No significant between-subgroup heterogeneity was observed between studies on smokers ($I^2=0%$, $p=0.54$) and the general population ($I^2=31%$, $p=0.22$). Egger's tests suggested no evidence of publication bias ($p=0.12$).

Association of PRISm with cardiovascular and respiratory-related mortality

Of the four studies reporting cardiovascular mortality, three reported a significant association between PRISm and an increased risk of cardiovascular mortality, with the HR ranging from 1.55 to 2.80 (figure 2b). The pooled HR of cardiovascular mortality was 1.57 (95% CI 1.44–1.72) with moderate heterogeneity ($I^2=35%$, $p=0.20$). For respiratory-related mortality, the meta-analysis of two studies showed that the pooled HR was 1.97 (95% CI 1.55–2.49) with low heterogeneity ($I^2=0%$, $p=0.56$) (figure 2c).

Discussion

This systematic review and meta-analysis found that individuals with PRISm have significantly increased mortality compared with those with normal spirometry. Overall, the risk of all-cause mortality in PRISm population was increased by 71%. Moreover, individuals with PRISm have 57% and 97% increased risk of

TABLE 3 Quality assessment of included studies

Author, year [reference]	Selection				Comparability	Assessment of outcome [#]	Outcome		Total quality score
	Representativeness of exposed cohort [#]	Selection of nonexposed cohort [#]	Ascertainment of exposure [#]	Showing that outcome of interest was not present at the start of the study [#]	Comparability of cohorts based on design or analysis [¶]		Follow-up long enough for outcomes to occur [#]	Adequacy of follow-up of cohorts [#]	
WAN, 2018 [8]	0 ⁺	1	1.0	1	2	1	1	1	8.0
WIJNANT, 2020 [9]	1	1	0.5	1	2	1	1	1	8.5
MAROTT, 2021 [10]	1	1	0.5	1	1	1	1	1	7.5
WAN, 2021 [11]	1	1	0.5	1	2	1	1	1	8.5
HIGBEE, 2022 [12]	1	1	0.5	1	2	1	1	1	8.5
KAAKS, 2022 [13]	0 ⁺	1	0.5	1	2	1	1	1	7.5
WASHIO, 2022 [4]	1	1	0.5	1	2	1	1	1	8.5
ZHENG, 2023 [14]	1	1	0.5	1	2	1	1	1	8.5

[#]: maximum 1 star; [¶]: maximum 2 stars; ⁺: based on smoking population.

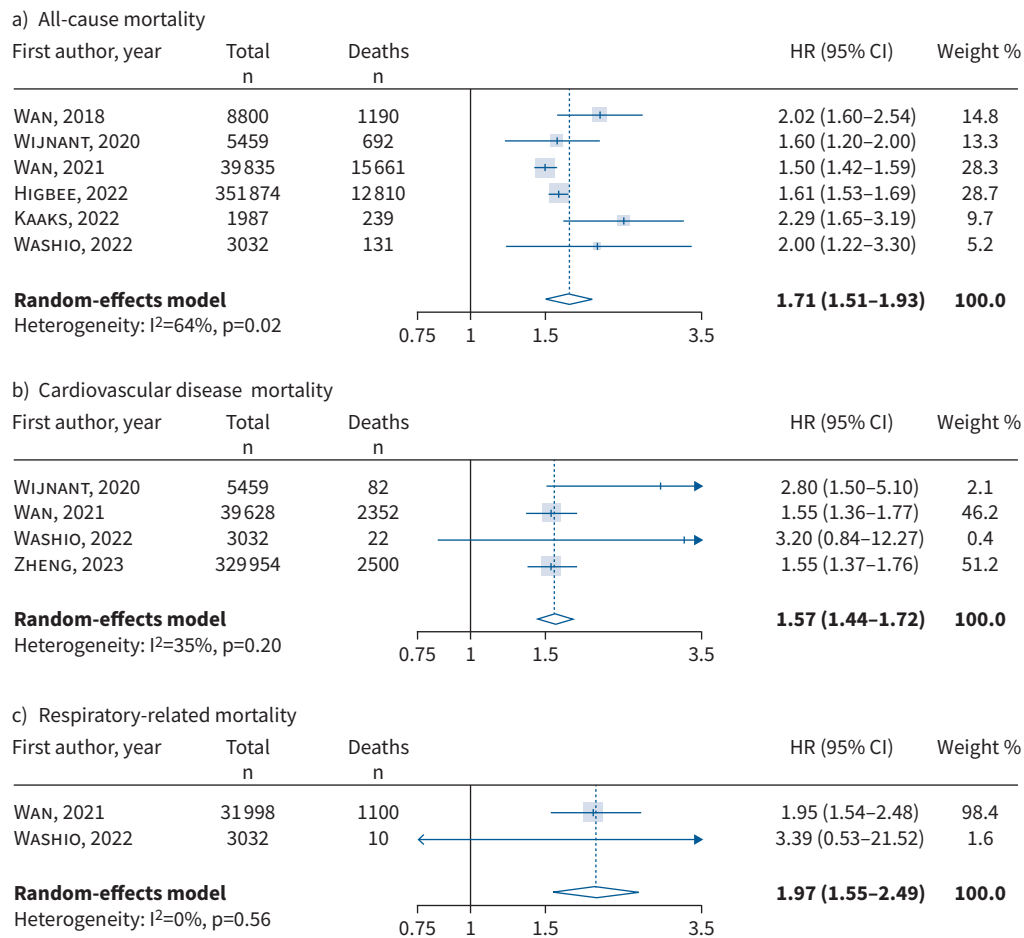


FIGURE 2 Forest plots for hazard ratios (HR) and 95% confidence intervals of a) all-cause, b) cardiovascular disease and c) respiratory-related mortality among individuals with preserved ratio impaired spirometry.

cardiovascular and respiratory-related mortality, respectively. Significant variations in the mortality estimates were observed across different population characteristics, e.g. sex ratio and smoking status.

PRISm has been associated with several comorbidities, e.g. cardiovascular diseases and COPD, which may increase the risk of mortality. Several large-scale population-based cohort studies, e.g. UK Biobank [14], Canadian Cohort Obstructive Lung Disease (CanCOLD) Study [7], the National Heart, Lung, and Blood Institute Pooled Cohorts Study [17] and the Jackson Heart Study [18] observed a significantly increased risk of heart attack among individuals with PRISm due to the increased systemic oxidative stress and the subsequent occurrence of myocardial hypertrophy and cardiac contractility [19, 20]. Besides, recent studies reported substantial transition rate from PRISm to obstructed spirometry ranging from 12.2% to 49.4%

	Coefficient (95% CI)	p-value	Heterogeneity accounted (R^2)
Mean age	1.005 (0.978–1.032)	0.72	0.0%
Percentage female	0.977 (0.965–0.990)	<0.001	100.0%
Percentage current smokers	1.006 (1.001–1.012)	0.03	59.1%
Mean/median pack-years	1.011 (1.005–1.018)	<0.001	100.0%
BMI	0.969 (0.869–1.079)	0.56	0.0%

BMI: body mass index.

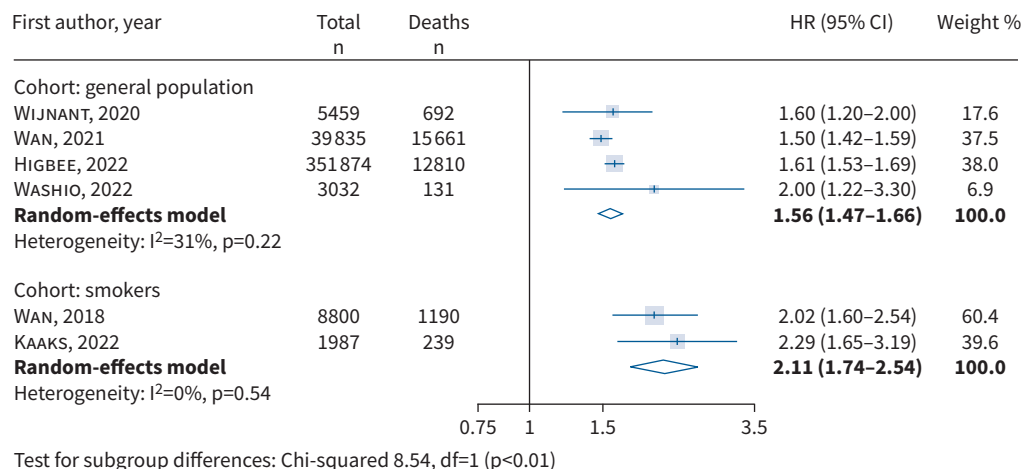


FIGURE 3 Pooled hazard ratios (HR) and 95% confidence intervals of all-cause mortality for preserved ratio impaired spirometry from studies based in the general population and in smokers.

[9, 12, 21], indicating that PRISm may be a precursor of COPD [4, 22]. In this systematic review, all eligible studies reported increased risk of mortality in PRISm, yielding pooled HRs of 1.71, 1.57 and 1.97 for all-cause, cardiovascular and respiratory-related mortality, respectively. These findings suggested that the significantly increased all-cause mortality associated with PRISm may be partially attributed to the extra deaths from cardiovascular diseases and respiratory-related diseases caused by the increased cardiovascular events and COPD. In addition, while many of the previous reports on the mortality risk of PRISm were based in the Western population, studies included in this review suggested a positive relationship between PRISm and heightened mortality risk across various ethnic groups. For example, WAN *et al.* [8] reported that the mortality risk associated with PRISm is higher in African Americans than that of non-Hispanic white subjects. WASHIO *et al.* [4] found that, in the Japanese population, individuals with PRISm have a higher mortality risk than those with normal spirometry. However, although PRISm is described as a transitory state with distinct trajectories (*e.g.* “PRISm-to-normal” and “persistent PRISm”) [10], studies on the trajectories of this phenotype and their differentiated prognosis are few. Besides, lack of post-bronchodilator spirometry may overestimate the prevalence of PRISm [5] and thus bias the association between PRISm and mortality. Therefore, further research is warranted to assess the prognosis of post-bronchodilator PRISm, especially the subsets of PRISm with distinct trajectories.

Interpreting the association of PRISm with increased all-cause mortality may be complicated by tobacco smoking. Univariate meta-regression suggested that smoking is a significant source of the substantial heterogeneity between the included studies, and the Baujat plot further indicated that the major contributors to the total heterogeneities were the two studies [8, 13] focused on smokers. The subsequent subgroup analysis by excluding these two studies revealed that the risk of all-cause mortality in PRISm was higher among smokers (pooled HR 2.11, 95% CI 1.74–2.54) than that in the general population (pooled HR 1.56, 95% CI 1.47–1.66). It indicates a potential interaction between smoking and PRISm in respect to the increased all-cause mortality, which is concordant with the findings reported by WASHIO *et al.* [4] in a Japanese population-based cohort study. These findings suggested that the recognising and managing PRISm among individuals with a history of smoking might be of a higher priority for preventing premature death.

Our study has several limitations that are partially related to the use of published data. First, our analyses were based on the aggregated data from cohort studies instead of individual participant data, which make it impractical to untangle the drivers of mortality by accounting for the clinical parameters or behavioural factors that affecting the mortality. Secondly, the setting of the included studies may limit the generalisation of our findings. The recent-era datasets that we identified were from high-income countries (USA, United Kingdom, Denmark, the Netherlands and Japan) and may not well represent the populations from developing countries given a large geographical and temporal difference in socioeconomic conditions, nutrition, burden of diseases and mortality patterns between countries [23]. Thirdly, although we explored the heterogeneity using the pre-defined subgroup analyses, there was moderate between-study heterogeneity that is hard to explain. The sources of between-study heterogeneity may derive from the

study methodology, such as the selection of study population, duration of follow-up, the diagnostic criteria of PRISm (especially the adoption of reference equation) and study quality; however, a further exploration of such heterogeneity was limited by the small number of eligible studies. Therefore, future systematic review with individual participant data meta-analysis on the studies from different populations is warranted. Lastly, an overestimation of PRISm related to an artificially lower FVC may be a concern, as some subjects may not adequately exhale forcefully for >6 s during lung function tests, particularly those with comorbidities. This could potentially result in a falsely normal FEV₁/FVC ratio and led individuals with airflow obstruction to be misclassified as PRISm. However, this methodological issue was not sufficiently discussed in the included original studies.

In conclusion, our systematic review and meta-analysis provided synthesised evidence that individuals with PRISm had increased all-cause mortality and specific mortality from cardiovascular and respiratory-related diseases, while higher mortality risks occurred predominantly among tobacco smokers. These findings suggested the necessity of further research on the structural, functional and genetic pathophysiology of this spirometry phenotype.

Points for clinical practice

Individuals with PRISm have a significantly increased risk of all-cause, cardiovascular and respiratory-related mortality compared with those with normal spirometry. These findings highlight the importance of recognising PRISm in clinical settings.

Provenance: Submitted article, peer reviewed.

Data availability statement: The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Conflict of interest: All authors have nothing to disclose.

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