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The rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies

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The rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies

Authors

Elizabeth T Thomas[1], Medical student

Dr. Michelle Guppy[2,3], Associate Professor of General Practice, PhD candidate

Prof. Sharon Straus[4,5], Professor of Medicine, Director of Knowledge Translation Program

Dr. Katy JL Bell[3,6] NHMRC Senior Research Fellow

Prof. Paul Glasziou[3], Professor of Evidence-Based Medicine, Director of the Centre for Research in Evidence-Based Practice

Author affiliations

1. Faculty of Health Sciences and Medicine, Bond University, Robina QLD 4226, Australia
2. School of Rural Medicine, University of New England, Armidale NSW 2351, Australia
3. Centre for Research in Evidence-Based Practice, Bond University, Robina QLD 4226, Australia
4. Department of Medicine, University of Toronto, Toronto, Ontario, Canada
5. Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada
6. Sydney School of Public Health, Sydney Medical School, Edward Ford Building (A27), University of Sydney, Sydney, Australia

Corresponding Author: Elizabeth T Thomas. Email: elizabeth.thomas@student.bond.edu.au

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Key Words Ageing, age-related decline, lung function tests, cohort studies, systematic review

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ABSTRACT

Objective To conduct a systematic review investigating the normal age-related changes in lung function in adults without known lung disease.

Design Systematic review.

Data sources MEDLINE, Embase and CINAHL were searched for eligible studies from inception to December 11, 2017. This was supplemented by manual searches of reference lists and clinical trial registries.

Eligibility criteria We planned to include prospective cohort studies and randomised controlled trials (control arms) that measured changes in lung function over time in asymptomatic adults without known respiratory disease.

Review methods Two authors independently determined the eligibility of studies, extracted data, and assessed the risk of bias of included studies using the modified Newcastle Ottawa Scale.

Results From 2194 records screened, we identified 15 cohort studies with 30,712 participants. All included studies demonstrated decline in lung function - FEV1, FVC and peak expiratory flow rate (PEFR) with age. In studies with longer follow-up (>10 years), rates of decline in FEV_1 ranged from 17.7 to 29.2 ml/year (median 21.3 ml/year). Overall, men had faster absolute rates of decline (median 43.5ml/year) compared to women (median 30.5ml/year). Differences in relative FEV_1 change from baseline, however, were not observed between men and women. The

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ratio of FEV1/FVC was reported as an outcome in only one study, declining by 0.29% per year. An age-specific analysis showed that the rate of FEV_1 function decline accelerates with each decade of age.

Conclusions Lung function - FEV1, FVC and PEFR - decline with age in people without known lung disease. The definition of chronic airway disease may need to be reconsidered to allow for normal ageing, and ensure that people likely to benefit from interventions are identified rather than healthy people who may be harmed by potential overdiagnosis and overtreatment. The first step would be to apply age, sex and ethnicity-adjusted FEV_1/FVC thresholds to the disease definition of COPD.

Registration PROSPERO CRD42018087066

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Strengths and limitations

- This is the first review to provide estimates for the median decline in spirometry measures including the FEV_1, FVC and the FEV_1/FVC ratio based on longitudinal data.
- We used a modified version of the Newcastle-Ottawa Scale to assess risk of bias.
- The review may be prone to volunteer bias, and therefore may underestimate lung function decline among asymptomatic people.
- Only one study specifically reported the change of the FEV_1/FVC ratio with age, and we did not have access to unpublished individual participant data to allow calculation of the FEV_1/FVC ratio change where this was not reported.

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INTRODUCTION

In 2016, the World Health Organization estimated that chronic obstructive pulmonary disease (COPD) affected 251 million people worldwide, with its prevalence continuing to rise with an ageing population.[1] Current guidelines in UK[2], Australasia[3], Europe and the United States[4] recommend that COPD is diagnosed if an individual has symptoms such as dyspnoea or sputum production, if they have known risk factors such as smoking or biomass fuel exposure, and if they demonstrate post-bronchodilator airflow limitation on spirometry. Airflow limitation on spirometry is defined when the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) is less than 70% after bronchodilator administration.[2,3] However, this arbitrary diagnostic threshold has attracted criticism as it does not adjust for age or sex.[5-10]

Ageing is invariably accompanied by changes in lung function due to factors such as loss of lung elasticity, weakened muscles of respiration, and decreased surface area for alveolar gas exchange. Several published cross-sectional studies[9 11-13] and longitudinal studies[14 15] report that lung function parameters such as FEV_1 and FVC decline with age.

The 2018 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[16] continues to suggest the use of the fixed ratio rather than an FEV1 or FVC that lies outside of

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the lower limit of normal (LLN) range. While the fixed ratio threshold may be simple for clinicians to use, it does not consider that lung function measurements may change with age and vary with gender and ethnicity. Many laboratory tests already have different reference range values for different ages and electronic spirometry machines do the same. The GOLD criteria acknowledge that this arbitrary fixed threshold may overdiagnose normal healthy older adults as diseased and underdiagnose some younger people with disease as healthy.[17 18]

Longitudinal studies need to be identified so that normal changes in lung function can be calculated for different ages. Monitoring change could be used in practice to complement a single time point measurement to identify people who are not within the expected normal range. We aimed to perform a systematic review of prospective cohort studies and randomised controlled trials, that examined changes in lung function with age in asymptomatic individuals with no known lung disease who have never smoked. This knowledge will enable further work to develop age-, sex- and ethnicity-specific estimates that may be especially useful in a primary care setting. This implies that people are only diagnosed with COPD if their spirometry measurements fall outside of the normal range for their age, sex and ethnicity, rather than on the basis of a fixed value.

METHODS

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Protocol registration

The protocol for this review was drafted in accordance with the PRISMA statement and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines. It was registered on PROSPERO (CRD42018087066) and is available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087066, see Supplementary File 1.

Search strategy and inclusion criteria

We conducted electronic searches of MEDLINE, EMBASE and CINAHL databases from inception through to December 2017, using the search strategy specified in Supplementary File 2. This was developed with an information specialist. Electronic searches were complemented by manual searching through reference lists of studies that were identified for potential inclusion as well as backwards and forward searching. We also searched the WHO Clinical Trials registry and ClinicalTrials.gov registries using the key words "normal ageing", "lung function decline", "FEV1 decline", "FVC decline" and "lung decline".

We included cohort studies and also planned to include the control arms of randomised controlled trials that measured the decline of lung function in an aging population. The inclusion criteria were:

- Longitudinal studies that followed adults past the age of 65 years;
- Participants did not have a known risk factor for respiratory disease (such as smoking, occupational

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inhalation), though studies could have included a comparator arm with participants with risk factors;

- Participants without respiratory symptoms such as wheeze, dyspnoea, chronic cough;
- Participants without known respiratory disease (chronic airways disease, asthma);
- Three or more measurements of lung function undertaken;
- Studies with a follow-up period of three years or longer; and
- Studies that measure lung function (i.e. FEV_1, FVC, peak expiratory flow rate [PEFR]).

Study selection and data extraction

Two authors (ETT, MG) independently screened the titles and abstracts of studies identified in the initial search for eligibility. Prior to commencing screening, a small subset of 50 titles were screened by the two reviewers as a calibration exercise to check for >80% agreement. Similarly, after screening, a calibration exercise was conducted for screening the full texts of the studies and targeting >80% agreement. The remaining full texts were retrieved and reviewed independently by the authors to determine eligibility for inclusion. Non-English publications were translated using Google Translate or with the assistance of a translator. Disagreements were resolved by consensus through discussion or with a third reviewer (PG).

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If there were multiple reports of the same study, the most recent publication with longest length of follow up was selected for inclusion, and if the two studies had a similar length of follow up then the study with the largest sample size was included. Two authors independently extracted data from the studies. The Excel data extraction form was piloted using ten studies prior to data extraction as a calibration exercise to check for adequate agreement (>80%) between the reviewers. Any disagreements were resolved by consensus or with a third reviewer. Extracted measures included study setting, year and duration, participant eligibility criteria, sample size, participants demographics (ethnicity, gender, baseline age), any known risk factors or exposures, baseline organ function, organ function measurements, number and frequency of measurements, average length of follow up and loss to follow up. We also accounted for the proportion of the cohort that subsequently developed symptoms or disease during the course of the follow-up.

We assessed risk of bias of included studies using the six items of the Newcastle Ottawa Scale (NOS)[19] for assessing quality of included cohort studies. Disagreements were resolved by discussion or a third reviewer.

Assessed factors included:

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- Representativeness of the exposed cohort (e.g. low risk: random selection; high risk: non-random selection e.g. volunteer sampling)
- Ascertainment of exposure – age (e.g. low risk: from medical records; high risk: self-reported)
- Demonstration that the outcome of interest was not present at start of study (e.g. low risk: participants were excluded on the basis of demonstrated air flow limitation; high risk: if participants were not screened)
- Assessment of outcome (e.g. low risk: spirometry; high risk: subjective measure of lung function)
- Adequate duration of follow up (e.g. low risk: equal to or greater than 3 years follow-up; high risk: less than 3 years of follow-up)
- Adequate follow up of cohorts (e.g. low risk: less than 20% attrition, loss to follow-up explained; high risk: greater than 20% attrition, unexplained loss to follow-up)

Studies were assessed as good quality if they had low risk of bias in all six domains, moderate quality if they had low risk of bias in four or five domains and low quality if they had low risk of bias for three or fewer domains.

Statistical analysis

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For each study cohort, we extracted the annual decline rates for each lung function measure. If these were not reported, we calculated crude decline rates for all reported lung function measure by subtracting the final measure from the initial measure and dividing the result by the duration of follow up. If these data were not available, we determined crude rates of decline from the graphs provided or contacted the study authors for original data. The data were first analysed descriptively using graphs to determine whether it was appropriate to pool the data. For continuous outcomes, the mean difference (MD) (or standardized mean difference if studies used different measuring scales) and standard deviations were calculated. The data were reported as an annual decline (unit/year). The overall rates of decline and corresponding 95% confidence intervals were presented in a forest plot. We planned to perform a meta-analysis to pool the estimates of decline.

We presented the data by functional parameter (FEV_1, $FEV_{0.75}$, FVC, PEFR), and planned to compare annual decline rates by sex and ethnicity in absolute and relative terms, where data were available. We also extracted and presented age-specific decline rates by decade of age if studies reported these data. We planned to separately analyse the data of those who developed disease during follow-up. We also planned to examine for birth cohort effects if the data were available. Sensitivity analyses were planned for study duration greater than ten years.

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Patient and Public Involvement

Patients were not involved in the design, data extraction or data analysis of this review.

RESULTS

Study characteristics

From searches of Medline, Embase and CINAHL performed on December 11 2017, we identified 2,194 records. An additional 54 records were identified from clinical trials registries and reference list searches. From these, we retrieved 130 papers for full text review; 114 of these did not meet our selection criteria and a further six were removed as duplicates. In total, 15 studies[20-34] were included in the systematic review (with one study contributing two data sets[29]) (Figure 1). The studies included 30,712 participants and were conducted between 1959 and 2012 ranging from five to twenty-four years in duration (Table 1).

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Table 1. Characteristics of included studies

Source ID	Cohort	Study duration (years)	Study Centres	Study Setting	Study period	Sample Size	Mean Age (SD)	%Male	Outcome	Time points of measurement
Ahmadi-Abhari 2014	EPIC-Norfolk	13	1	England	1993 - 2011	8062	58.5 (9.2)**	45	FEV1, FVC	3 (0, 4,13 years)
Bartholomew 1998	Busselton Population Health Surveys	6	1	Australia	1966 - 1981	1499	41.6 (16.1)	29.7	FEV1, FVC	3 (0,3,6 years)
Burchfiel 1995	Kuakini Honolulu Heart Program	6	1	USA	1965 - 1975	1248	54.6*	100	FEV1	3 (0,2,6 years)
Burrows 1986	Tucson Epidemiological study of obstructive Lung Disease (TESOLD)	9.6	1	USA	1972 - 1983	466	48.3 (19.1)	33.9	FEV1	mean 5.2
Griffith 2001	Cardiovascular Health Study	7	4	USA	1989 - 1997	5242	73.5 / 72.7 (5.5)/ (5.2)	42.4	FEV1, FVC	3 (0,4,7 years)
Lange 1998	Copenhagen City Heart Study	15	1	Denmark	1976 - 1994	4305	51.7^	37	FEV1	3- Cycle 1: 1976 - 1978, Cycle 2: 1981-1983, Cycle 3: 1991-1994
Liao 2015	Framingham Heart Study	17	1	USA	1983 - 2007	543	47.6 (10.5)**	38.1**	FEV1, FEV1/FVC	5 - Cycle 1: 1983-1987, Cycle 2: 1987-1991, Cycle 3: 1991-1995, Cycle 4: 1995-1998, Cycle 5: 2007
Maselko 2006	MacArthur Successful Aging study	7	3	USA	1988-1995	544	74	31.8	PEFR	3 (0,3,7 years),
Pearson 1998	Baltimore Longitudinal Study of Aging	Males: 11.5 Females: 5.7	1	USA	1962 - 1991	173	42.4	52.6	FEV1	4.6 / 3 (every 2 years)
Pelkonen 2001	Seven Countries Study	30	2	Finland	1959 - 1989	200	47.6 (30 years) 49.4 (15 years)	100	FEV0.75	6 (0,5,10,15,20,25,30 years)

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Proctor 2006	Origins of Variance in the Old-Old (OCTO-Twin)	8	1	Sweden	1991 – 2003		83.2 (2.8)	33.0	PEFR	5 (0,2,4,6,8 years)
Sherman 1992	Six Cities study of Air Pollution and Health	12	6	USA	1974-1989	1486	47.2 / 48.2** (12.3) / (12.5)	32.0	FEV1, FVC	4 (0,3,6,12 years)
Triebner 2017	European Community Respiratory Health Survey	19.7^	8	Denmark; Germany; Spain; France; Iceland; Norway; Sweden; Estonia	1991-2012	648	36.2**^	0	FEV1, FVC	3 - Cycle 1: 1991-1994 Cycle 2: 1998-2002 Cycle 3: 2010-2012
Wang 2004	-	5	1	USA	1985 - 1992	71	37^ (19-65)**	100	FEV1	3-11; every 6 months
Xu 1995	Dutch Study on Asthma and Chronic Obstructive Pulmonary Diseases	24	2	The Netherlands	1965-1990	6293	35.06 / 44.5 (10.5)/ (11.4)	22.5	FEV1	9 (every 3 years)

*Calculated from taking the midpoint of each age group and averaging according to number of people in each age group

** estimates include smokers

^ Median (Range)

/ # indicates Males / Females

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Overall age-related lung function decline

A meta-analysis was not performed due to substantial heterogeneity across the included studies, and a narrative synthesis was undertaken instead. Twelve studies reported changes in FEV_1 as an outcome. All studies demonstrated a decline with age, with overall rates of decline from each study ranging from 9.9 to 56.0ml/year (median 27.5ml/year). Seven of these studies examined the differences in rates of decline between males and females, showing greater absolute FEV_1 decline in males (median 43.5ml/year) than females (median 30.5ml/year) (Table 2, Figure 2). Relative rates of FEV_1 decline were calculated for men in eight studies and women in six studies that reported baseline FEV_1 values. There was no statistically significant difference between men and women's relative change of FEV_1 from baseline (p=0.7). $FEV_{0.75}$ decline was reported in one study.[29] This study provided two data sets (follow up after 15 years, 30 years) provided in Table 2.

Four studies reported changes in FVC, with rate of decline estimates ranging from 14.1ml/year in the youngest cohort[32] (median age 36.2 years) to 65.6ml/year in the older cohort[24] (mean age 73.0 years). In studies that measured FEV1 and FVC over time, there was a greater decline in FEV1 than FVC in one study, and greater decline in FVC than FEV1 in three studies. These measures are average estimates across study participants

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and do not enable calculation of individuals' FEV1/FVC ratios. In the one study where individuals' FEV_1/FVC ratios were reported as an outcome[26], there was a decline by 0.29% per year. PEFR was reported as an outcome in two studies,[27 30] which showed decline rates ranging from -6.6L/min/year in females to -11.5L/min/year in males.

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Table 2. Reported rates of annual lung function decline (FEV1, FVC, PEFR, FEV0.75) in a non-smoking, non-diseased, asymptomatic population from 16 cohort studies.

Source ID	Mean age	Duration	Sample size		Mean absolute unit decline/yr (SD)		Overall relative decline (%)		Confounding variables
			MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	
FEV_1 (mL)									
Ahmadi 2014	58.5** (9.2)	13	3621	4441	−17.7 (78.6)				Smoking; CRP categories
Bartholomew 1998	41.6 (16.1)	6	445	1054	-43.5 (100.4)	-30.5 (144.8)	1.1	1.2	Smoking; Increased BMI
Burchfiel 1995	54.6^	6	1248		-21.6°		0.7		Smoking status
Burrows 1986	48.3 (19.1)	9.6	158	308	-10.3° (6.3)	-9.1° (5.7)			-
Griffith 2001	73.0** (5.3)	7	1976**	2604**	-52.3 (3.1)[a]	-47.0 (2.8)[a]	1.9	1.7	Caucasian vs African American (only 2 measurements), Smoking
Lange 1998	51.7^	15	1592	2713	-23.5 (10.4)	-18.3 (10.0)	0.8	0.8	Asthmatics vs non-asthmatic, Smoker vs non smoker
Liao 2015	47.4** (10.6)	17	207***	336***	-25.8 (14.0)**				Smoking, Height, Less vs more likely dust exposure
Pearson 1998	42.4	11.5/5.7	91	82	-43.5	-35.1	1.0	1.3	-
Sherman 1992	47.9 (12.4)	12	475	1011	-32.8 (29.5)	-27.5 (20.4)	1.0	1.1	Smoking
Triebner 2017	36.2†	19.7†		648		-22.4 (36.4)			Menopausal status, BMI
Wang 2004	37† (19-65)	5	71		-56.0 (45.0)		1.3		
Xu 1995*	42.4^ (11.9)	24	1418	4875	-28.3 (138.5)	-16.0 (135.5)	0.7	0.5	

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FVC (mL)									
Ahmadi 2014	58.5** (9.2)	13	3621	4441	-31.1 (118.1)				Smoking; CRP categories
Bartholomew 1998	41.6 (16.1)	6	445	1054	-47.2 (104.0)	-36.0 (154.5)	1.0	1.1	Smoking
Griffith 2001	73.0** (5.3)	7	1976**	2604**	-78.4[a] (4.2)	-65.6[a] (3.8)	2.9	2.4	Caucasian vs African American (only 2 measurements), Smoking
Triebner 2017	36.2†	19.7†		648		-14.1 (42.8)			Menopausal status, BMI
FEV_1/FVC									
Liao 2015	47.4** (10.6)	17	207**	336**	-0.0029 (0.0023)**				Smoking, Less vs more likely dust exposure
$FEV_{0.75}$ (mL)									
Pelkonen 2001(a)	47.6	30	100		-34.8		1.0		Smoking
Pelkonen 2001(b)	49.4	15	200		-46.4		1.4		Smoking
PEFR (L/min)									
Maselko 2006	74	7	173	371	-8.6 (30.3)	–8.6 (34.7)	2.0	2.3	Smoking
Proctor 2006*	83.2 (2.8)	8	191	388	-11.5 (2.2)[a]	-6.6 (1.1)[a]	2.9	2.4	

*A non-linear relationship was also reported in the authors' data analysis.
** Based on estimates including smokers
***Estimates based on the assumption that there was an equal proportion of non-smokers who were male/female.
ˆAverage derived from taking the midpoint value of each age group and calculating the overall mean age according to proportion in each group.
† median
SDs were calculated from 95% CI by subtracting the highest from the lowest confidence interval and dividing the result by 3.92.
#/# indicates Male/Female
°Estimates adjust for covariates including height and age
[a]mean (Standard error)

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Age-specific lung function decline by decade of age

The age-specific rates of FEV_1 change by decade of age were extracted or calculated from three studies.[22 23 28] In all but one study, estimates of decline increased from the fourth (age 30-40 years) to eighth (age 70-80 years) decades of life (Table 3). Two other studies also reported that the rate of decline may be non-linear in multiple regression models of FEV_1 and FVC decline (where age squared was also a statistically significant variable).[34 35]

Study ID	Sample Size (n)	Absolute mean decade-specific FEV_1 function decline rates (ml/year)				
		30-39	40-49	50-59	60-69	70-79
Burchfiel 1995*	Male (1248)		-19.5**	-21.6	-25.0	
Burrows 1986	Male (158)	+2.83	-3.01	-8.85	-14.69	-20.53
	Female (308)	+2.73	-2.51	-7.76	-13.01	-18.26
Pearson 1998	Female (82)	-23.8	-33.4	-30	-23.4	-25.8
	Male (91)	-34	-34	-34	-34	-34

Table 3. Age-specific lung function decline by decade of age as reported in three cohorts

*Estimates adjust for covariates including height and age
**Includes participants 45-49.

Two studies examined lung function change within age brackets that did not conform to our decade-specific analysis.

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Bartholomew 1998[21] reported greater decline rates in never smokers aged above 45 years (females: -30.7ml/year, males -45.8ml/year) compared to those aged below 45 years (females: -24.3ml/year, males: -36.8ml/year). Lange 1998[25] compared decline rates in both male and female non-smokers in 20-year age groups. Females aged 60-79 years had the greatest decline rates (-31.7 ± 2.1ml/year) compared to the 40-59 age group (-17.7 ± 1.4ml/year) and the 20-39 age group which reported an increase of 5.0 ± 2.7ml/year. Similarly, males aged 60-79 years had the greatest decline rates (-37.1 ± 3.7ml/year) compared to the 40-59 year age group (-24.2 ± 2.6ml/year) and the 20-39 year age group (-4.6 ± 4.2ml/year).

Overall rates of mortality/symptom/disease development

Few studies reported these outcomes in an initially asymptomatic, non-smoking population. One study (Proctor)[30] reported 85% mortality rate in the elderly cohort (age range 79 – 96) over eight years. Another study (Lange 1998)[25] reported that in their study of non-asthmatics, 364 (2%) patients who did not report having asthma at the beginning of the study, later reported it in follow up. However, this estimate included smokers. One study (Wang)[33] performed their analyses on a highly screened population, meaning they excluded participants from all analyses who developed disease or symptoms during study follow up. No studies reported the rates of lung function change in

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those who developed disease during the course of the study compared with those who did not.

Sensitivity analyses

Heterogeneity in study duration was explored in Figure 3A. After removing studies with a follow up of less than ten years, the median rate of decline of FEV_1 was 21.3ml/year (Figure 3B).

Predictors of the rate of decline in lung function in people without known lung disease

Smoking

Although we didn't include smokers in our main analysis, some studies did compare non-smokers and smokers which we report here. The decline rates were compared in non-smokers with smokers in eight studies[21 22 24-27 29 31]. In all six studies measuring FEV_1, smoking was observed to increase the rate of FEV_1 decline.[21 22 24-26 31] In the two studies measuring FVC, smoking increased FVC decline[21 24]. FEV_1/FVC decline was greater in smokers than nonsmokers in one study[26] and $FEV_{0.75}$ in another study[29].

BMI

Two studies reported the association of BMI with FEV_1 change. In Bartholomew 1998[21], increased BMI significantly affected FEV_1 decline ($p = 0.008$ for females; $p=0.007$ for males). However, an estimate for this association was not provided. In Triebner

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2017[32], obese individuals reported greater declines of FEV1 (29ml/year) and FVC (25ml/year) compared to individuals with normal BMI (FEV1 22ml/year, FVC 10ml/year).

Ethnicity

Griffith[24] was the only study that assessed ethnicity, specifically comparing African-American participants to White participants. We did not include the African-American cohort in our analysis as only two measurements were performed on this population. However, FEV_1 and FVC declines were greater in Whites compared to African-Americans.

Systolic blood pressure

Griffith[24] examined the correlation of systolic blood pressure greater than 160mmHg with FEV_1 and FVC decline and found that declines were on average 5.6ml/year and 10.9ml/year greater respectively ($p < 0.01$).

Dust exposure

Liao[26] explored the effects of dust exposure on FEV_1 and FEV_1/FVC decline. Participants with more dust exposure experienced a mean FEV_1 decline that was 4.5ml/year greater than participants with less dust exposure ($p = 0.007$). Dust exposure did not significantly affect FEV_1/FVC ratio decline, suggesting that FVC declined in parallel to FEV1.

Menopausal status

Triebner[32] reported that menopausal status affected the rate of decline, with rates of FEV_1 decline on average 3.8ml/year greater

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in peri-menopausal women, and 5.2ml/year greater in postmenopausal women. FVC decline was 10.2ml/year greater in peri-menopausal women, and 12.5ml/year greater in post-menopausal women, compared to pre-menopausal women.

Risk of bias

Risk of bias was determined using a modified version of the Newcastle-Ottawa Scale[19] (Figures 4, 5). No studies received low risk of bias in all domains, but four studies had a low risk of bias in all but one domain.[23 28 31] Thirteen studies (81%) were graded as having low risk of bias for representativeness of the population. Six studies (38%) were judged as low risk of bias on how they ascertained the age of the participants (from Medicare eligibility lists or health records). Five cohort studies (31%) clearly demonstrated that pulmonary impairment was not present in participants at the beginning of the study. All studies (100%) used a spirometer to measure lung function which is a validated objective instrument. All studies (100%) had adequate duration of follow-up (three years or longer). Fourteen studies (88%) had a high risk of bias for having high attrition rates in their studies (>20%).

DISCUSSION

Statement of principal findings

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This systematic review of fifteen prospective cohort studies conducted in thirteen countries provides a summary of all the available evidence looking at lung function change with age. Lung function declines with age in normal, asymptomatic adults with higher rates of decline in absolute lung function parameters in men compared to women. However, the relative rates of decline from baseline between men and women do not differ significantly. The decline in absolute and relative lung function parameters also accelerates with age and is exacerbated by factors such as smoking and BMI. We were unable to compare lung function decline rates of different ethnicities due to insufficient data. There was a paucity of longitudinal studies that reported changes in FEV_1/FVC rather than reporting the two parameters separately.

Strengths and weaknesses of the study

This systematic review examined all the available primary studies to allow an examination of the consistency of estimates of decline in FEV1, FVC, FEV_1/FVC ratio and PEFR. This review particularly focused on older adults; this group is relatively understudied and yet more prone to overdiagnosis and misdiagnosis.[6 8 18] While the majority of current prediction equations of lung function are based on cross-sectional studies[36-39] our review searched for longitudinal studies as they change in lung function may provide a complement to measurement

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at one time point in predicting future lung function.[37] Our review included participants who were ageing normally, but may have had non-pulmonary co-morbidities such as hypertension and diabetes mellitus. This enabled us to investigate a population that was more representative of a normal ageing population.

Our review has some limitations. We did not have access to unpublished individual participant data to allow calculation of FEV_1/FVC for the majority of studies, where this were not reported. Individual patient data would also allow a more robust analysis of changes in lung function between individuals in the studies. We were unable to pool the results due to significant heterogeneity across the populations. This review's findings are also limited by the quality of the included studies, all of which were judged moderate or low quality. Since this review is based on limited populations, the findings may not be generalisable to all individuals, especially those of non-Caucasian ethnicities or from less economically developed countries where smoking and air pollution may be more prevalent for example. The review's findings may underestimate lung function decline among asymptomatic people, as volunteer bias may be present with cohort studies where healthier individuals may be more likely to participate.

Our review did not consider the extent of short term within-person variation, or "noise", in lung function measurements,

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which is likely to be considerable.[40 41] Any observed change in measurement is a combination of the true change, or "signal", and the random background "noise". The clinical utility of monitoring lung function to decide whether or not COPD is present, is in part determined by the ratio of signal to noise in the measurements.[42] Changes in measured lung function over a longer period of time may be more likely to indicate some true change rather than just background noise[43], therefore we specified in our inclusion criteria that eligible studies should measure lung function on a minimum of three occasions.

We observed substantial heterogeneity across all of the included studies and results. This may be due to inherent differences within the populations studied (including distribution of ages, proportion of men vs women and ethnicities) or the duration of follow up, or that decline in normal healthy people may vary across individuals without causing disease. We explored differences in duration of follow-up as a potential source of heterogeneity in a sensitivity analysis excluding studies with less than ten years of follow up, but found that this did not change the median estimate substantially.

Variation within the results may be explained by the "horse-racing effect", where an initially low FEV_1 measurement may reflect a greater loss of function in the preceding years and hence predicts faster decline in subsequent years.[44 45] Regression to the mean, due to inclusion of people with randomly high (or

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low) measured lung function in the primary studies, may also have contributed to heterogeneity of the results.[46] A simple way that primary studies may assess for a horse racing effect, while allowing for regression to the mean, is by constructing Bland-Altman plots of change vs mean FEV1 level[47] (or substituting PEFR for mean FEV1as these are highly correlated.[48])

Comparison with previous research

A number of cross-sectional studies have compared people diagnosed with COPD using a fixed threshold and the lower limit of normal (LLN) definition, reporting that the GOLD criteria leads to misdiagnosis of COPD.[5-8 49] A prospective cohort study found that the fixed threshold of the GOLD criteria overdiagnosed a large proportion of elderly people over the age of 70, and the LLN criteria tended to under-diagnose COPD, when compared to the reference standard which consisted of an expert panel who used all available diagnostic information including spirometry.[18]

Meaning of the study: possible explanations and implications for clinicians and policymakers

This review has found that lung function declines with age in all studied populations. The rate of decline appears to accelerate with age, and age-specific estimates of FEV_1, FVC and FEV_1/FVC ratio may be more appropriate for diagnosis of COPD than

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the fixed threshold currently used across all ages. Currently, prediction equations for calculating mean lung function values as well as the lower-limit of normal (LLN) for all ages are based on data from cross-sectional studies, however it is argued that this is problematic as they do not factor in the important dimension of time.[50 51] Therefore, more reliable age-specific estimates and prediction equations are required.

Clinicians need to consider whether 'abnormal' spirometry results may in fact represent normal ageing. This is especially true for making a formal diagnosis of COPD. If a patient is symptomatic and has airflow obstruction as defined by GOLD criteria, it may be necessary to consider alternative diagnoses such as a dyspnoea of cardiac origin. One proposal for identifying individuals who are experiencing greater loss of lung function than expected, is to develop 'decline charts' that predict FEV_1 or FEV_1/FVC loss for different ages. This can allow clinicians to monitor lung function over time and assess whether individuals are tracking along expected decline curves. These would also need to account for noise in measurement.

Future research should focus on conducting long-term longitudinal studies in less-studied populations, with emphasis on older adults. These studies should examine the rates of decline in people who eventually become symptomatic or develop

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disease. This information can guide clinicians to predict what rate of lung function decline may be a prognostic indicator of COPD onset and progression. Further well-designed prospective studies that investigate changes in FEV_1/FVC may allow for the development of algorithms that predict individuals' expected lung function over time according to their sex, smoking history, age, BMI and ethnicity. The observed change in lung function parameters might then be compared to the expected change to help the clinician determine whether this is extreme enough to warrant diagnosis of disease.

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This manuscript was prepared in accordance with the PRISMA statement and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines.

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ETHICAL APPROVAL

Ethical approval was not required for this study.

DATA SHARING STATEMENT

No additional data available.

CONTRIBUTOR STATEMENT

ETT was involved with devising the review methods, conducting electronic searches, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. MG was involved with devising the review methods, screening of abstracts, data extraction, data analysis and interpretation and co-drafting the review. KJLB was involved with devising the review methods, data analysis and interpretation, and co-drafting the review. SS was involved with devising the review methods, data analysis and interpretation, and co-drafting the

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review. PG was involved with devising the review methods, data analysis and interpretation, and co-drafting the review.

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COMPETING INTERESTS

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

TRANSPARENCY DECLARATION

The lead author (ETT) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and

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that any discrepancies from the study as originally planned have been explained.

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REFERENCES

1. Chronic obstructive pulmonary disease (COPD): World Health Organization; 2017 [Available from: http://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) accessed 5 Aug 2018.
2. Chronic obstructive pulmonary disease in over 16s: diagnosis and management: National Institute for Health and Care Excellence; 2010 [Available from: https://www.nice.org.uk/guidance/cg101 accessed 5 Aug 2018.
3. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary disease 2018: Lung Foundation Australia; 2018 [Available from: https://copdx.org.au/wp-content/uploads/2018/06/COPDX-V2-53-March-2018_2.pdf accessed 5 Aug 2018.
4. Qaseem A, Wilt T, Weinberger S, et al. Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Int Med* 2011;155:179-91. doi: 10.7326/0003-4819-155-3-201108020-00008
5. Schermer T, Smeele I, Thoonen B, et al. Current clinical guideline definitions for airflow obstruction leads to substantial overdiagnosis of COPD in primary care. *Eur Respir J* 2008;52(2) doi: 10.1183/09031936.00170307

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

6. Swanney M, Ruppel G, Enright P, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;63(12):1046-51. doi: 10.1136/thx.2008.098483 [published Online First: Sep 11 2018]

7. Shirtcliffe P, Weatherall M, Marsh S, et al. COPD prevalence in a random population survey: a matter of definition. *Eur Respir J* 2007;30:232-9.

8. Hardie J, Buist A, Vollmer W, et al. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002;20:1117-22.

9. Medbø A, Melbye H. Lung function testing in the elderly—Can we still use FEV1/FVC<70% as a criterion of COPD? *Respir Med* 2007;101(6):1097-105. doi: https://doi.org/10.1016/j.rmed.2006.11.019

10. Miller M, Levy M. Chronic obstructive pulmonary disease: missed diagnosis versus misdiagnosis. *BMJ* 2015;351:h3021. doi: 10.1136/bmj.h3021

11. Morris J, Temple W, Koski A. Normal Values for The Ratio of One-Second Forced Expiratory Volume to Forced Vital Capacity. *Am Rev Respir Dis* 1973;108(4)

12. Hankinson J, Odencrantzm J, Fedan K. Spirometric Reference Values from a Sample of the General U.S. Population. *Am J Respir Crit Care Med* 1999;159:179-87.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

13. Glindmeyer H, Lefante J, McColloster C, et al. Blue-collar normative spirometric values for Caucasian and African-American men and women aged 18 to 65. *Am J Respir Crit Care Med* 1995;151(2) doi: https://doi.org/10.1164/ajrccm.151.2.7842200

14. Bossé R, Sparrow D, Garvey A, et al. Cigarette smoking, aging and decline in pulmonary function: A longitudinal study. *Arch Environ Health* 1980;35:247-52.

15. Huhti E, Ikkala J. A 10-year follow-up study of respiratory symptoms and ventilatory function in a middle-age rural population. *Eur J Resp Dis* 1980;61:33-45.

16. Pocket Guide to COPD Diagnosis, Management and Prevention: a guide for health care professionals: Global Initiative for Chronic Obstructive Lung Disease; 2018 [Available from: https://goldcopd.org/wp-content/uploads/2018/02/WMS-GOLD-2018-Feb-Final-to-print-v2.pdf accessed 5 Aug 2018.

17. Van Dijk W, Tan W, Li P, et al. Clinical relevance of fixed ratio vs lower limit of normal of FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam Med* 2015;13(1):41-8.

18. Güder G, Brenner S, Angermann C, et al. GOLD or lower limit of normal definition? a comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res* 2012;13(1):13. doi: 10.1186/1465-9921-13-13

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

19. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses: The Ottawa Hospital; [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed 12 Aug 2018.

20. Ahmadi-Abhari S, Kaptoge S, Luben R, et al. Longitudinal Association of C-Reactive Protein and Lung Function Over 13 Years: The EPIC-Norfolk Study. *Am J Epidemiol* 2014;179(1):48-56. doi: 10.1093/aje/kwt208

21. Bartholomew H, Knuiman M. Longitudinal analysis of the effect of smoking cessation on cardiovascular risk factors in a community sample: the Busselton Study. *J Cardiovasc Risk* 1998;5:263-71.

22. Burchfiel C, Marcus E, Curb J, et al. Effects of Smoking and Smoking Cessation on Longitudinal Decline in Pulmonary Function. *Am J Respir Crit Care Med* 1995;151:1778-85.

23. Burrows B, Lebowitz M, Camilli A, et al. Longitudinal Changes in Forced Expiratory Volume in One Second in Adults: Methodologic Considerations and Findings in Healthy Nonsmokers. *Am Rev Respir Dis* 1986;133:974-80.

24. Griffith K, Sherrill D, Siegel E, et al. Predictors of Loss of Lung Function in the Elderly: The Cardiovascular Health Study. *Am J Respir Crit Care Med* 2001;163:61-8.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

25. Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.

26. Liao S, Lin X, Christiani D. Occupational Exposures and Longitudinal Lung Funciton Decline. *Am J Ind Med* 2015;58:14-20.

27. Maselko J, Kubzansky L, Kawachi I, et al. Religious Service Attendance and Decline in Pulmonary Function in a High-Functioning Elderly Cohort. *Ann Behav Med* 2006;32(3):245-53.

28. Pearson J, Kao S, Brant L, et al. Longitudinal Change in Forced Expiratory Volume in Healthy, Non-smoking Men and Women: The Baltimore Longitudinal Study of Aging. *Am J Hum Biol* 1998;10:471-81.

29. Pelkonen M, Notkola I, Tukiainen H, et al. Smoking cessation, decline in pulmonary function and total mortality: a 30 year follow up study among the Finnish cohorts of the Seven Countries Study. *Thorax* 2001;56:703-7.

30. Proctor D, Fauth E, Hoffman L, et al. Longitudinal changes in physical functional performance among the oldest old: insight from a study of Swedish twins. *Aging Clin Exp Res* 2006;18:517-30.

31. Sherman C, Xu X, Speizer F, et al. Longitudinal Lung Function Decline in Subjects with Respiratory Symptoms. *Am Rev Respir Dis* 1992;148:855-9.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

32. Triebner K, Matulonga B, Johannessen A, et al. Menopause Is Associated with Accelerated Lung Function Decline. *Am J Respir Crit Care Med* 2017;195(8):1058-65.

33. Wang M, Petsonk E. Repeated Measures of FEV1 Over Six to Twelve Months: What Change is Abnormal? *J Occup Environ Med* 2004;46:591-95.

34. Xu X, Laird N, Dockery D, et al. Age, Period, and Cohort Effects on Pulmonary Function in a 24-Year Longitudinal Study. *Am J Epidemiol* 1995;141:554-66.

35. Ware J, Dockery D, Louis T, et al. Longitudinal and cross-sectional estimates of pulmonary function decline in never-smoking adults. *Am J Epidemiol* 1990;132:685-700.

36. Cherniack R, Raber M. Normal Standards for Ventilatory Function Using an Automated Wedge Spirometer. *Am Rev Respir Dis* 1971;106(1) doi: https://doi.org/10.1164/arrd.1972.106.1.38

37. Lung Function Testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;144:1202-18.

38. Morris J, Koski A, Johnson L. Spirometric Standards for Healthy Nonsmoking Adults. *Am Rev Respir Dis* 1971;103(1)

39. Paoletti P, Pistelli G, Fazzi P, et al. Reference values for vital capacity and flow-volume curves from a general population study. *Bull Eur Physiopathol Respir* 1986;22:451-9.

For peer review only

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

40. MacIntyre N. Finding Signals Amidst the Noise in Pulmonary Function Testing. *Chest* 2007;132(2):367-8.

41. Becklake M, White N. Sources of variation in spirometric measurements. Identifying the signal and dealing with noise. *Occup Med* 1993;8(2):241-64.

42. Bell K, Glasziou P, Hayen A, et al. Criteria for monitoring tests were described: validity, responsiveness, detectability of long-term change, and practicality. *J Clin Epidemiol* 2014;67(2):152-9. doi: 10.1016/j.jclinepi.2013.07.015

43. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.

44. Fletcher C, Peto R, Tinker C, et al. The natural history of chronic bronchitis and emphysema. Oxford: Oxford University Press 1970.

45. Peto R. The horse-racing effect. *Lancet* 1981;2(8244):467-8.

46. Bland J, Altman D. Statistics Notes: Some examples of regression towards the mean. *BMJ* 1994;309:780. doi: https://doi.org/10.1136/bmj.309.6957.780

47. Bland J, Altman D. Statistics Notes: Measurement error proportional to the mean. *BMJ* 1996;313:106. doi: https://doi.org/10.1136/bmj.313.7049.106

48. Gautrin D, D'Aquino L, Gagnon G, et al. Comparison Between Peak Expiratory Flow Rates (PEFR) and FEV1 in the

For peer review only

Monitoring of Asthmatic Subjects at an Outpatient Clinic. *Chest* 1994;106(5):1419-26.

49. Wang Y, Xiao W, Ma D, et al. Predicted lower limit of normal reduces misclassification risk of airflow limitation in asymptomatic elderly never-smokers. *Chin Med J* 2013;126(18):3486-92.

50. Brändli O, Schindler C, Künzli N, et al. Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. *Thorax* 1996;51:277-83.

51. Marks G. Are reference equations for spirometry an appropriate criterion for diagnosing disease and predicting prognosis? *Thorax* 2012;67:85-7. doi: 10.1136/thoraxjnl-2011-200584

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Figure Legends

Figure 1. Study flow diagram showing the process for inclusion of prospective RCTs and cohort studies for estimating the rate of lung function decline with age.

Figure 2. Estimates of the rate of FEV_1 decline in males and females

Figure 3A. Effect of duration of study on the estimates of FEV_1 decline

Figure 3B. Sensitivity analysis exploring the effect of study duration on the estimates of FEV_1 decline with studies with less than ten years of follow-up removed.

Figure 4. Risk of bias summary for prospective cohort studies estimating the rate of lung function decline with age, assessed using a modified form of the Newcastle-Ottawa Scale.

Figure 5. Graphical representation of the risk of bias in prospective cohort studies estimating the rate of lung function decline with age.

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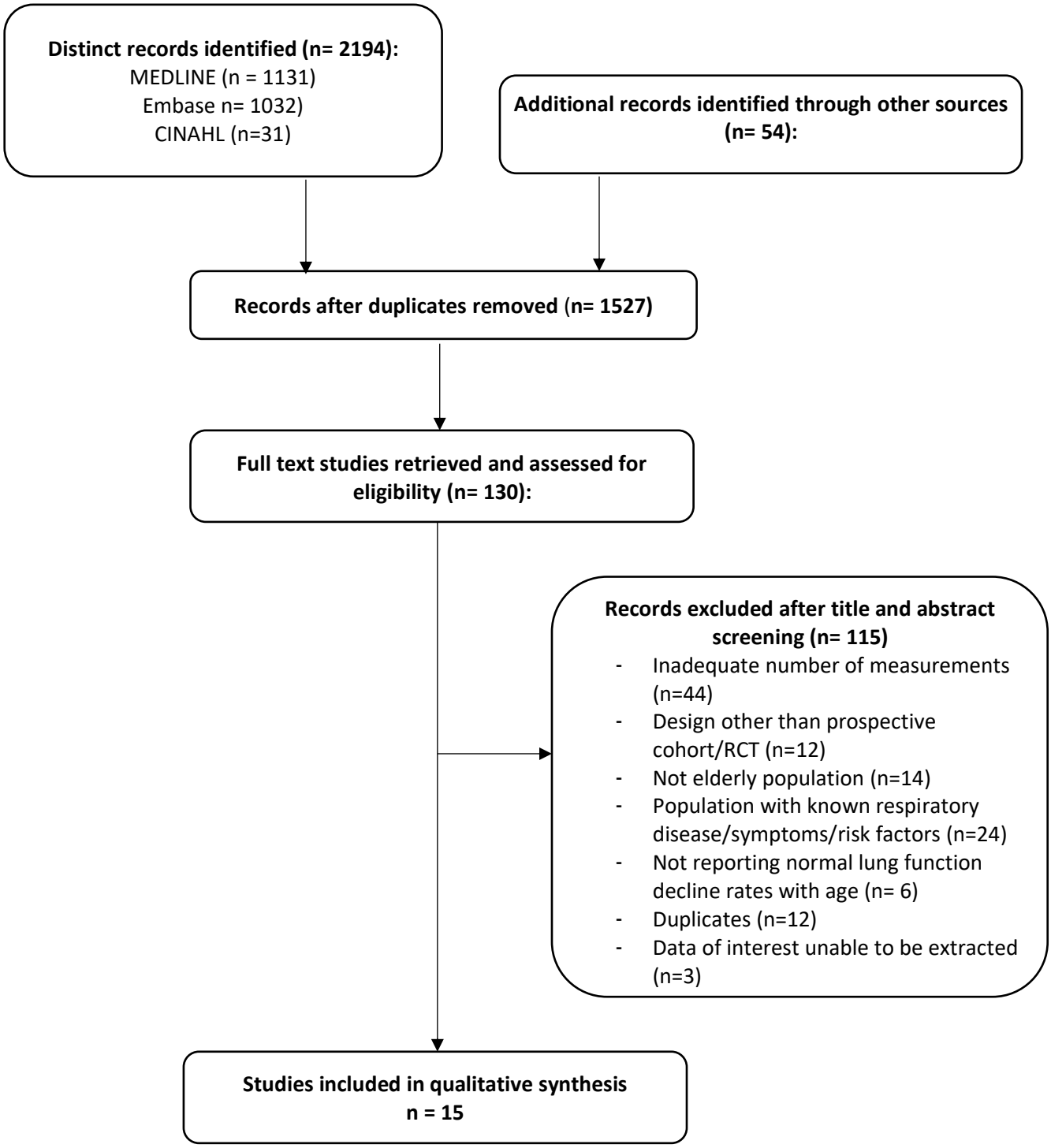
Figure 1. Flow Diagram of study selection for systematic review



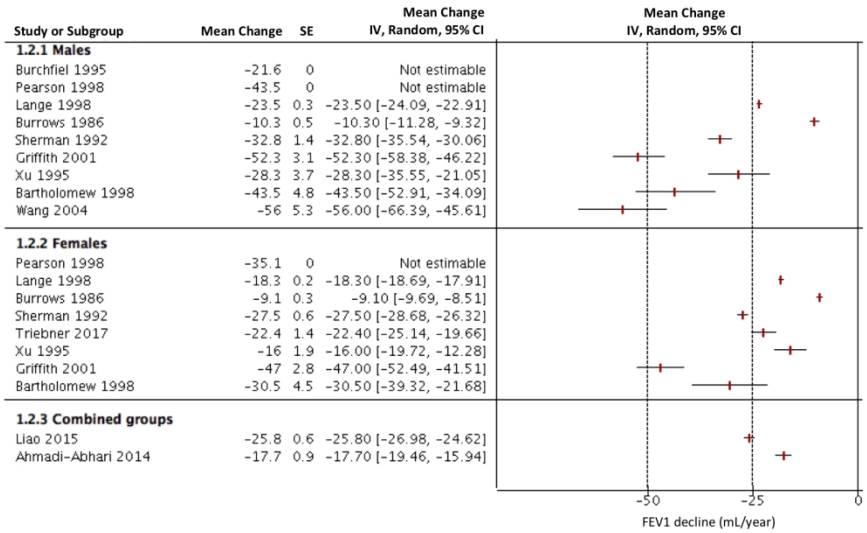


Figure 2. Estimates of the rate of FEV1 decline in males and females

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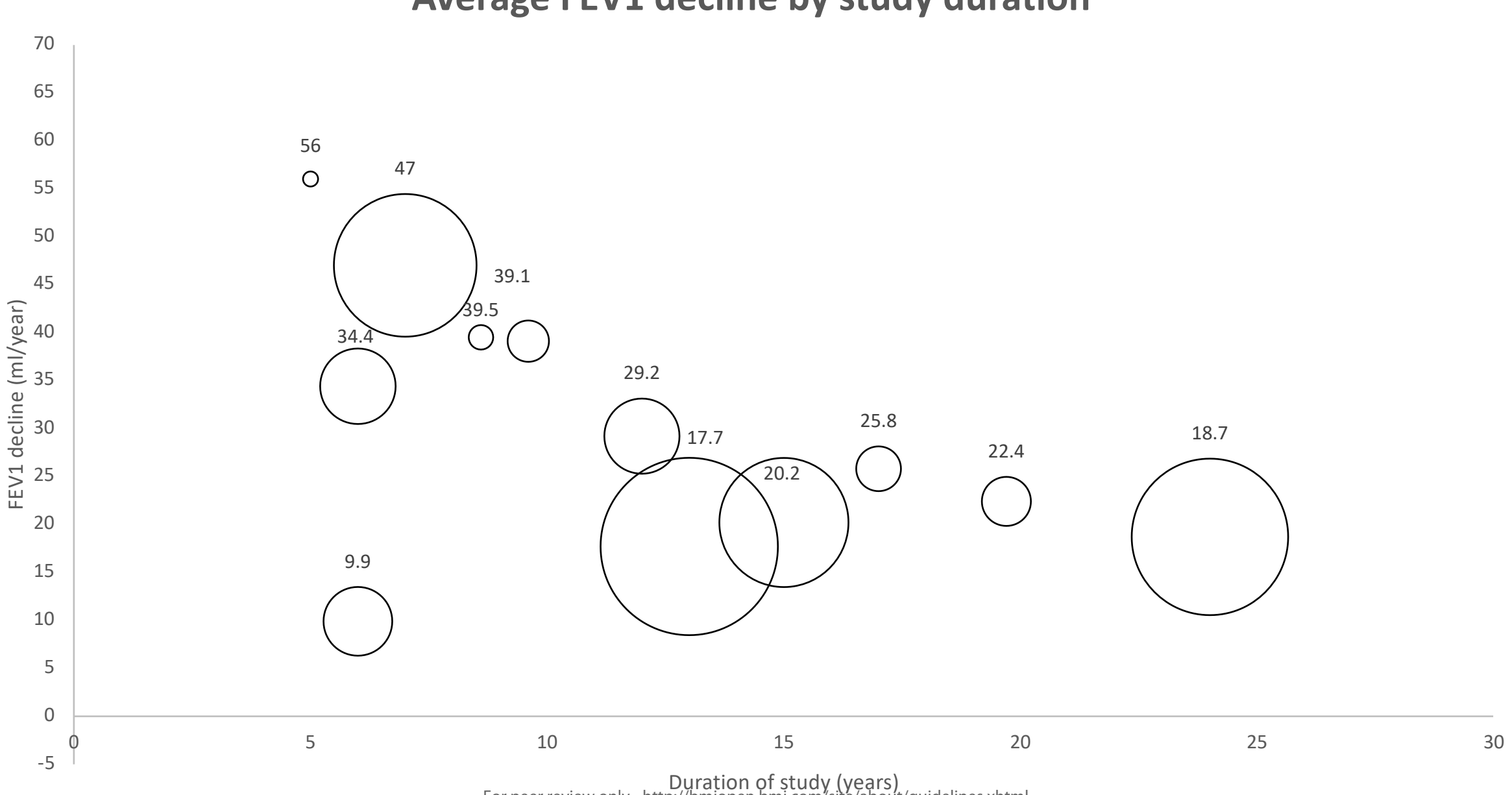
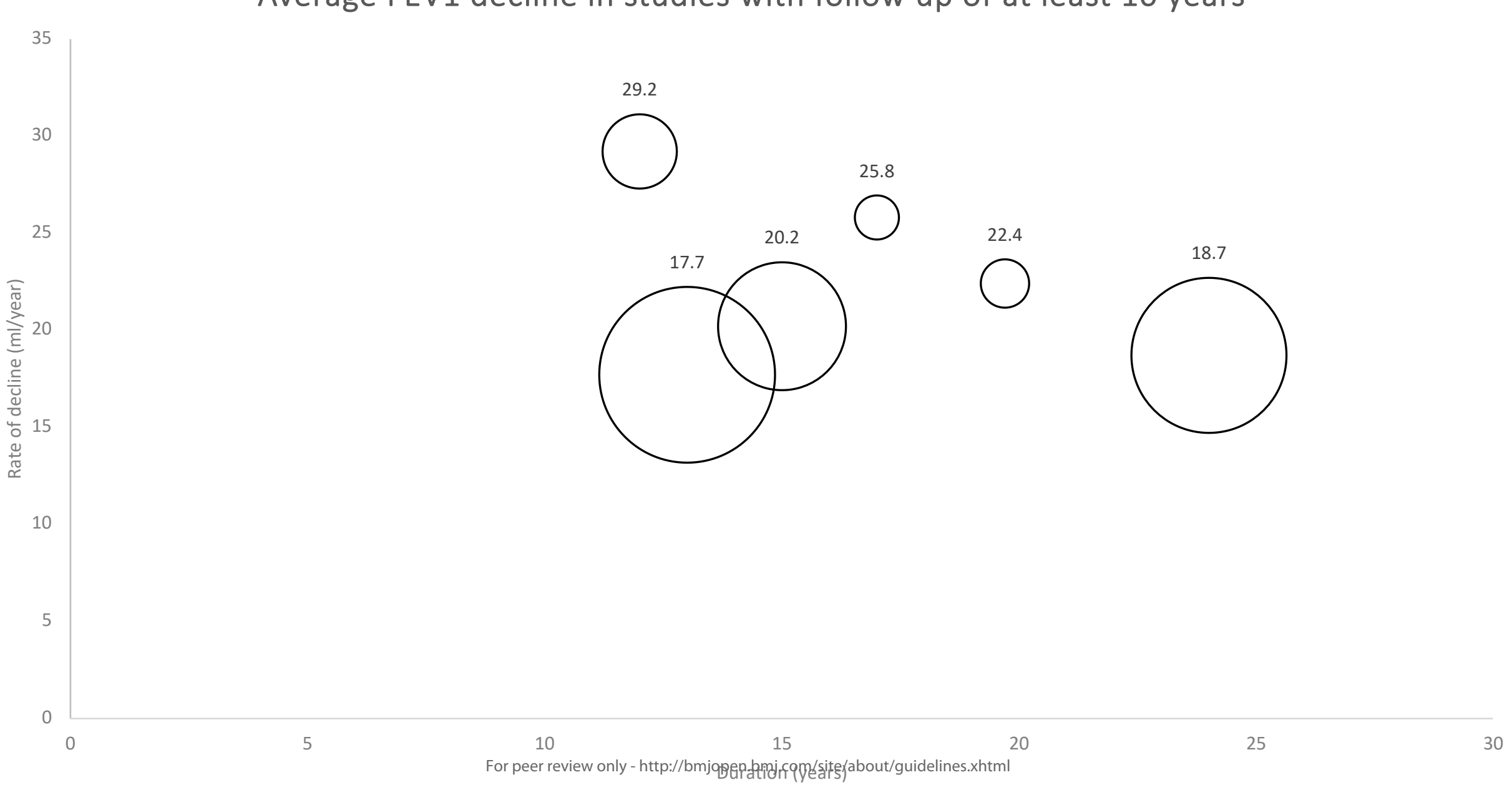

Average FEV1 decline by study duration
FEV1 decline (ml/year)
70
65
60
55
50
45
40
35
30
25
20
15
10
5
0
-5
0
5
10
15
20
25
30
Duration of study (years)
56
47
39.1
39.5
34.4
29.2
17.7
25.8
22.4
20.2
18.7
9.9



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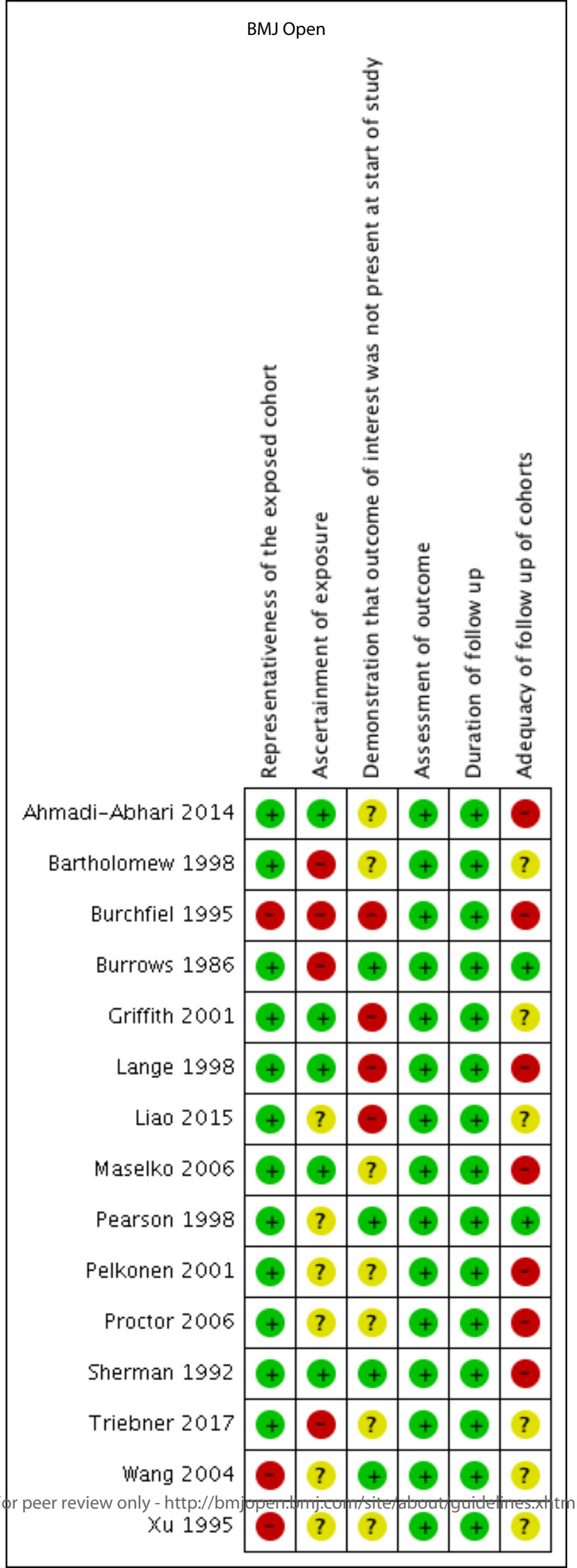

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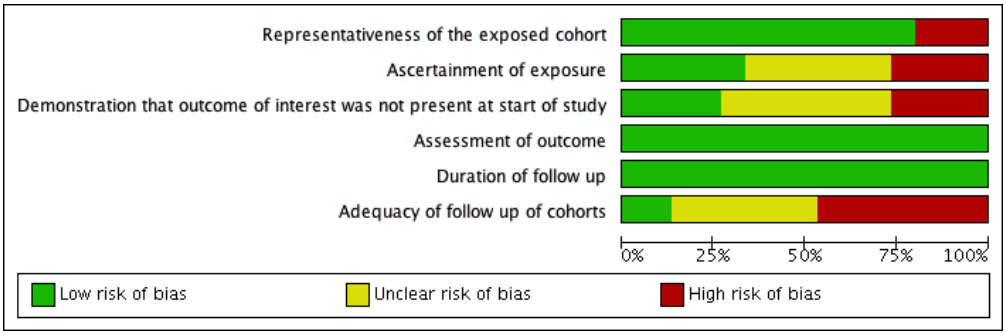

Figure 5. Graphical representation of the risk of bias in prospective cohort studies estimating the rate of lung function decline with age.

249x81mm (72 x 72 DPI)

The rate of normal organ function decline with advancing age: protocol for a systematic review.

Authors
Elizabeth T Thomas[1]
Michelle Guppy[2,3]
Sharon Straus[4]
Katy Bell[2,5]
Paul Glasziou[2]

Author affiliations
1. Faculty of Health Sciences and Medicine, Bond University, Robina QLD 4226, Australia
2. Centre for Research in Evidence-based Practice, Bond University, Robina QLD 4226, Australia
3. School of Rural Medicine, University of New England, Armidale NSW 2351, Australia
4. Department of Medicine, University of Toronto, Toronto, Ontario, Canada
5. Sydney School of Public Health, Sydney Medical School, Edward Ford Building (A27), University of Sydney, Sydney, Australia

Corresponding Author: Elizabeth T Thomas. Email: elizabeth.thomas@student.bond.edu.au

Key Words
Normal ageing, organ function, age-related decline

ABSTRACT

Background The unprecedented rise in life expectancy in the last few decades has led to an increasing proportion of elderly people. Elderly individuals present a particularly complex challenge to health care due to their multiple comorbidities, frailty as well as their functional decline. In order to better understand and guide the care of geriatric patients, it is necessary to understand the natural rate of decline of various organ functions, so as not to inappropriately label them as having disease. This protocol is for a systematic review, which aims to calculate the rate of annual decline of lung, liver and pancreatic function as well as bone mineral density.

Methods An electronic literature search will be conducted in MEDLINE, EMBASE AND CINAHL from inception. Reference lists of included studies will also be searched for relevant prospective cohort studies and randomized controlled trials, which meet the pre-specified inclusion and exclusion criteria. The article selection and risk of bias of included studies will be determined independently by two reviewers. If possible, a meta-analysis will be conducted to pool estimates on the overall rate as well as the decade-specific rates of decline of the specified organ functions in a healthy aging cohort, and compare these estimates with cohorts that are exposed to risk factors.

Discussion This review aims to determine the rate of decline of organ function with age, and determine any predictors of decline. The results from this review will enable clinicians to better differentiate between physiological age-related decline and pathological decline when interpreting laboratory test results. This will prevent the overdiagnosis of elderly people with diseases that in fact represent normal ageing.

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Systematic review registration PROSPERO CRD42018087066

BACKGROUND

Description of the condition

Advances in modern medicine have resulted in unprecedented rise in life expectancy. The average person's life expectancy has risen by 5 years in the last fifteen years alone, the fastest rate of growth since the 1960s[1]. This has led to a rise in the number and proportion of persons aged 65 years and older with multiple chronic conditions and frailty, posing a complex social and economic challenge to healthcare systems.

Ageing is accompanied by physiological changes in the function of most (if not all) organs and senses. The physiological functions of some organs, including the lungs and kidneys, have been documented to reach a peak in early adulthood and then decline thereafter with age[2]. The rates of age-related functional decline are dependent on a number of factors, including genetics and environmental factors[3,4].

Measured lung function parameters decrease with age, due to factors such as loss of elasticity, weakened muscles of respiration and decreased surface area for alveolar gas exchange[6]. Several longitudinal studies have been performed to monitor and calculate the rate of FEV_1 (Forced expiratory volume in 1 second) decline, and highlight those who are at risk of developing disease[3,7,8].

The liver also demonstrates measurable changes with age, with liver weight reported to decrease by as much as 20% after the age of 50 years[2]. Although some studies show that liver function tests do not change with age[2,9,10], it is also established that albumin,- which is a marker of synthetic liver function, decreases with age (though this may in part, be due to other factors such as malnutrition or renal losses[11]). It has also been shown that the liver metabolises drugs slower in aged cohorts compared to younger cohorts[2,12,13].

With advancing age, there is a progressive loss in number and function of insulin-producing beta-cells in the pancreas. This, coupled with increasing systemic insulin resistance in glucose receptors can result in the development of diabetes mellitus in the elderly[14]. Few studies have demonstrated this by monitoring healthy individuals for the development of impaired glucose tolerance or fasting glucose[15].

Bone mineral density measurements also exhibits change with age, resulting in an increased risk of developing osteoporosis, which predisposes older people to minimal trauma fractures. Females have an accelerated decline of bone mass after the onset of menopause, due to declining oestrogen levels. Other factors, such as vitamin D, calcium levels, parathyroid gland function, renal function and gastrointestinal absorption also play a role in maintaining bone mass and skeletal function[16].

Normal ageing may result in changes in laboratory test values and biomarkers, but these changes do not necessarily represent clinical impairment.[5] Even if laboratory tests show values that lie outside the reference ranges, organs have functional reserves that cannot easily be measured by standard laboratory testing. Laboratory test results should not be used as the sole basis for which a diagnosis of disease is made; rather, these values should be integrated with the patient's clinical symptoms in order to make a diagnosis.[5] A measured decrease in organ function also may not represent clinically significant decline,

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instead demonstrating the normal process of ageing. One explanation for this may be that the demands of the elderly cohorts' activities of daily living are no longer the same as their younger counterparts.

Why it is important to do this review

Elderly people have increasingly been labelled with conditions such as prediabetes, chronic airways disease, osteopenia or liver disease as a result of laboratory testing. Although these conditions may represent a risk of progression to serious disease, which causes premature death, in many cases they may never progress to symptomatic disease and may even represent an expected level of function at that age.

A commonly-reported example is in chronic kidney disease, which is arbitrarily diagnosed by an eGFR (estimated glomerular filtration rate) threshold less than 60ml/min/1.73^2 for more than 3 months. There are no adjustments to this eGFR threshold for age, race or gender. Over 45% of the population over the age of 70 years have a diagnosis of chronic kidney disease according to this threshold[17,18]. Many of these individuals, however, never develop kidney failure or end stage renal disease, and have been inappropriately labeled (overdiagnosed) as having disease[19].

It is important to distinguish pathological aging from physiological decline. Some measures of organ function (such as eGFR) are not calibrated by age or gender, causing overdiagnosis of healthy individuals with disease, which may never manifest or cause harm, and subsequent overtreatment. It is therefore important to clarify what constitutes normal for healthy, aging individuals. To our knowledge, no systematic review has been done to identify and compare the rates of functional decline across organs, and whether there are risk factors/predictors that are in common.

OBJECTIVE

This review aims to determine the average rate of decline of lung function, liver function, pancreatic endocrine function and bone mineral density in healthy individuals with advancing age.

METHODS

Eligibility criteria

Types of studies

This review will consider prospective cohort studies or randomised controlled trials, which employ longitudinal designs (only if they include a control arm that does not receive treatment) with a minimum duration of three years and three separate measurements. Studies that report the age-related decline of the specified organ functions will be eligible for inclusion, irrespective of publication status and language of publication.

Types of participants

Studies will be considered eligible for inclusion if they follow a cohort of adults to the age of 65 years or more. Participants who have a known risk factor, medical illness or pre-disease specific to the outcome being studied (i.e. participants with diabetes when investigating pancreatic function decline) will be excluded. Appropriate participants will be included irrespective of sex or ethnicity. Studies including pregnant women or children will be excluded.

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Type of exposure

We will include studies involving ageing adults with no known comorbidities. Studies will be eligible for inclusion if they follow a normal cohort. Studies that only followed cohorts with risk factors or known exposures and did not compare them to a normal cohort will be excluded. We plan to assess whether there are certain predictors of decline that organs have in common. Examples of risk factors may include:

- Smoking
- Symptomatic hypertension
- High BMI
- Hyperlipidemia
- Diabetes mellitus
- Alcohol consumption

Types of outcome measures

We will include studies which report annual decline, or repeated measurements of organ function over time, to at least the age of 65 years. Studies should record a minimum of three measurements of organ function. Examples of these parameters include:

- Forced expiratory volume in 1 second (FEV_1) for lung function
- Albumin as a marker of synthetic liver function
- Fasting blood sugar levels for pancreatic endocrine function
- Bone mineral density

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Electronic searches

We conducted electronic searches of MEDLINE, EMBASE and CINAHL databases from inception through to October 2017, using the search strategy at the end of this document. This was developed with the assistance of an information specialist.

Searching other resources

Electronic searches were complemented by manual searching through reference lists of studies that were identified for potential inclusion as well as backwards and forward searching.

DATA COLLECTION AND ANALYSIS

Selection of studies

Two authors will independently screen titles and abstracts of all studies identified by the searches for potential inclusion. Prior to commencing screening, a small subset of 50 titles will be screened by the two reviewers as a calibration exercise to check for >80% agreement. After screening, a calibration exercise will be conducted screening the full texts of the studies targeting >80% agreement. The remaining full texts will then be retrieved and reviewed independently by the authors to determine eligibility for inclusion. Disagreements will be resolved by discussion or with another reviewer. If there are multiple reports of the same study, the most recent publication with longest length of follow up will be included.

Data extraction and management

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Two authors will independently extract data from the studies using a data extraction form. This form will be piloted using ten studies prior to data extraction as a calibration exercise to check for adequate agreement (>80%) between the reviewers. Data extraction will be performed using Excel and any disagreements will be resolved by discussion or by another reviewer. Extracted measures will include setting and year of the study, duration of the study, population size, ethnicity, baseline age, baseline organ function, organ function measurements, number and frequency of measurements, any known risk factors or exposures, proportion of those exposed, average length of follow up and loss to follow up. A random sample of the extraction will also be cross-checked by a third reviewer. All the measured outcomes (functional parameters) will initially be charted to show how often they are used in studies. A group of geriatricians and primary care physicians will be recruited from Bond University and Gold Coast Hospital and Health Service. Using the modified Delphi approach, these clinicians will be asked to independently rank the organ function parameters that they deem to be the most clinically relevant marker of organ function. The survey will be performed online. The highest ranked outcomes will then be included in the data analysis.

Assessment of risk of bias in included studies

Two authors will independently appraise the quality of the included studies, using the Newcastle Ottawa Scale (NOS) for assessing risk of bias in cohort studies. Disagreements will be resolved by discussion or a third reviewer. Factors that will be assessed include:

- Representativeness of the exposed cohort
- Selection of the non-exposed cohort
- Ascertainment of exposure
- Demonstration that the outcome of interest was not present at start of study
- Comparability of cohorts on the basis of design or analysis
- Assessment of outcome
- Adequate duration of follow up
- Adequate follow up of cohorts
- Other important biases

Risk of bias for randomised controlled trials will be assessed using the Cochrane Risk of Bias tool which assesses the following domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessors
- Incomplete outcome data
- Selective reporting
- Other biases

Measures of treatment effect

The data will first be extracted and analysed descriptively using graphs, to determine whether it is appropriate to pool the data. If deemed appropriate, RevMan will be used to pool the data. For continuous outcomes the mean difference (MD) (or standardized mean difference if studies use different measuring scales) and corresponding 95% confidence interval (95% CI) will be calculated. The data will be extracted and reported as an annual percentage decline. The overall rates of decline and corresponding

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confidence intervals will be presented visually in a forest plot. If the data allow, we will also extract and stratify decade-specific decline rates. If this is not possible, then a descriptive synthesis will be presented.

Subgroup analysis

We plan to re-analyse the data by organ function parameter if more than one marker is deemed appropriate as a useful measure of a certain organ's function (e.g. location of bone mineral density measurement). We will compare decline rates of different ethnicities and sex. As well as this we will separately analyse the data of those develop disease during the course of the study and those who had known risk factors. We will also look for birth cohort effects if the data allow (i.e. cohorts who have suffered deprivation early in life may show more functional decline later in life).

Dealing with missing data

If data were missing from studies published within the last 5 years, we plan to contact authors via email to obtain the individual data set.

Assessment of heterogeneity

Statistical heterogeneity may be assessed by calculating the chi squared score, as well as the I^2 statistic. Studies will be judged to have significant heterogeneity if the P value for the chi squared test was <0.1. If using mixed models, we will report random effects as the measure of heterogeneity. The degree of heterogeneity will be determined by the I^2 as follows (as specified in the Cochrane handbook):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If there is considerable heterogeneity within the studies for the outcome, reasons for heterogeneity will be explored and results will not be pooled.

Assessment of reporting biases

If available, outcomes reported in the protocol of the studies will be judged against the final publication to assess for any reporting bias. If there are any discrepancies, these will be reported. If study protocols are not available, the outcomes listed in the methodology of the study will compared to the final reported outcomes in the results. Authors will be contacted if there are any missing data or outcomes.

Data synthesis

Where data are sufficiently similar and are thought to be clinically relevant by a group of geriatricians and primary care physicians, we will pool the study estimates of organ function. A random effects model will be used in the meta-analysis to allow for between study differences.

Sensitivity analysis

Sensitivity analyses will be conducted to check whether heterogeneity in the overall outcomes can be explained by either of the following:

- the presence of low quality studies with high risk of bias (assessed as having one or more domains with a high risk of bias according to the NOS).
- duration of the study or time-points of measurement

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DISCUSSION

This review aims to provide an estimate of annual organ function decline across various organs that is part of normal aging in people without symptomatic disease. This will enable clinicians to distinguish age-appropriate laboratory test results from values which represent increased risk of disease. It is more reasonable to assess the health of individuals with reference to others in their age cohorts, not in comparison to healthy young individuals. Determining these 'normal' changes with aging will also avoid the psychological consequences of disease-labelling and side effects of unnecessary drug treatment. Researchers will be able to use this data to plan more longitudinal studies in different cohorts and investigate additional factors that affect changes in organ function. Further research will also be required to determine whether it is possible to regain function and if so, up until what point this is possible once a risk factor is removed.

ABBREVIATIONS

FEV_1 – Forced expiratory volume in 1 second
eGFR - estimated glomerular filtration rate
NOS- Newcastle Ottawa Scale

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DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

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AUTHORS' CONTRIBUTIONS

ETT, SS and PG were involved in the conception and design of the review. ETT developed the search strategy. ETT drafted the manuscript, and MG, SS, KB and PG contributed to the drafting of the review protocol. All authors approved the final version of the article.

ACKNOWLEDGEMENTS

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SEARCH STRATEGY

Query number	Medline Search
1	("Aging/ethnology"[Mesh] OR "Aging/physiology"[Mesh] OR “Age-related”[tiab] OR “Age related”[tiab] OR Function[tiab] OR Healthy[tiab])
2	(Decline[tiab] OR Declines[tiab] OR Declined[tiab] OR Decrease[tiab] OR Decreased[tiab])
3	("Middle Aged"[Mesh] OR "Aged"[Mesh] OR Aged[tiab] OR Elderly[tiab] OR Old[tiab] OR Older[tiab])
4	("Longitudinal Studies"[Mesh] OR Longitudinal[tiab] OR Trend[tiab] OR Trends[tiab] OR Trajectories[tiab] OR Trajectory[tiab] OR “Follow-up”[tiab] OR “Follow up”[tiab] OR “Rate of”[tiab] OR “Rates of”[tiab])
5	(Cohort[tiab] OR Observational[tiab] OR Prospective[tiab] OR Compared[tiab] OR Investigated[tiab] OR Evaluating[tiab] OR Analysis[tiab] OR Analyzed[tiab] OR Statistics[tiab] OR Data[tiab] OR Baseline[tiab])
6	(Humans[Mesh] OR Humans[tiab] OR Human[tiab] OR Population[tiab])
7	1 - 6
8	“Lung Volume Measurement”[tiab] OR “Lung Capacities”[tiab] OR “Respiratory Function Test”[tiab] OR “Pulmonary Function Tests”[tiab] OR “Lung Function Tests”[tiab] OR “Lung Function Test”[tiab] OR “Pulmonary Function Test”[tiab] OR “Airway Resistance”[tiab] OR “Blood Gas Analysis”[tiab] OR “Oximetry”[tiab] OR “Bronchial Provocation Tests”[tiab] OR “Capnography”[tiab] OR “Exercise Test”[tiab] OR “Lung Compliance”[tiab] OR “Lung Volume Measurements”[tiab] OR “Total Lung Capacity”[tiab] OR “Maximal Respiratory Pressures”[tiab] OR “Plethysmography, Whole Body”[tiab] OR “Pulmonary Gas Exchange”[tiab] OR “Pulmonary Diffusing Capacity”[tiab] OR “Ventilation-Perfusion Ratio”[tiab] OR “Pulmonary Ventilation”[tiab] OR “Forced Expiratory Flow Rates”[tiab] OR “Forced Expiratory Volume”[tiab] OR “Maximal Voluntary Ventilation”[tiab] OR “Spirometry”[tiab] OR “Bronchospirometry”[tiab] OR “Work of Breathing”[tiab] OR “Maximal Expiratory Flow Rate”[tiab] OR “Maximal Expiratory Flow-Volume Curves”[tiab] OR “Maximal Midexpiratory Flow Rate”[tiab] OR “Peak Expiratory Flow Rate”[tiab] OR “Expiratory Volume, Forced”[tiab] OR “Expiratory Volumes, Forced”[tiab] OR “FEVt”[tiab] OR “Forced Vital Capacity, Timed”[tiab] OR “Timed Vital Capacity”[tiab] OR “Capacity, Timed Vital”[tiab]

9	"Liver Function Test"[tiab] OR "Serum Albumin"[tiab] OR "Plasma Albumin"[tiab] OR "Bilirubin"[tiab] OR "Prothrombin Time"[tiab] OR "International Normalized Ratios"[tiab] OR "International Normalized Ratio"[tiab] OR "INR"[tiab] OR "Thrombotest"[tiab] OR "Quick Test"[tiab] OR "Transaminases"[tiab] OR "Aminotransferases"[tiab] OR "Alanine Transaminase"[tiab] OR "Aspartate Aminotransferases"[tiab] OR "Aspartate Aminotransferase, Cytoplasmic"[tiab] OR "Aspartate Aminotransferase, Mitochondrial"[tiab] OR "Liver/anatomy and histology"[Mesh] OR "Liver/diagnostic imaging"[Mesh] OR "Echography"[tiab] OR "Ultrasound Imaging"[tiab] OR "Ultrasonic Imaging"[tiab] OR "Medical Sonography"[tiab] OR "Diagnostic Ultrasound"[tiab] OR "Diagnostic Ultrasounds"[tiab] OR "Echotomography"[tiab] OR "Ultrasonic Diagnosis"[tiab] OR "Computer Echotomography"[tiab] OR "Ultrasonic Tomography"[tiab] OR "Organ Size"[tiab] OR "Organ Weight"[tiab] OR "Organ Volume"[tiab]
10	"Blood Sugar"[tiab] OR "Sugar, Blood"[tiab] OR "Glucose, Blood"[tiab] OR "Blood Glucose"[tiab] OR "Glucose Tolerance Test"[tiab] OR "Glucose Tolerance Tests"[tiab] OR "Oral Glucose Tolerance Test"[tiab] OR "OGTT"[tiab] OR "Oral Glucose Tolerance"[tiab] OR "Intravenous Glucose Tolerance Test"[tiab] OR "Intravenous Glucose Tolerance"[tiab] OR "Endocrine Diagnostic Technic"[tiab] OR "Endocrine Diagnostic Technique"[tiab] OR "Endocrine Diagnostic Techniques"[tiab] OR "Blood Glucose Self Monitoring"[tiab] OR "Blood Glucose Self-Monitoring"[tiab] OR "Blood Sugar Self Monitoring"[tiab] OR "Blood Sugar Self-Monitoring"[tiab] OR "Home Blood Glucose Monitoring"[tiab] OR "Glucose Clamp Technique"[tiab] OR "Glucose Clamp Techniques"[tiab] OR "Glucose Clamp Technic"[tiab] OR "Glucose Clamp Technics"[tiab] OR "Glucose Clamping"[tiab] OR "Euglycaemic Clamping"[tiab] OR "Euglycaemic Clamp"[tiab] OR "Euglycaemic Clamps"[tiab] OR "Glucose Clamp"[tiab] OR "Glucose Clamps"[tiab] OR "Hb A1a+b"[tiab] OR "Hb A1c"[tiab] OR "HbA1"[tiab] OR "Glycosylated Hemoglobin A"[tiab] OR "Hb A1"[tiab] OR "Glycohemoglobin A"[tiab] OR "Hemoglobin A(1)"[tiab] OR "Hemoglobin, Glycosylated A1b"[tiab] OR "Hb A1b"[tiab] OR "Hemoglobin, Glycosylated A1a-1"[tiab] OR "Hemoglobin, Glycosylated A1a 1"[tiab] OR "Hb A1a-1"[tiab] OR "Hb A1a-2"[tiab] OR "Glycosylated Hemoglobin"[tiab] OR "Glycated Hemoglobins"[tiab] OR "Insulin Resistance"[tiab] OR "Insulin Sensitivity"[tiab] OR "Langerhans Islets"[tiab] OR "Pancreatic Islets"[tiab] OR "Endocrine Pancreas"[tiab] OR "Langerhans Islands"[tiab] OR "Islet Cells"[tiab] OR "Islet Cell"[tiab]
11	"Bone Densities"[tiab] OR "Bone Density"[tiab] OR "Bone Mineral Density"[tiab] OR "Bone Mineral Densities"[tiab] OR "Bond Mineral Content"[tiab] OR "Bone Mineral Contents"[tiab] OR ""Photon Absorptiometry"[tiab] OR X-Ray Densitometry"[tiab] OR "Single-Photon Absorptiometry"[tiab] OR "Dual Energy X-Ray Absorptiometry Scan"[tiab] OR "DXA Scan"[tiab] OR "DEXA Scan"[tiab] OR "Dual-Photon Absorptiometry"[tiab] OR "Dual Energy Radiographic Absorptiometry"[tiab] OR "X-Ray Absorptiometry"[tiab]
12	7 AND 8
13	7 AND 9
14	7 AND 10
15	7 AND 11

REFERENCES

1. Mathers C, Stevens G, Mahanani W, Ho J, Fat D, Hogan D. WHO methods and data sources for country-level causes of death 2000-2015. Geneva: Department of Information, Evidence and Research WHO; 2017.
2. Boss G, Seegmiller J. Age-Related Physiological Changes and their Clinical Significance. West J Med 1981;135:434-40.
3. Aalami O, Fang T, Song H, Nacamuli R. Physiological Features of Aging Persons. Arch Surg 2003;138:1068-76.
4. Rodríguez-Rodero S, Fernández-Morera J, Menéndez-Torre E, Calvanese V, Fernández A, Fraga M. Aging Genetics and Aging. Aging and Disease 2011;2:186-95. .
5. Vásárhelyi B, Debreczeni L. Lab test findings in the elderly. J Int Fed Clin Chem 2017;28:328-32.
6. Navaratnarajah A, Jackson S. The physiology of ageing. Medicine 2017;45:6-10.
7. Knudson R, Lebowitz M, Holberg C, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983;127:725-34.
8. Zaugg M, Lucchinetti E. Respiratory Function in the Elderly. Anesthesiol Clin North America 2000;18:47-58.
9. Vestal R, McGuire E, Tobin J, al e. Aging and ethanol metabolism Clin Pharmacol Ther 1977;21:343-54.
10. Adkins R, Marshall B. Anatomic and physiologic aspects of aging.
. In: Adkins R, Scott H, eds. Surgical Care for the Elderly. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1998:xxi531.
11. Van Tongeren J, Cluysenaer O, Lamers C, De Mulder P, Yap S. Causes of hypoalbuminemia. In: Yap S, Majoor C, van Tongeren J, eds. Clinical Aspects of Albumin. Dordrecht: Springer; 1978.
12. George J, Byth K, Farrell G. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. . Biochem Pharmacol 1995;50:727-30.
13. Loi C, Parker B, Cusack B, Vestal R. Aging and drug interactions. III. Individual and combined effects of cimetidine and cimetidine and ciprofloxacin on theophylline metabolism in healthy male and female nonsmokers. J Pharmacol Exp Ther 1997;280:627-37.
14. McConnell J, Buchanan K, Ardill J, Stout R. Glucose tolerance in the elderly: the role of insulin and its receptor. Eur J Clin Invest 1982;12:55-61.
15. Meigs J, Muller D, Nathan D, Blake D, R A. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes 2003;52:1475-84.
16. Pathy J, Sinclair A, Morley J, Vellas B. Pathy's Principles and Practice of Geriatric Medicine. Oxford: UK: John Wiley & Sons, Ltd; 2012.
17. Levey A, Stevens L, Coresh J. Conceptual model of CKD: applications and implications. Am J Kidney Dis 2009;53:S4-16.
18. Stevens L, Viswanathan G, Weiner D. CKD and ESRD in the Elderly: Current Prevalence, Future Projections and Clinical Significance. Adv Chronic Kidney Dis 2010;17:293-301.
19. Moynihan R, Glassock R, Doust J. Chronic kidney disease controversy: how expanding definitions are unnecessarily labelling many people as diseased. BMJ 2013;347:f4298.

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SEARCH STRATEGY

Query number	Medline Search	Hits
1	("Aging/ethnology"[Mesh] OR "Aging/physiology"[Mesh] OR "Age-related"[tiab] OR "Age related"[tiab] OR Function[tiab] OR Healthy[tiab])	2500185
2	(Decline[tiab] OR Declines[tiab] OR Declined[tiab] OR Decrease[tiab] OR Decreased[tiab])	2111642
3	("Middle Aged"[Mesh] OR "Aged"[Mesh] OR Aged[tiab] OR Elderly[tiab] OR Old[tiab] OR Older[tiab])	5507544
4	("Longitudinal Studies"[Mesh] OR Longitudinal[tiab] OR Trend[tiab] OR Trends[tiab] OR Trajectories[tiab] OR Trajectory[tiab] OR "Follow-up"[tiab] OR "Follow up"[tiab] OR "Rate of"[tiab] OR "Rates of"[tiab])	1973987
5	(Cohort[tiab] OR Observational[tiab] OR Prospective[tiab] OR Compared[tiab] OR Investigated[tiab] OR Evaluating[tiab] OR Analysis[tiab] OR Analyzed[tiab] OR Statistics[tiab] OR Data[tiab] OR Baseline[tiab])	9089651
6	(Humans[Mesh] OR Humans[tiab] OR Human[tiab] OR Population[tiab])	17712772
7	1 - 6	22913
8	"Lung Volume Measurement"[tiab] OR "Lung Capacities"[tiab] OR "Respiratory Function Test"[tiab] OR "Pulmonary Function Tests"[tiab] OR "Lung Function Tests"[tiab] OR "Lung Function Test"[tiab] OR "Pulmonary Function Test"[tiab] OR "Airway Resistance"[tiab] OR "Blood Gas Analysis"[tiab] OR "Oximetry"[tiab] OR "Bronchial Provocation Tests"[tiab] OR "Capnography"[tiab] OR "Exercise Test"[tiab] OR "Lung Compliance"[tiab] OR "Lung Volume Measurements"[tiab] OR "Total Lung Capacity"[tiab] OR "Maximal Respiratory Pressures"[tiab] OR "Plethysmography, Whole Body"[tiab] OR "Pulmonary Gas Exchange"[tiab] OR "Pulmonary Diffusing Capacity"[tiab] OR "Ventilation-Perfusion Ratio"[tiab] OR "Pulmonary Ventilation"[tiab] OR "Forced Expiratory Flow Rates"[tiab] OR "Forced Expiratory Volume"[tiab] OR "Maximal Voluntary Ventilation"[tiab] OR "Spirometry"[tiab] OR "Bronchospirometry"[tiab] OR "Work of Breathing"[tiab] OR "Maximal Expiratory Flow Rate"[tiab] OR "Maximal Expiratory Flow-Volume Curves"[tiab] OR "Maximal Midexpiratory Flow Rate"[tiab] OR "Peak Expiratory Flow Rate"[tiab] OR "Expiratory Volume, Forced"[tiab] OR "Expiratory Volumes, Forced"[tiab] OR "FEVt"[tiab] OR "Forced Vital Capacity, Timed"[tiab] OR "Timed Vital Capacity"[tiab] OR "Capacity, Timed Vital"[tiab]	81312
9	7 AND 8	1131

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4-5
3	Description of study outcome(s)	5-6
4	Type of exposure or intervention used	6
5	Type of study designs used	6
6	Study population	6
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	5, Title page
8	Search strategy, including time period included in the synthesis and key words	5-6, Appendix 1
9	Effort to include all available studies, including contact with authors	5-6
10	Databases and registries searched	5-6
11	Search software used, name and version, including special features used (eg, explosion)	5-6
12	Use of hand searching (eg, reference lists of obtained articles)	5-6
13	List of citations located and those excluded, including justification	9, Figure 1
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	-
16	Description of any contact with authors	8
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	5-9
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-8
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-8
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-8
22	Assessment of heterogeneity	8-9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	8-9
24	Provision of appropriate tables and graphics	Table 1-3, Figures 2-5
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	Figure 2,3
26	Table giving descriptive information for each study included	Table 1
27	Results of sensitivity testing (eg, subgroup analysis)	15,16, Figure 2,3
28	Indication of statistical uncertainty of findings	-

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Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	18, Figure 4,5
30	Justification for exclusion (eg, exclusion of non-English language citations)	Figure 1
31	Assessment of quality of included studies	18,19
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	18-22
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	21,22
34	Guidelines for future research	22
35	Disclosure of funding source	23

From: Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Group. Meta-analysis of Observational Studies in Epidemiology. A Proposal for Reporting. *JAMA*. 2000;283(15):2008-2012. doi: 10.1001/jama.283.15.2008.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3,4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7,8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8,9

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7,8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	18, Figure 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-16, Table 2,3, Figure 2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	18, Figure 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	18
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	19,20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

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PRISMA 2009 Checklist

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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The rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies

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The rate of normal lung function decline in ageing adults: a systematic review of prospective cohort studies

Authors

Dr. Elizabeth T Thomas[1,2], Medical intern

Dr. Michelle Guppy[1,3], Associate Professor of General Practice, PhD candidate

Prof. Sharon Straus[4,5], Professor of Medicine, Director of Knowledge Translation Program

Dr. Katy JL Bell[1,6] NHMRC Senior Research Fellow

Prof. Paul Glasziou[1], Professor of Evidence-Based Medicine, Director of the Centre for Research in Evidence-Based Practice

Author affiliations

1. Centre for Research in Evidence-Based Practice, Bond University, Robina QLD 4226, Australia
2. Gold Coast University Hospital, 1 Hospital Boulevard, Southport QLD 4215, Australia
3. School of Rural Medicine, University of New England, Armidale NSW 2351, Australia
4. Department of Medicine, University of Toronto, Toronto, Ontario, Canada
5. Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada
6. Sydney School of Public Health, Sydney Medical School, Edward Ford Building (A27), University of Sydney, Sydney, Australia

Corresponding Author: Elizabeth T Thomas. Email: ethomas@bond.edu.au

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ABSTRACT

Objective To conduct a systematic review investigating the normal age-related changes in lung function in adults without known lung disease.

Design Systematic review.

Data sources MEDLINE, Embase and CINAHL were searched for eligible studies from inception to February 12, 2019, supplemented by manual searches of reference lists and clinical trial registries.

Eligibility criteria We planned to include prospective cohort studies and randomised controlled trials (control arms) that measured changes in lung function over time in asymptomatic adults without known respiratory disease.

Data Extraction and Synthesis Two authors independently determined the eligibility of studies, extracted data, and assessed the risk of bias of included studies using the modified Newcastle Ottawa Scale.

Results From 4385 records screened, we identified 16 cohort studies with 31,099 participants. All included studies demonstrated decline in lung function - FEV_1, FVC and peak expiratory flow rate (PEFR) with age. In studies with longer follow-up (>10 years), rates of FEV_1 decline ranged from 17.7 to 46.4 ml/year (median 22.4 ml/year).

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Overall, men had faster absolute rates of decline (median 43.5ml/year) compared to women (median 30.5ml/year). Differences in relative FEV_1 change, however, were not observed between men and women. FEV_1/FVC change was reported in only one study, declining by 0.29% per year. An age-specific analysis suggested the rate of FEV_1 function decline may accelerate with each decade of age.

Conclusions Lung function - FEV_1, FVC and PEFR - decline with age in individuals without known lung disease. The definition of chronic airway disease may need to be reconsidered to allow for normal ageing, and ensure that people likely to benefit from interventions are identified rather than healthy people who may be harmed by potential overdiagnosis and overtreatment. The first step would be to apply age, sex and ethnicity-adjusted FEV_1/FVC thresholds to the disease definition of COPD.

Registration PROSPERO CRD42018087066

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Strengths and limitations

- This is the first review to provide estimates for the median decline in spirometry measures including the FEV_1, FVC and the FEV_1/FVC ratio based on longitudinal data.
- We used a modified version of the Newcastle-Ottawa Scale to assess risk of bias.
- The review may be prone to volunteer bias, and therefore may underestimate lung function decline among asymptomatic people.
- Only one study specifically reported the change of the FEV_1/FVC ratio with age, and we did not have access to unpublished individual participant data to allow calculation of the FEV_1/FVC ratio change where this was not reported.

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INTRODUCTION

In 2016, the World Health Organization estimated that chronic obstructive pulmonary disease (COPD) affected 251 million people worldwide, with its prevalence continuing to rise with an ageing population.[1] Current guidelines in UK[2], Australasia[3], Europe and the United States[4] recommend that COPD is diagnosed if an individual has symptoms such as dyspnoea or sputum production, if they have known risk factors such as smoking or biomass fuel exposure, and if they demonstrate post-bronchodilator airflow limitation on spirometry. Airflow limitation on spirometry is defined when the ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) is less than 70% after bronchodilator administration.[2,3] However, this arbitrary diagnostic threshold has attracted criticism as it does not adjust for age or sex.[5-10]

Ageing is invariably accompanied by changes in lung function due to factors such as loss of lung elasticity, weakened muscles of respiration, and decreased surface area for alveolar gas exchange. Several published cross-sectional studies[9 11-13] and longitudinal studies[14 15] report that lung function parameters such as FEV_1 and FVC decline with age.

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The 2018 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[16] continues to suggest the use of the fixed ratio rather than an FEV_1 or FVC that lies outside of the lower limit of normal (LLN) range. While the fixed ratio threshold may be simple for clinicians to use, it does not consider that lung function measurements may change with age and vary with gender and ethnicity. Many laboratory tests already have different reference range values for different ages and electronic spirometry machines do the same. The GOLD criteria acknowledge that this arbitrary fixed threshold may overdiagnose normal healthy older adults as diseased and underdiagnose some younger people with disease as healthy.[17 18]

Longitudinal studies need to be identified so that normal changes in lung function can be calculated for different ages. Monitoring change could be used in practice to complement a single time point measurement to identify people who are not within the expected normal range. We aimed to perform a systematic review of prospective cohort studies and randomised controlled trials, that examined changes in lung function with age in asymptomatic individuals with no known lung disease who have never smoked.

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This knowledge would enable further work to develop age-, sex- and ethnicity-specific estimates that may be especially useful in a primary care setting. This implies that people are only diagnosed with COPD if their spirometry measurements fall outside of the normal range for their age, sex and ethnicity, rather than on the basis of a fixed value.

METHODS

Protocol registration

The protocol for this review was drafted in accordance with the PRISMA statement and the Meta-analyses of Observational Studies in Epidemiology (MOOSE) reporting guidelines. It was registered on PROSPERO (CRD42018087066) and is available from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018087066, see Supplementary File 1.

Search strategy and inclusion criteria

We conducted electronic searches of MEDLINE, EMBASE and CINAHL databases from inception through to February 2019, using the search strategy specified in Supplementary File 2.

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This was developed with an information specialist. Electronic searches were complemented by manual searching through reference lists of studies that were identified for potential inclusion as well as backwards and forward searching. We also searched the WHO Clinical Trials registry and ClinicalTrials.gov registries using the key words “normal ageing”, “lung function decline”, “FEV1 decline”, “FVC decline” and “lung decline”.

We included cohort studies and also planned to include the control arms of randomised controlled trials that measured the decline of lung function in an ageing population. The inclusion criteria were:

- Longitudinal studies that followed some or all of the adult participants past the age of 65 years;
- Three or more measurements of lung function undertaken;
- Studies with a follow-up period of three years or longer; and
- Studies that measure lung function (i.e. FEV_1, FVC, peak expiratory flow rate [PEFR]).

We excluded studies if the participants did not meet the pre-specified age criteria; if the population of interest were reported to include smokers or those with risk factors such as occupational inhalation; if participants were reported to have respiratory symptoms such as wheeze, dyspnea or chronic cough; or if the study included participants with known respiratory disease such as asthma or COPD.

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Study selection and data extraction

Two authors (ETT, MG) independently screened the titles and abstracts of studies identified in the initial search for eligibility. Prior to commencing screening, a small subset of 50 titles were screened by the two reviewers as a calibration exercise to check for >80% agreement. Similarly, after screening, a calibration exercise was conducted for screening the full texts of the studies and targeting >80% agreement. The remaining full texts were retrieved and reviewed independently by the authors to determine eligibility for inclusion. Non-English publications were translated using Google Translate or with the assistance of a translator. Disagreements were resolved by consensus through discussion or with a third reviewer (PG). If there were multiple reports of the same study, the most recent publication with longest length of follow up was selected for inclusion, and if the two studies had a similar length of follow up then the study with the largest sample size was included. Two authors independently extracted data from the studies. The Excel data extraction form was piloted using ten studies prior to data extraction as a calibration exercise to check for adequate agreement (>80%) between the reviewers. Any disagreements were resolved by

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consensus or with a third reviewer. Extracted measures included study setting, year and duration, participant eligibility criteria, sample size, participants demographics (ethnicity, gender, baseline age), any known risk factors or exposures, baseline lung function, lung function measurements, number and frequency of measurements, average length of follow up and loss to follow up. We also aimed to report the proportion of the cohort that subsequently developed symptoms or disease during follow-up.

We assessed risk of bias of included studies using the six items of the Newcastle Ottawa Scale (NOS)[19] for assessing quality of included cohort studies. Disagreements were resolved by discussion or a third reviewer.

Assessed factors included:

- Representativeness of the exposed cohort (e.g. low risk: random selection; high risk: non-random selection e.g. volunteer sampling)
- Ascertainment of exposure – age (e.g. low risk: from medical records; high risk: self-reported)

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- Demonstration that the outcome of interest was not present at start of study (e.g. low risk: participants were excluded on the basis of demonstrated airflow limitation; high risk: if participants were not screened)
- Assessment of outcome (e.g. low risk: spirometry; high risk: subjective measure of lung function)
- Adequate duration of follow up (e.g. low risk: equal to or greater than three years follow-up; high risk: less than three years of follow-up)
- Adequate follow up of cohorts (e.g. low risk: less than 20% attrition, loss to follow-up explained; high risk: greater than 20% attrition, unexplained loss to follow-up)

Studies were assessed as good quality if they had low risk of bias in all six domains, moderate quality if they had low risk of bias in four or five domains and low quality if they had low risk of bias for three or fewer domains.

Statistical analysis

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For each study cohort, we extracted the annual decline rates for each lung function measure. If these were not reported, we calculated crude decline rates for all reported lung function measure by subtracting the final measure from the initial measure and dividing the result by the duration of follow up. If these data were not available, we determined crude rates of decline from the graphs provided or contacted the study authors for original data. The data were first analysed descriptively using graphs to determine whether it was appropriate to pool the data. For continuous outcomes, the mean difference (MD) (or standardized mean difference if studies used different measuring scales) and standard deviations were calculated. The data were reported as an annual decline (unit/year). The overall rates of decline and corresponding 95% confidence intervals were presented in a forest plot. We planned to perform a meta-analysis to pool the estimates of decline.

We presented the data by functional parameter (FEV_1, $FEV_{0.75}$, FVC, PEFR), and planned to compare annual decline rates by sex and ethnicity in absolute and relative terms, where data were available. We also extracted and presented age-specific decline rates by decade of age if studies reported these data. We planned to separately analyse

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the data of those who developed disease during follow-up. We also planned to examine for birth cohort effects if the data were available. Sensitivity analyses were planned for study duration greater than ten years.

Patient and Public Involvement

Patients were not involved in the design, data extraction or data analysis of this review.

RESULTS

Study characteristics

From searches of Medline, Embase and CINAHL performed on February 12 2019, we identified 4331 records. An additional 54 records were identified from clinical trials registries and reference list searches. From these, we retrieved 143 papers for full text review; 115 of these did not meet our selection criteria and a further twelve were removed as duplicates. In total, 16 studies[20-35] were included in the systematic review (with one study contributing two data sets[29]) (Figure 1). The studies included 31,099 participants and were conducted between 1959 and 2014 ranging from five to thirty years in duration (Table 1).

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Table 1. Characteristics of included studies

Source ID	Cohort	Study duration (years)	Study centres	Study setting	Study period	Sample Size	Mean age of sample (years, SD)	%Male	Outcome	Time points of measurement
Ahmadi-Abhari 2014	EPIC-Norfolk	13	1	England	1993 - 2011	8062	58.5** (9.2)	45	FEV_1, FVC	3 (0, 4,13 years)
Bartholomew 1998	Busselton Population Health Surveys	6	1	Australia	1966 - 1981	1499	41.6 (16.1)	29.7	FEV_1, FVC	3 (0,3,6 years)
Burchfiel 1995	Kuakini Honolulu Heart Program	6	1	USA	1965 - 1975	1248	54.6*	100	FEV_1	3 (0,2,6 years)
Burrows 1986	Tucson Epidemiological study of obstructive Lung Disease (TESOLD)	9.6	1	USA	1972 - 1983	466	48.3 (19.1)	33.9	FEV_1	mean 5.2
Griffith 2001	Cardiovascular Health Study	7	4	USA	1989 - 1997	5242	73.5 / 72.7 (5.5)/ (5.2)	42.4	FEV_1, FVC	3 (0,4,7 years)
Lange 1998	Copenhagen City Heart Study	15	1	Denmark	1976 - 1994	4305	51.7^	37	FEV_1	3- Cycle 1: 1976 - 1978, Cycle 2: 1981-1983, Cycle 3: 1991-1994
Liao 2015	Framingham Heart Study	17	1	USA	1983 - 2007	543	47.6** (10.5)	38.1**	FEV_1, FEV_1/FVC	5 - Cycle 1: 1983-1987, Cycle 2: 1987-1991, Cycle 3: 1991-1995, Cycle 4: 1995-1998, Cycle 5: 2007
Luoto 2018	Good Aging in Skåne	13.5	1	Sweden	2001 – 2014	387	70.6** (10.6)	44.2**	FEV_1, FVC	Aged <80: every 6 years Aged 80 or over: every 3 years
Maselko 2006	MacArthur Successful Aging study	7	3	USA	1988-1995	544	74	31.8	PEFR	3 (0,3,7 years),

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Pearson 1998	Baltimore Longitudinal Study of Aging	Males: 11.5 Females: 5.7	1	USA	1962 - 1991	173	42.4	52.6	FEV_1	4.6 / 3 (every 2 years)
Pelkonen 2001	Seven Countries Study	30	2	Finland	1959 - 1989	200	47.6 (30 years) 49.4 (15 years)	100	$FEV_{0.75}$	6 (0,5,10,15,20,25,30 years)
Proctor 2006	Origins of Variance in the Old-Old (OCTO-Twin)	8	1	Sweden	1991 – 2003		83.2 (2.8)	33.0	PEFR	5 (0,2,4,6,8 years)
Sherman 1992	Six Cities study of Air Pollution and Health	12	6	USA	1974-1989	1486	47.2 / 48.2** (12.3) / (12.5)	32.0	FEV_1, FVC	4 (0,3,6,12 years)
Triebner 2017	European Community Respiratory Health Survey	19.7^	8	Denmark; Germany; Spain; France; Iceland; Norway; Sweden; Estonia	1991-2012	648	36.2**^	0	FEV_1, FVC	3 - Cycle 1: 1991-1994 Cycle 2: 1998-2002 Cycle 3: 2010-2012
Wang 2004	-	5	1	USA	1985 - 1992	71	37^** (19-65)	100	FEV_1	3-11; every 6 months
Xu 1995	Dutch Study on Asthma and Chronic Obstructive Pulmonary Diseases	24	2	The Netherlands	1965-1990	6293	35.06 / 44.5 (10.5)/ (11.4)	22.5	FEV_1	9 (every 3 years)

*Calculated from taking the midpoint of each age group and averaging according to number of people in each age group

** estimates include smokers

^ Median (Range)

/ # indicates Males / Females

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Overall age-related lung function decline

A meta-analysis was not performed due to substantial heterogeneity across the included studies, and a narrative synthesis was undertaken instead. Thirteen studies reported changes in FEV_1 as an outcome. All studies demonstrated a decline with age, with overall rates of decline from each study ranging from 9.9 to 56.0ml/year (median 29.2ml/year). Seven of these studies examined the differences in rates of decline between males and females, showing greater absolute FEV_1 decline in males (median 43.5ml/year) than females (median 30.5ml/year) (Table 2, Figure 2). Relative rates of FEV_1 decline were calculated for men in eight studies and women in six studies that reported baseline FEV_1 values. There was no statistically significant difference between men and women's relative change of FEV_1 from baseline (p=0.7). $FEV_{0.75}$ decline was reported in one study.[29] This study provided two data sets (follow up after 15 years, 30 years) provided in Table 2.

Five studies reported changes in FVC, with rate of decline estimates ranging from 14.1ml/year in the youngest cohort[32] (median age 36.2 years) to 65.6ml/year in the older cohort[24] (mean age 73.0 years). In studies that measured both FEV_1 and FVC over

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time, there was a greater decline in FEV_1 than FVC in two studies, and greater decline in FVC than FEV_1 in three studies. These measures are average estimates across study participants and do not enable calculation of individuals' FEV_1 /FVC ratios. In the one study where individuals' FEV_1/FVC ratios were reported as an outcome[26], there was a decline by 0.29% per year.

PEFR was reported as an outcome in two studies,[27 30] which showed decline rates ranging from -6.6L/min/year in females to -11.5L/min/year in males.

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Table 2. Reported annual rates of absolute and relative lung function decline (FEV_1, FVC, PEFR, $FEV_{0.75}$) in 16 prospective cohort

Source ID	Mean age of sample (years, SD)	Duration	Sample size		Mean absolute unit decline/yr (SD)		Overall relative decline (%)		Variables reported to alter the rate of change
			MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	
FEV_1 (mL)									
Ahmadi 2014	58.5** (9.2)	13	3621	4441	−17.7 (78.6)				Smoking; CRP categories
Bartholomew 1998	41.6 (16.1)	6	445	1054	-43.5 (100.4)	-30.5 (144.8)	1.1	1.2	Smoking; Increased BMI
Burchfiel 1995	54.6^	6	1248		-21.6°		0.7		Smoking status
Burrows 1986	48.3 (19.1)	9.6	158	308	-10.3° (6.3)	-9.1° (5.7)			-
Griffith 2001	73.0** (5.3)	7	1976**	2604**	-52.3 (3.1) [a]	-47.0 (2.8) [a]	1.9	1.7	Caucasian vs African American (only 2 measurements), Smoking
Lange 1998	51.7^	15	1592	2713	-23.5 (10.4)	-18.3 (10.0)	0.8	0.8	Asthmatics vs non-asthmatic, Smoker vs non smoker
Liao 2015	47.4** (10.6)	17	207***	336***	-25.8 (14.0)**				Smoking, Height, Less vs more likely dust exposure
Luoto 2018	70.6** (10.6)	13	171***	216***	-46.4° (47.7)		2.2°		Smoking, female sex (relative), male sex (absolute), elevated CRP (relative), BMI (absolute)
Pearson 1998	42.4	11.5/5.7	91	82	-43.5	-35.1	1.0	1.3	-
Sherman 1992	47.9 (12.4)	12	475	1011	-32.8 (29.5)	-27.5 (20.4)	1.0	1.1	Smoking
Triebner 2017	36.2†	19.7†		648		-22.4 (36.4)			Menopausal status, BMI
Wang 2004	37† (19-65)	5	71		-56.0 (45.0)		1.3		

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Xu 1995*	42.4^ (11.9)	24	1418	4875	-28.3 (138.5)	-16.0 (135.5)	0.7	0.5	
FVC (mL)									
Ahmadi 2014	58.5** (9.2)	13	3621	4441	-31.1 (118.1)				Smoking; CRP categories
Bartholomew 1998	41.6 (16.1)	6	445	1054	-47.2 (104.0)	-36.0 (154.5)	1.0	1.1	Smoking
Griffith 2001	73.0** (5.3)	7	1976**	2604**	-78.4[a] (4.2)	-65.6[a] (3.8)	2.9	2.4	Caucasian vs African American (only 2 measurements), Smoking
Luoto 2018	70.6** (10.6)	13	171***	216***	-43.7° (67.2)		1.7		Smoking, female sex (relative), male sex (absolute), low educational level, elevated CRP (relative)
Triebner 2017	36.2†	19.7†		648		-14.1 (42.8)			Menopausal status, BMI
FEV_1/FVC									
Liao 2015	47.4** (10.6)	17	207**	336**	-0.0029 (0.0023)**				Smoking, Less vs more likely dust exposure
$FEV_{0.75}$ (mL)									
Pelkonen 2001(a)	47.6	30	100		-34.8		1.0		Smoking
Pelkonen 2001(b)	49.4	15	200		-46.4		1.4		Smoking
PEFR (L/min)									
Maselko 2006	74	7	173	371	-8.6 (30.3)	–8.6 (34.7)	2.0	2.3	Smoking
Proctor 2006*	83.2 (2.8)	8	191	388	-11.5 (2.2)[a]	-6.6 (1.1)[a]	2.9	2.4	

*A non-linear relationship was also reported in the authors' data analysis.
** Based on estimates including smokers
***Estimates based on the assumption that there was an equal proportion of non-smokers and smokers who were male/female.
^Average derived from taking the midpoint value of each age group and calculating the overall mean age according to proportion in each group.

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† median
SDs were calculated from 95% CI by subtracting the highest from the lowest confidence interval and dividing the result by 3.92.
#/# indicates Male/Female
°Estimates adjust for covariates including height and age
[a]mean (Standard error)

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Age-specific lung function decline by decade of age

The age-specific rates of FEV_1 change by decade of age were extracted or calculated from three studies.[22 23 28 35] In all but one study, estimates of decline increased from the fourth (age 30-40 years) to eighth decades of life (Table 3). One study could not be included in this comparative analysis as they included smokers and reported decline rates at the end of study follow up (rather than baseline age).[35] This study reported that the rates of relative decline increase from the seventh (-1.7%/year) through to the tenth decade (-3.1%/year), though absolute rates of decline varied. Another study also reported that the rate of decline may be non-linear in multiple regression models of

Absolute mean decade-specific FEV_1 function decline rates (ml/year)

Study ID	Sample Size (n)	Baseline age (years) 30-39	40-49	50-59	60-69	70-79
Burchfiel 1995*	Male (1248)		-19.5**	-21.6	-25.0	
Burrows 1986	Male (158)	+2.83	-3.01	-8.85	-14.69	-20.53
	Female (308)	+2.73	-2.51	-7.76	-13.01	-18.26
Pearson 1998	Female (82)	-23.8	-33.4	-30	-23.4	-25.8
	Male (91)	-34	-34	-34	-34	-34

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FEV_1 and FVC decline (where age squared was also a statistically significant variable).[34]

Table 3. Age-specific lung function decline by decade of age as reported in four cohorts

*Estimates adjust for covariates including height and age
**Includes participants 45-49.
The estimates from Burrows were derived from formulae modelling change in FEV_1 with age. See Supplementary File 3 for calculations.

Two studies examined lung function change within age brackets that did not conform to our decade-specific analysis. Bartholomew 1998[21] reported greater decline rates in never smokers aged above 45 years (females: -30.7ml/year, males -45.8ml/year) compared to those aged below 45 years (females: -24.3ml/year, males: -36.8ml/year). Lange 1998[25] compared decline rates in both male and female non-smokers in 20-year age groups. Females aged 60-79 years had the greatest decline rates (-31.7 ± 2.1ml/year) compared to the 40-59 age group (-17.7 ± 1.4ml/year) and the 20-39 age group which reported an increase of 5.0 ± 2.7ml/year. Similarly, males aged 60-79 years had the greatest decline rates (-37.1 ± 3.7ml/year) compared to the 40-59 year age group (-24.2 ± 2.6ml/year) and the 20-39 year age group (-4.6 ± 4.2ml/year).

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Overall rates of mortality/symptom/disease development

Few studies reported these outcomes in an initially asymptomatic, non-smoking population. One study (Proctor)[30] reported 85% mortality rate in the elderly cohort (age range 79 – 96) over eight years. Another study (Lange 1998)[25] reported that in their study of non-asthmatics, 364 (2%) patients who did not report having asthma at the beginning of the study, later reported it in follow up. However, this estimate included smokers. One study (Wang)[33] performed their analyses on a highly screened population, meaning they excluded participants from all analyses who developed disease or symptoms during study follow up. No studies reported the rates of lung function change in those who developed disease during the course of the study compared with those who did not.

Sensitivity analyses

Heterogeneity in study duration was explored in Figure 3. After removing studies with a follow up of less than ten years, the median rate of decline of FEV_1 was 22.4ml/year (Figure 4).

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Predictors of the rate of decline in lung function in people without known lung disease

Smoking

Although smokers were not included in our main analysis, some studies did compare non-smokers and smokers which we report here. The decline rates were compared in non-smokers or former smokers with current smokers in nine studies[21 22 24-27 29 31 35]. In the seven studies measuring FEV_1 decline, current smokers were observed to have a faster rate of decline.[21 22 24-26 31 35] In the three studies measuring FVC, smoking increased FVC decline[21 24 35]. FEV_1/FVC decline was greater in smokers than nonsmokers in one study[26] and $FEV_{0.75}$ in another study[29].

BMI

Three studies reported the association of BMI with FEV_1 change. In Bartholomew 1998[21], increased BMI significantly affected FEV_1 decline ($p = 0.008$ for females; $p=0.007$ for males). However, an estimate for this association was not provided. In Triebner 2017[32], obese individuals reported greater declines of FEV1 (29ml/year) and FVC (25ml/year) compared to individuals with normal BMI (FEV1 22ml/year, FVC 10ml/year). In Luoto 2018[35], having a BMI greater than 35 was significantly associated

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with a slower decline of FEV_1 (32ml/year compared to 46ml/year, p = 0.04), but it did not significantly affect FVC decline.

Ethnicity

Griffith[24] was the only study that assessed ethnicity, specifically comparing African-American participants to White participants. We did not include the African-American cohort in our analysis as only two measurements were performed on this population. However, FEV_1 and FVC declines were greater in Whites compared to African-Americans.

Systolic blood pressure

Griffith[24] examined the correlation of systolic blood pressure greater than 160mmHg with FEV_1 and FVC decline and found that declines were on average 5.6ml/year and 10.9ml/year greater respectively (p <0.01).

Dust exposure

Liao[26] explored the effects of dust exposure on FEV_1 and FEV_1/FVC decline. Participants with more dust exposure experienced a mean FEV_1 decline that was 4.5ml/year greater than participants with less dust exposure (p= 0.007). Dust exposure

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did not significantly affect FEV_1/FVC ratio decline, suggesting that FVC declined in parallel to FEV1.

Menopausal status

Triebner[32] reported that menopausal status affected the rate of decline, with rates of FEV_1 decline on average 3.8ml/year greater in peri-menopausal women, and 5.2ml/year greater in postmenopausal women. FVC decline was 10.2ml/year greater in peri-menopausal women, and 12.5ml/year greater in post-menopausal women, compared to pre-menopausal women.

Risk of bias

Risk of bias was determined using a modified version of the Newcastle-Ottawa Scale[19] (Figures 5, 6). No studies received low risk of bias in all domains, but four studies had a low risk of bias in all but one domain.[23 28 31] Thirteen studies (81%) were graded as having low risk of bias for representativeness of the population. Six studies (38%) were judged as low risk of bias on how they ascertained the age of the participants (from Medicare eligibility lists or health records). Four cohort studies (25%) clearly demonstrated that pulmonary impairment was not present in participants at the

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beginning of the study. All studies (100%) used a spirometer to measure lung function which is a validated objective instrument. All studies (100%) had adequate duration of follow-up (three years or longer). Eight studies (50%) had a high risk of bias for having high attrition rates in their studies (>20%).

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DISCUSSION

Statement of principal findings

This systematic review of sixteen prospective cohort studies conducted in thirteen countries provides a summary of all the available evidence looking at lung function change with age. Lung function declines with age in normal, asymptomatic adults with higher rates of decline in absolute lung function parameters in men compared to women. However, the relative rates of decline from baseline between men and women do not differ significantly. The decline in absolute and relative lung function parameters may accelerate with age and is also exacerbated by smoking. We were unable to compare lung function decline rates of different ethnicities due to insufficient data. There was a paucity of longitudinal studies that reported changes in FEV_1/FVC rather than reporting the two parameters separately.

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Strengths and weaknesses of the study

This systematic review examined all the available primary studies to allow an examination of the consistency of estimates of decline in FEV_1, FVC, FEV_1/FVC ratio and PEFR. This review particularly focused on older adults; this group is relatively understudied and yet more prone to overdiagnosis and misdiagnosis.[6 8 18] While the majority of current prediction equations of lung function are based on cross-sectional studies[36-39] our review searched for longitudinal studies as they change in lung function may provide a complement to measurement at one time point in predicting future lung function.[37] Our review included participants who were ageing normally, but may have had non-pulmonary co-morbidities such as hypertension and diabetes mellitus. This enabled us to investigate a population that was more representative of a normal ageing population.

Our review has some limitations. We did not have access to unpublished individual participant data to allow calculation of FEV_1/FVC for the majority of studies, where this were not reported. Five studies separately measured changes in both FEV_1 and FVC,

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however is difficult to conclude whether the rate of decline in FEV_1 and FVC is proportional. Out of the five studies that reported both FEV_1 and FVC decline, two studies[32] demonstrated that FEV_1 declines faster than FVC, but in the three remaining studies[20 21 24], the FVC declined at a faster rate (See Table 2). Longitudinal studies that specifically measure the FEV_1/FVC would provide the most reliable measure of this decline. Individual patient data would also allow a more robust analysis of changes in lung function between individuals in the studies.

We were unable to pool the results due to significant heterogeneity across the populations. This review's findings are also limited by the quality of the included studies, all of which were judged moderate or low quality. Since this review is based on limited populations, the findings may not be generalisable to all individuals, especially those of non-Caucasian ethnicities or from less economically developed countries where smoking and air pollution may be more prevalent for example. The review's findings may underestimate lung function decline among asymptomatic people, as volunteer bias may be present with cohort studies where healthier individuals may be more likely to participate. Our study aimed to examine the rate of lung function change in the

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elderly, however the majority of included studies did not focus on this age group. COPD misdiagnosis particularly affects those older than 80 years of age, therefore more studies are required in the elderly.

Our review did not consider the extent of short term within-person variation, or "noise", in lung function measurements, which is likely to be considerable.[40 41] Any observed change in measurement is a combination of the true change, or "signal", and the random background "noise". The clinical utility of monitoring lung function to decide whether or not COPD is present, is in part determined by the ratio of signal to noise in the measurements.[42] Changes in measured lung function over a longer period of time may be more likely to indicate some true change rather than just background noise[43], therefore we specified in our inclusion criteria that eligible studies should measure lung function on a minimum of three occasions.

We observed substantial heterogeneity across all of the included studies and results. This may be due to inherent differences within the populations studied (including distribution of ages, proportion of men vs women and ethnicities) or the duration of follow up, or that decline in normal healthy people may vary across individuals without

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causing disease. We explored differences in duration of follow-up as a potential source of heterogeneity in a sensitivity analysis excluding studies with less than ten years of follow up, but found that this did not change the median estimate substantially.

Quality of spirometry, as well as properly maintained and calibrated equipment, causing measurement error and contributing to the "noise" in measurement discussed above, is likely to have contributed to variation in the results. Only nine of the included studies specifically reported that the spirometers used in their studies were calibrated and the measurements had to be acceptable and reproducible, following the American Thoracic Society guidelines on the standardization of spirometry.[44] Two studies used peak flow meters to measure PEFR. These instruments are well known to vary in consistency and accuracy. Maselko et al, used a Mini-Wright meter, but the second study by Proctor et al, did not specify which peak flow meter they used.

The majority of studies specified that they excluded patients with known disease or symptoms at the commencement of the study. However most of the studies did not report whether any of the participants in their study sample developed symptoms or

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respiratory disease in the course of follow-up. Thus, undiagnosed COPD or other respiratory, cardiac, renal or other diseases that cause decline in lung function, may have contributed to heterogeneity in the results.

Variation within the results may be also explained by the "horse-racing effect", where an initially low FEV_1 measurement may reflect a greater loss of function in the preceding years and hence predicts faster decline in subsequent years (just as the position of the horse in halfway through the race is related to its speed in the early part of the race and hence speed for the final part of the race).[45 46] Regression to the mean, due to inclusion of people with randomly high (or low) measured lung function in the primary studies, may also have contributed to heterogeneity of the results.[47] A simple way that primary studies may assess for a horse racing effect, while allowing for regression to the mean, is by constructing Bland-Altman plots of change vs mean FEV_1 level[48] (or substituting PEFR for mean FEV_1 as these are highly correlated.[49])

Comparison with previous research

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To date, there have been no systematic reviews or meta-analyses examining the rate of lung function decline with age, to assess the potential impact of the fixed threshold on COPD misdiagnosis. Cross-sectional studies have compared people diagnosed with COPD using a fixed threshold and the lower limit of normal (LLN) definition, reporting that the GOLD criteria leads to misdiagnosis of COPD.[5-8 50] A prospective cohort study found that the fixed threshold of the GOLD criteria overdiagnosed a large proportion of elderly people over the age of 70, and the LLN criteria tended to under-diagnose COPD, when compared to the reference standard which consisted of an expert panel who used all available diagnostic information including spirometry.[18]

Meaning of the study: possible explanations and implications for clinicians and policymakers

This review has found that lung function declines with age in all studied populations. The rate of decline appears to accelerate with age, and age-specific estimates of FEV_1, FVC and FEV_1/FVC ratio may be more appropriate for diagnosis of COPD than the fixed threshold currently used across all ages. Currently, prediction equations for calculating mean lung function values as well as the lower-limit of normal (LLN) for all ages are

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based on data from cross-sectional studies, however it is argued that this is problematic as they do not factor in the important dimension of time.[51 52]Spirometers used in practice commonly derive their reference values from the National Health and Nutrition Examination Survey (NHANES), a cross-sectional study which was conducted in the USA between 1988 – 1994. Though the predicted values do reflect a decline in FEV_1 and FEV_1/FVC with age, these decline rates may not be as reliable as the estimates from longitudinal studies included in our review. According to the NHANES III, the median rate of FEV_1 decline for a Caucasian male of 1.75m aged between 30-80 is 32ml/year and a female with an average height of 1.6m has an FEV_1 that declines a median of 25ml/year. Both of these estimates are lower than the median FEV_1 decline of the studies in our review, which was 43.5ml/year and 30.5ml/year for men and women respectively. Therefore the predicted age-specific lung function used in spirometers may often mislabel people as having abnormal lung function when they are actually within normal limits.[53] More reliable age-specific estimates and prediction equations are required.

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Clinicians need to consider whether 'abnormal' spirometry results may in fact represent normal ageing. This is especially true for making a formal diagnosis of COPD. If a patient is symptomatic and has airflow obstruction as defined by GOLD criteria, it may be necessary to consider alternative diagnoses such as a dyspnoea of cardiac origin. One proposal for identifying individuals who are experiencing greater loss of lung function than expected, is to develop 'decline charts' that predict FEV_1 or FEV_1/FVC loss for different ages. This can allow clinicians to monitor lung function over time and assess whether individuals are tracking along expected decline curves. These would also need to account for noise in measurement.

Future research should focus on conducting long-term longitudinal studies in less-studied populations, with emphasis on older adults. These studies should examine the rates of decline in people who eventually become symptomatic or develop disease. This information can guide clinicians to predict what rate of lung function decline may be a prognostic indicator of COPD onset and progression. Further well-designed prospective studies that investigate changes in FEV_1/FVC may allow for the development of algorithms that predict individuals' expected lung function over time according to their

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sex, smoking history, age, BMI and ethnicity. The observed change in lung function parameters might then be compared to the expected change to help the clinician determine whether this is extreme enough to warrant diagnosis of disease.

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CONTRIBUTOR STATEMENT

ETT was involved with devising the review methods, conducting electronic searches, screening of abstracts, data extraction, data analysis and interpretation, and co-drafting of the review. MG was involved with devising the review methods, screening of abstracts, data extraction, data analysis and interpretation and co-drafting the review. KJLB was involved with devising the review methods, data analysis and interpretation, and co-drafting the review. SS was involved with devising the review methods, data

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All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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TRANSPARENCY DECLARATION

The lead author (ETT) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned have been explained.

REFERENCES

1. Chronic obstructive pulmonary disease (COPD): World Health Organization; 2017 [Available from: http://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) accessed 5 Aug 2018.
2. Chronic obstructive pulmonary disease in over 16s: diagnosis and management: National Institute for Health and Care Excellence; 2010 [Available from: https://www.nice.org.uk/guidance/cg101 accessed 5 Aug 2018.
3. The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary disease 2018: Lung Foundation Australia; 2018 [Available from: https://copdx.org.au/wp-content/uploads/2018/06/COPDX-V2-53-March-2018_2.pdf accessed 5 Aug 2018.
4. Qaseem A, Wilt T, Weinberger S, et al. Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Ann Int Med* 2011;155:179-91. doi: 10.7326/0003-4819-155-3-201108020-00008
5. Schermer T, Smeele I, Thoonen B, et al. Current clinical guideline definitions for airflow obstruction leads to substantial overdiagnosis of COPD in primary care. *Eur Respir J* 2008;52(2) doi: 10.1183/09031936.00170307

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

6. Swanney M, Ruppel G, Enright P, et al. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008;63(12):1046-51. doi: 10.1136/thx.2008.098483 [published Online First: Sep 11 2018]
7. Shirtcliffe P, Weatherall M, Marsh S, et al. COPD prevalence in a random population survey: a matter of definition. *Eur Respir J* 2007;30:232-9.
8. Hardie J, Buist A, Vollmer W, et al. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002;20:1117-22.
9. Medbø A, Melbye H. Lung function testing in the elderly—Can we still use FEV1/FVC<70% as a criterion of COPD? *Respir Med* 2007;101(6):1097-105. doi: https://doi.org/10.1016/j.rmed.2006.11.019
10. Miller M, Levy M. Chronic obstructive pulmonary disease: missed diagnosis versus misdiagnosis. *BMJ* 2015;351:h3021. doi: 10.1136/bmj.h3021
11. Morris J, Temple W, Koski A. Normal Values for The Ratio of One-Second Forced Expiratory Volume to Forced Vital Capacity. *Am Rev Respir Dis* 1973;108(4)
12. Hankinson J, Odencrantzm J, Fedan K. Spirometric Reference Values from a Sample of the General U.S. Population. *Am J Respir Crit Care Med* 1999;159:179-87.
13. Glindmeyer H, Lefante J, McColloster C, et al. Blue-collar normative spirometric values for Caucasian and African-American men and women aged 18 to 65. *Am J Respir Crit Care Med* 1995;151(2) doi: https://doi.org/10.1164/ajrccm.151.2.7842200
14. Bossé R, Sparrow D, Garvey A, et al. Cigarette smoking, aging and decline in pulmonary function: A longitudinal study. *Arch Environ Health* 1980;35:247-52.
15. Huhti E, Ikkala J. A 10-year follow-up study of respiratory symptoms and ventilatory function in a middle-age rural population. *Eur J Resp Dis* 1980;61:33-45.
16. Pocket Guide to COPD Diagnosis, Management and Prevention: a guide for health care professionals: Global Initiative for Chronic Obstructive Lung Disease; 2018 [Available from: https://goldcopd.org/wp-content/uploads/2018/02/WMS-GOLD-2018-Feb-Final-to-print-v2.pdf accessed 5 Aug 2018.
17. Van Dijk W, Tan W, Li P, et al. Clinical relevance of fixed ratio vs lower limit of normal of FEV1/FVC in COPD: patient-reported outcomes from the CanCOLD cohort. *Ann Fam Med* 2015;13(1):41-8.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

18. Güder G, Brenner S, Angermann C, et al. GOLD or lower limit of normal definition? a comparison with expert-based diagnosis of chronic obstructive pulmonary disease in a prospective cohort-study. *Respir Res* 2012;13(1):13. doi: 10.1186/1465-9921-13-13
19. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses: The Ottawa Hospital; [Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp accessed 12 Aug 2018.
20. Ahmadi-Abhari S, Kaptoge S, Luben R, et al. Longitudinal Association of C-Reactive Protein and Lung Function Over 13 Years: The EPIC-Norfolk Study. *Am J Epidemiol* 2014;179(1):48-56. doi: 10.1093/aje/kwt208
21. Bartholomew H, Knuiman M. Longitudinal analysis of the effect of smoking cessation on cardiovascular risk factors in a community sample: the Busselton Study. *J Cardiovasc Risk* 1998;5:263-71.
22. Burchfiel C, Marcus E, Curb J, et al. Effects of Smoking and Smoking Cessation on Longitudinal Decline in Pulmonary Function. *Am J Respir Crit Care Med* 1995;151:1778-85.
23. Burrows B, Lebowitz M, Camilli A, et al. Longitudinal Changes in Forced Expiratory Volume in One Second in Adults: Methodologic Considerations and Findings in Healthy Nonsmokers. *Am Rev Respir Dis* 1986;133:974-80.
24. Griffith K, Sherrill D, Siegel E, et al. Predictors of Loss of Lung Function in the Elderly: The Cardiovascular Health Study. *Am J Respir Crit Care Med* 2001;163:61-8.
25. Lange P, Parner J, Vestbo J, et al. A 15-year follow-up study of ventilatory function in adults with asthma. *N Engl J Med* 1998;339:1194-200.
26. Liao S, Lin X, Christiani D. Occupational Exposures and Longitudinal Lung Funciton Decline. *Am J Ind Med* 2015;58:14-20.
27. Maselko J, Kubzansky L, Kawachi I, et al. Religious Service Attendance and Decline in Pulmonary Function in a High-Functioning Elderly Cohort. *Ann Behav Med* 2006;32(3):245-53.

For peer review only

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28. Pearson J, Kao S, Brant L, et al. Longitudinal Change in Forced Expiratory Volume in Healthy, Non-smoking Men and Women: The Baltimore Longitudinal Study of Aging. *Am J Hum Biol* 1998;10:471-81.
29. Pelkonen M, Notkola I, Tukiainen H, et al. Smoking cessation, decline in pulmonary function and total mortality: a 30 year follow up study among the Finnish cohorts of the Seven Countries Study. *Thorax* 2001;56:703-7.
30. Proctor D, Fauth E, Hoffman L, et al. Longitudinal changes in physical functional performance among the oldest old: insight from a study of Swedish twins. *Aging Clin Exp Res* 2006;18:517-30.
31. Sherman C, Xu X, Speizer F, et al. Longitudinal Lung Function Decline in Subjects with Respiratory Symptoms. *Am Rev Respir Dis* 1992;148:855-9.
32. Triebner K, Matulonga B, Johannessen A, et al. Menopause Is Associated with Accelerated Lung Function Decline. *Am J Respir Crit Care Med* 2017;195(8):1058-65.
33. Wang M, Petsonk E. Repeated Measures of FEV1 Over Six to Twelve Months: What Change is Abnormal? *J Occup Environ Med* 2004;46:591-95.
34. Xu X, Laird N, Dockery D, et al. Age, Period, and Cohort Effects on Pulmonary Function in a 24-Year Longitudinal Study. *Am J Epidemiol* 1995;141:554-66.
35. Luoto J, Pihlsgard M, Wollmer P, et al. Relative and absolute lung function change in a general population aged 60-102 years. *Eur Respir J* 2018 doi: 10.1183/13993003.01812-2017 [published Online First: 2018/12/24]
36. Cherniack R, Raber M. Normal Standards for Ventilatory Function Using an Automated Wedge Spirometer. *Am Rev Respir Dis* 1971;106(1) doi: https://doi.org/10.1164/arrd.1972.106.1.38
37. Lung Function Testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis* 1991;144:1202-18.
38. Morris J, Koski A, Johnson L. Spirometric Standards for Healthy Nonsmoking Adults. *Am Rev Respir Dis* 1971;103(1)
39. Paoletti P, Pistelli G, Fazzi P, et al. Reference values for vital capacity and flow-volume curves from a general population study. *Bull Eur Physiopathol Respir* 1986;22:451-9.
40. MacIntyre N. Finding Signals Amidst the Noise in Pulmonary Function Testing. *Chest* 2007;132(2):367-8.

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

41. Becklake M, White N. Sources of variation in spirometric measurements. Identifying the signal and dealing with noise. *Occup Med* 1993;8(2):241-64.
42. Bell K, Glasziou P, Hayen A, et al. Criteria for monitoring tests were described: validity, responsiveness, detectability of long-term change, and practicality. *J Clin Epidemiol* 2014;67(2):152-9. doi: 10.1016/j.jclinepi.2013.07.015
43. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26:948-68.
44. Miller M, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur J Resp* 2005;26:319-38.
45. Fletcher C, Peto R, Tinker C, et al. The natural history of chronic bronchitis and emphysema. Oxford: Oxford University Press 1970.
46. Peto R. The horse-racing effect. *Lancet* 1981;2(8244):467-8.
47. Bland J, Altman D. Statistics Notes: Some examples of regression towards the mean. *BMJ* 1994;309:780. doi: https://doi.org/10.1136/bmj.309.6957.780
48. Bland J, Altman D. Statistics Notes: Measurement error proportional to the mean. *BMJ* 1996;313:106. doi: https://doi.org/10.1136/bmj.313.7049.106
49. Gautrin D, D'Aquino L, Gagnon G, et al. Comparison Between Peak Expiratory Flow Rates (PEFR) and FEV1 in the Monitoring of Asthmatic Subjects at an Outpatient Clinic. *Chest* 1994;106(5):1419-26.
50. Wang Y, Xiao W, Ma D, et al. Predicted lower limit of normal reduces misclassification risk of airflow limitation in asymptomatic elderly never-smokers. *Chin Med J* 2013;126(18):3486-92.
51. Brändli O, Schindler C, Künzli N, et al. Lung function in healthy never smoking adults: reference values and lower limits of normal of a Swiss population. *Thorax* 1996;51:277-83.
52. Marks G. Are reference equations for spirometry an appropriate criterion for diagnosing disease and predicting prognosis? *Thorax* 2012;67:85-7. doi: 10.1136/thoraxjnl-2011-200584
53. NHANES - Normal values: Vitalograph; 2019 [Available from: https://vitalograph.com/resources/nhanes-normal-values] accessed February 9, 2019.

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Figure Legends

Figure 1. Study flow diagram showing the process for inclusion of prospective RCTs and cohort studies for estimating the rate of lung function decline with age.

Figure 2. The rate of FEV_1 decline in thirteen study populations, grouped by sex.

Figure 3. The rate of FEV_1 decline in thirteen study populations by years of follow-up. The size of the circle corresponds to individual study sample size.

Figure 4. Sensitivity analysis, excluding studies with less than ten years of follow-up. The size of the circle corresponds to individual study sample size.

Figure 5. Risk of bias summary for prospective cohort studies estimating the rate of lung function decline with age, assessed using a modified form of the Newcastle-Ottawa Scale.

Figure 6. Graphical representation of the risk of bias in prospective cohort studies estimating the rate of lung function decline with age.

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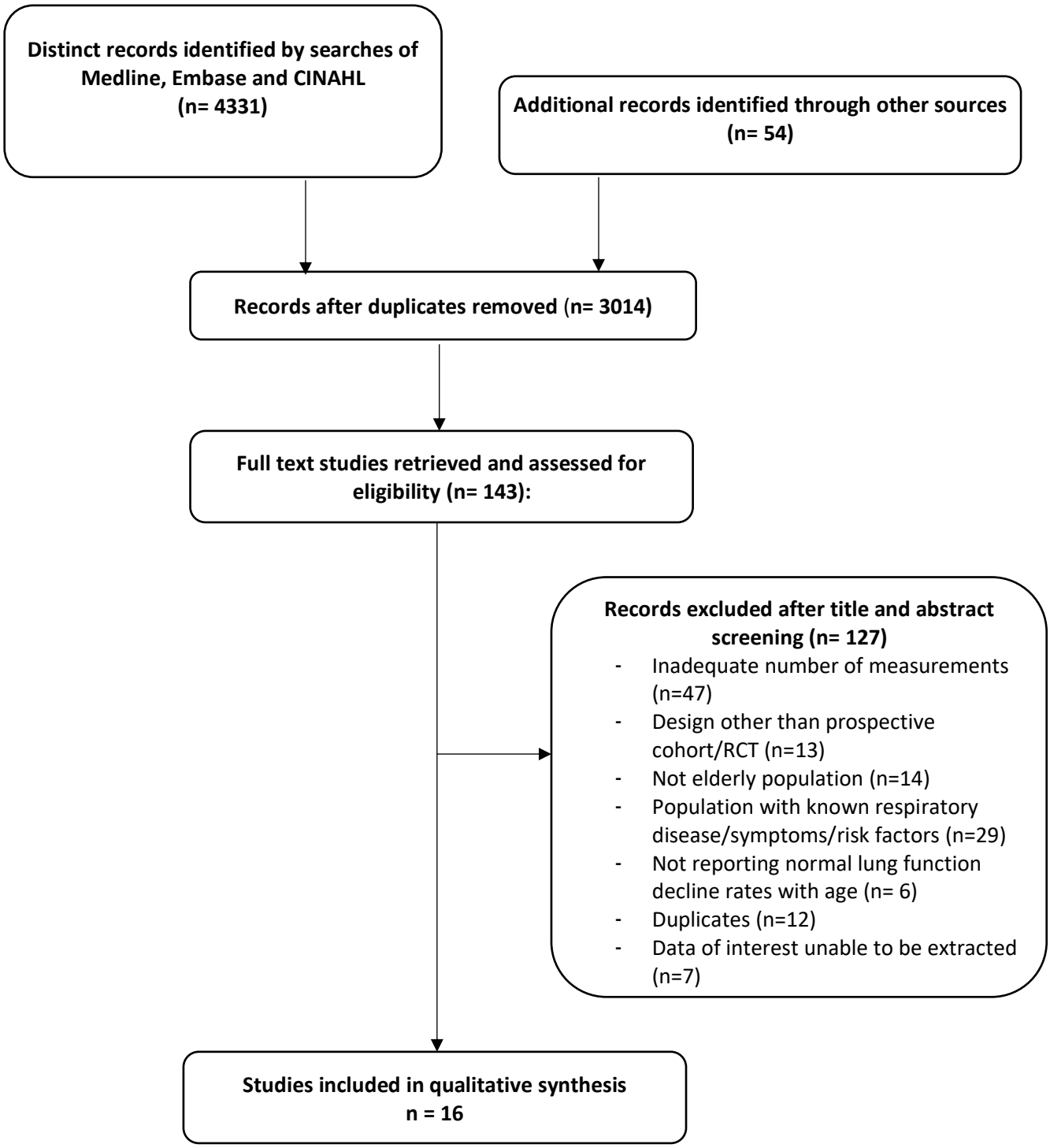
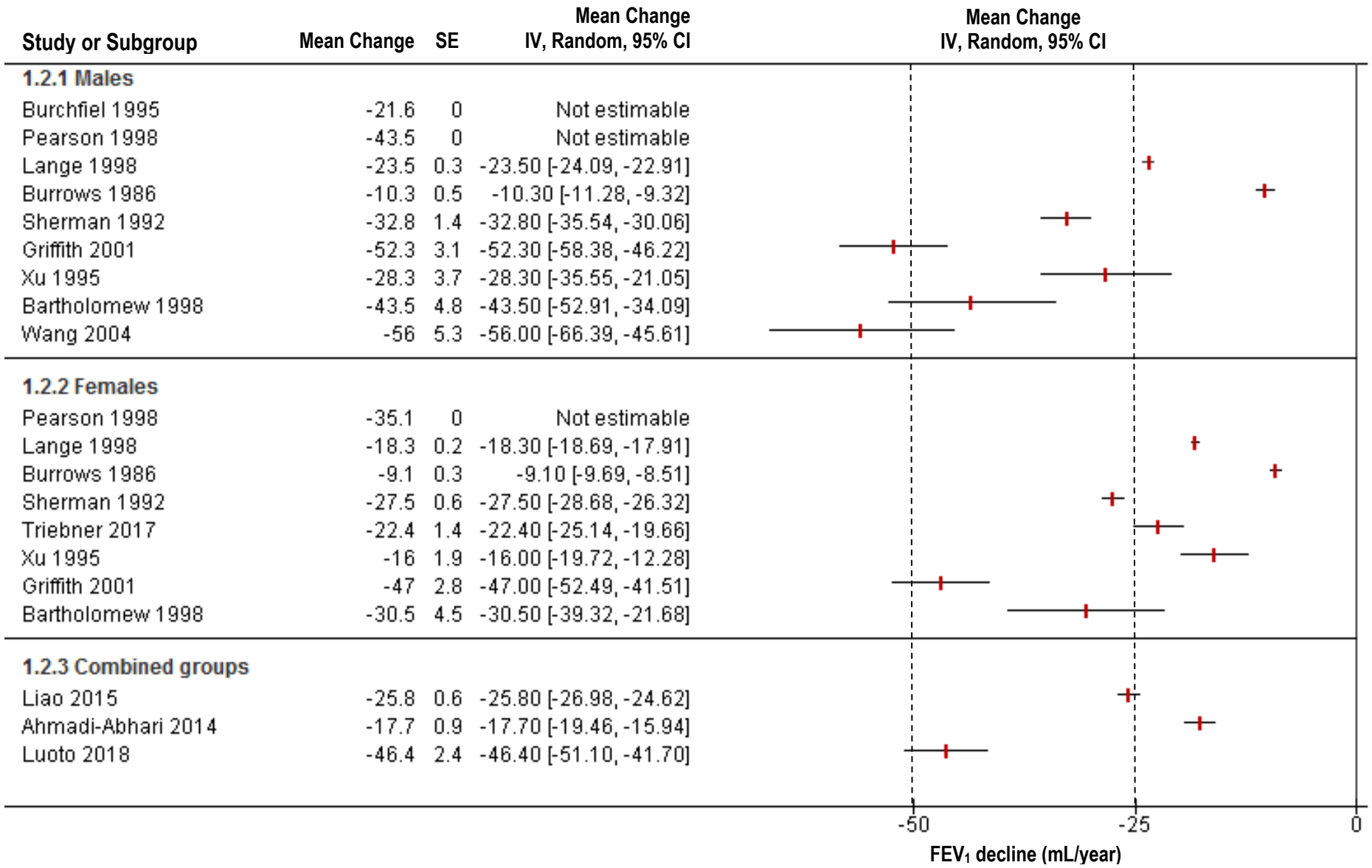
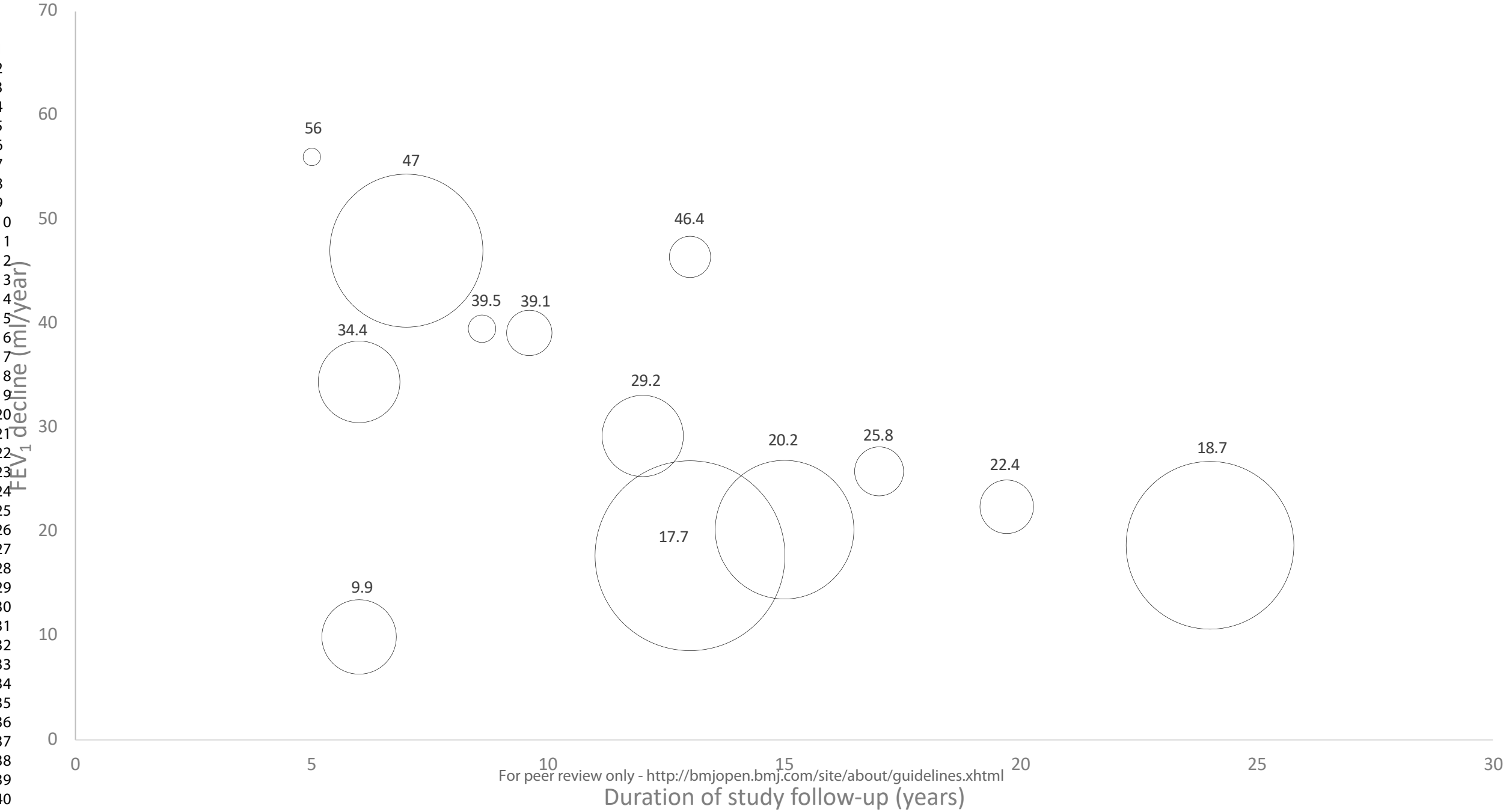
Figure 1. Study flow diagram showing the process for inclusion of prospective RCTs and cohort studies for estimating the rate of lung function decline with age.




Study or Subgroup
Mean Change
SE
Mean Change IV, Random, 95% CI
Mean Change IV, Random, 95% CI
1.2.1 Males
Burchfiel 1995 -21.6 0 Not estimable
Pearson 1998 -43.5 0 Not estimable
Lange 1998 -23.5 0.3 -23.50 [-24.09, -22.91]
Burrows 1986 -10.3 0.5 -10.30 [-11.28, -9.32]
Sherman 1992 -32.8 1.4 -32.80 [-35.54, -30.06]
Griffith 2001 -52.3 3.1 -52.30 [-58.38, -46.22]
Xu 1995 -28.3 3.7 -28.30 [-35.55, -21.05]
Bartholomew 1998 -43.5 4.8 -43.50 [-52.91, -34.09]
Wang 2004 -56 5.3 -56.00 [-66.39, -45.61]
1.2.2 Females
Pearson 1998 -35.1 0 Not estimable
Lange 1998 -18.3 0.2 -18.30 [-18.69, -17.91]
Burrows 1986 -9.1 0.3 -9.10 [-9.69, -8.51]
Sherman 1992 -27.5 0.6 -27.50 [-28.68, -26.32]
Triebner 2017 -22.4 1.4 -22.40 [-25.14, -19.66]
Xu 1995 -16 1.9 -16.00 [-19.72, -12.28]
Griffith 2001 -47 2.8 -47.00 [-52.49, -41.51]
Bartholomew 1998 -30.5 4.5 -30.50 [-39.32, -21.68]
1.2.3 Combined groups
Liao 2015 -25.8 0.6 -25.80 [-26.98, -24.62]
Ahmadi-Abhari 2014 -17.7 0.9 -17.70 [-19.46, -15.94]
Luoto 2018 -46.4 2.4 -46.40 [-51.10, -41.70]
-50
-25
0
FEV1 decline (mL/year)



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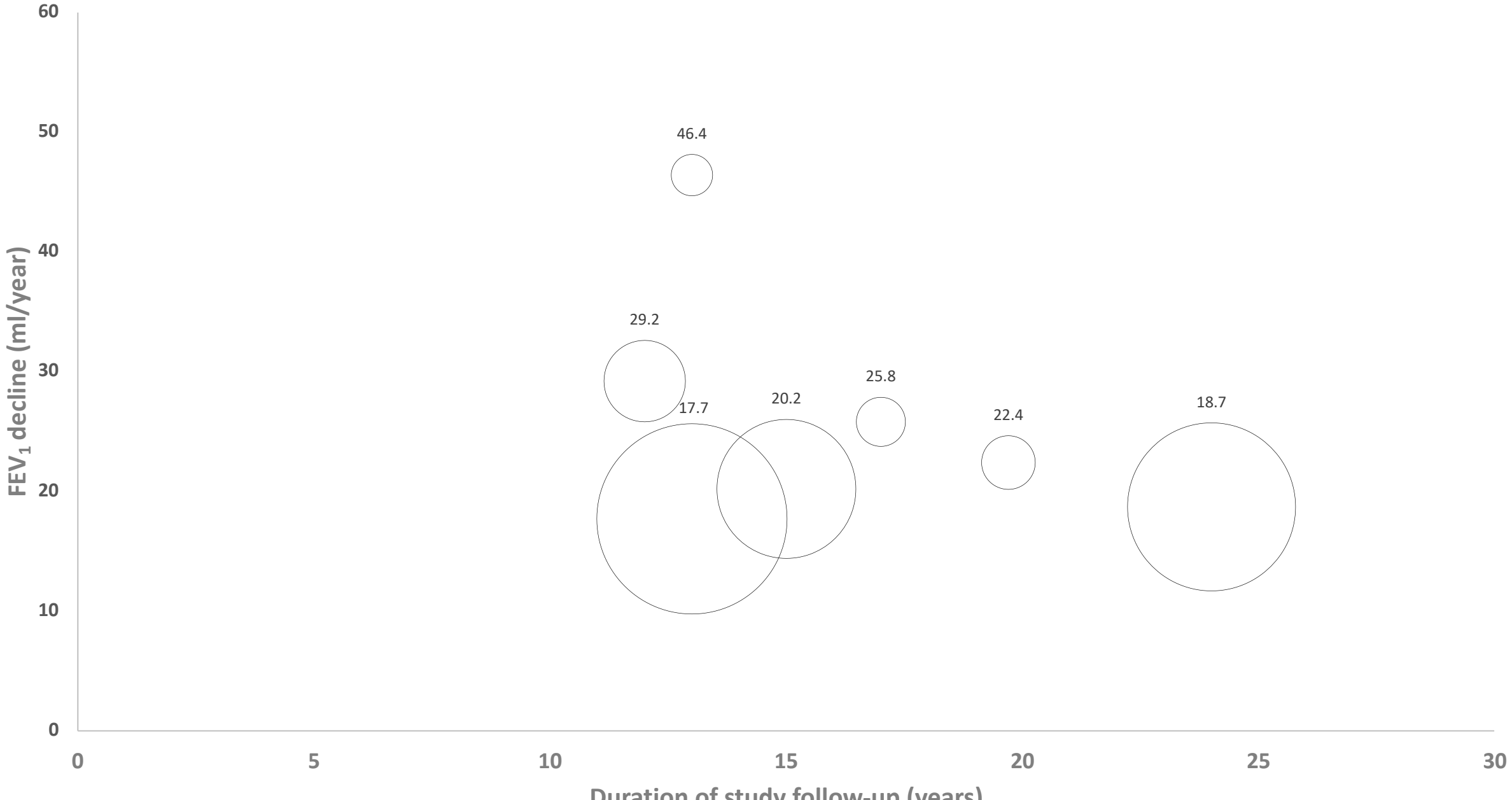
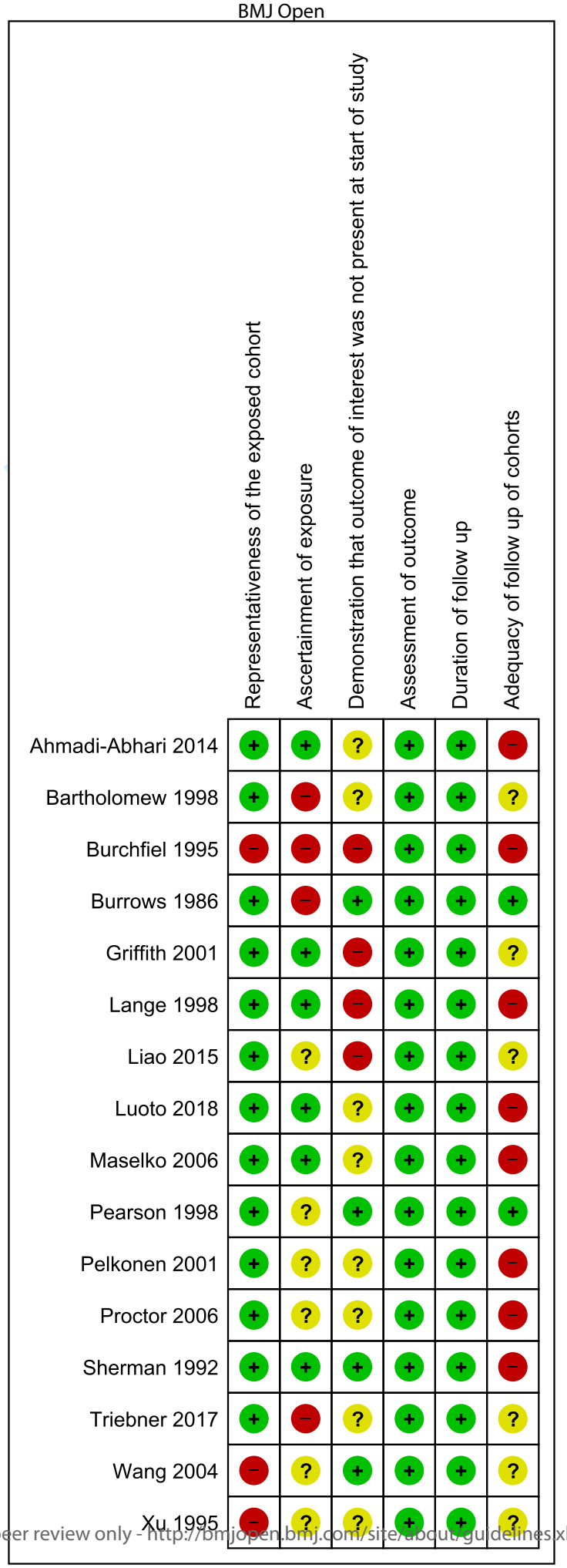

60
50
40
30
20
10
0
FEV1 decline (ml/year)
46.4
29.2
17.7
20.2
25.8
22.4
18.7
0
5
10
15
20
25
30
Duration of study follow-up (years)



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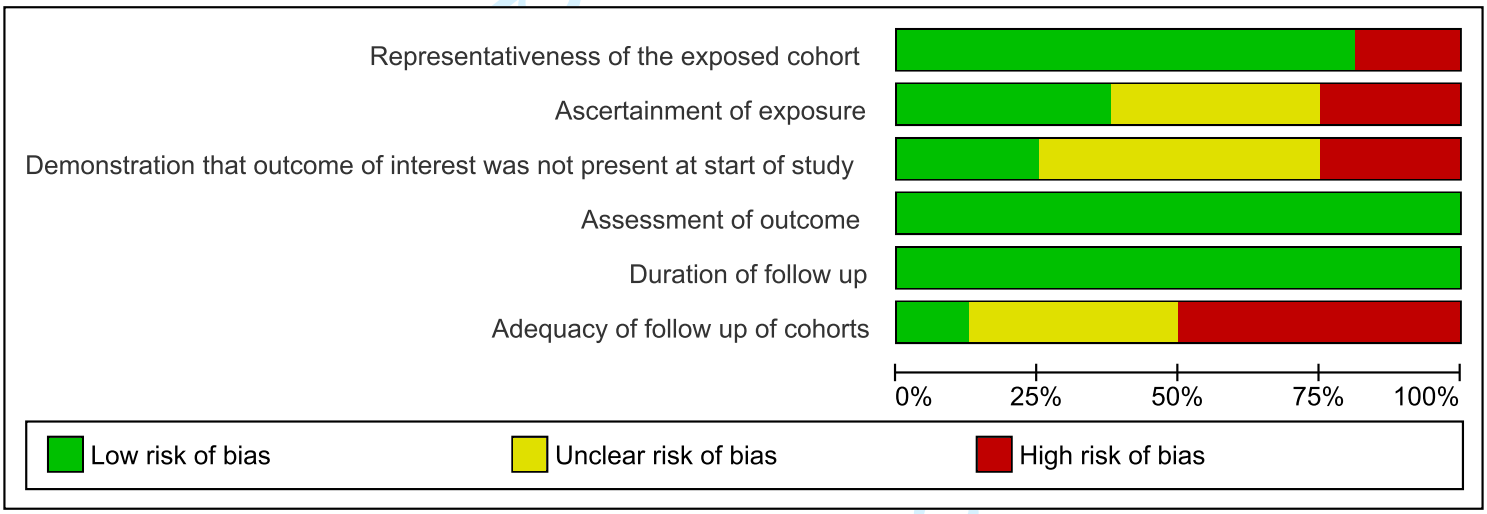

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Supplementary File 1. The rate of normal organ function decline with advancing age: protocol for a systematic review.

Authors

Elizabeth T Thomas[1]
Michelle Guppy[2,3]
Sharon Straus[4]
Katy Bell[2,5]
Paul Glasziou[2]

Author affiliations

1. Faculty of Health Sciences and Medicine, Bond University, Robina QLD 4226, Australia
2. Centre for Research in Evidence-based Practice, Bond University, Robina QLD 4226, Australia
3. School of Rural Medicine, University of New England, Armidale NSW 2351, Australia
4. Department of Medicine, University of Toronto, Toronto, Ontario, Canada
5. Sydney School of Public Health, Sydney Medical School, Edward Ford Building (A27), University of Sydney, Sydney, Australia

Corresponding Author: Elizabeth T Thomas. Email: elizabeth.thomas@student.bond.edu.au

Key Words

Normal ageing, organ function, age-related decline

ABSTRACT

Background The unprecedented rise in life expectancy in the last few decades has led to an increasing proportion of elderly people. Elderly individuals present a particularly complex challenge to health care due to their multiple comorbidities, frailty as well as their functional decline. In order to better understand and guide the care of geriatric patients, it is necessary to understand the natural rate of decline of various organ functions, so as not to inappropriately label them as having disease. This protocol is for a systematic review, which aims to calculate the rate of annual decline of lung, liver and pancreatic function as well as bone mineral density.

Methods An electronic literature search will be conducted in MEDLINE, EMBASE AND CINAHL from inception. Reference lists of included studies will also be searched for relevant prospective cohort studies and randomized controlled trials, which meet the pre-specified inclusion and exclusion criteria. The article selection and risk of bias of included studies will be determined independently by two reviewers. If possible, a meta-analysis will be conducted to pool estimates on the overall rate as well as the decade-specific rates of decline of the specified organ functions in a healthy aging cohort, and compare these estimates with cohorts that are exposed to risk factors.

Discussion This review aims to determine the rate of decline of organ function with age, and determine any predictors of decline. The results from this review will enable clinicians to better differentiate

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between physiological age-related decline and pathological decline when interpreting laboratory test results. This will prevent the overdiagnosis of elderly people with diseases that in fact represent normal ageing.

Systematic review registration PROSPERO CRD42018087066

BACKGROUND

Description of the condition

Advances in modern medicine have resulted in unprecedented rise in life expectancy. The average person's life expectancy has risen by 5 years in the last fifteen years alone, the fastest rate of growth since the 1960s[1]. This has led to a rise in the number and proportion of persons aged 65 years and older with multiple chronic conditions and frailty, posing a complex social and economic challenge to healthcare systems.

Ageing is accompanied by physiological changes in the function of most (if not all) organs and senses. The physiological functions of some organs, including the lungs and kidneys, have been documented to reach a peak in early adulthood and then decline thereafter with age[2]. The rates of age-related functional decline are dependent on a number of factors, including genetics and environmental factors[3,4].

Measured lung function parameters decrease with age, due to factors such as loss of elasticity, weakened muscles of respiration and decreased surface area for alveolar gas exchange[6]. Several longitudinal studies have been performed to monitor and calculate the rate of FEV_1 (Forced expiratory volume in 1 second) decline, and highlight those who are at risk of developing disease[3,7,8].

The liver also demonstrates measurable changes with age, with liver weight reported to decrease by as much as 20% after the age of 50 years[2]. Although some studies show that liver function tests do not change with age[2,9,10], it is also established that albumin,- which is a marker of synthetic liver function, decreases with age (though this may in part, be due to other factors such as malnutrition or renal losses[11]). It has also been shown that the liver metabolises drugs slower in aged cohorts compared to younger cohorts[2,12,13].

With advancing age, there is a progressive loss in number and function of insulin-producing beta-cells in the pancreas. This, coupled with increasing systemic insulin resistance in glucose receptors can result in the development of diabetes mellitus in the elderly[14]. Few studies have demonstrated this by monitoring healthy individuals for the development of impaired glucose tolerance or fasting glucose[15].

Bone mineral density measurements also exhibits change with age, resulting in an increased risk of developing osteoporosis, which predisposes older people to minimal trauma fractures. Females have an accelerated decline of bone mass after the onset of menopause, due to declining oestrogen levels. Other factors, such as vitamin D, calcium levels, parathyroid gland function, renal function and gastrointestinal absorption also play a role in maintaining bone mass and skeletal function[16].

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Normal ageing may result in changes in laboratory test values and biomarkers, but these changes do not necessarily represent clinical impairment.[5] Even if laboratory tests show values that lie outside the reference ranges, organs have functional reserves that cannot easily be measured by standard laboratory testing. Laboratory test results should not be used as the sole basis for which a diagnosis of disease is made; rather, these values should be integrated with the patient's clinical symptoms in order to make a diagnosis.[5] A measured decrease in organ function also may not represent clinically significant decline, instead demonstrating the normal process of ageing. One explanation for this may be that the demands of the elderly cohorts' activities of daily living are no longer the same as their younger counterparts.

Why it is important to do this review

Elderly people have increasingly been labelled with conditions such as prediabetes, chronic airways disease, osteopenia or liver disease as a result of laboratory testing. Although these conditions may represent a risk of progression to serious disease, which causes premature death, in many cases they may never progress to symptomatic disease and may even represent an expected level of function at that age.

A commonly-reported example is in chronic kidney disease, which is arbitrarily diagnosed by an eGFR (estimated glomerular filtration rate) threshold less than 60ml/min/1.73^2 for more than 3 months. There are no adjustments to this eGFR threshold for age, race or gender. Over 45% of the population over the age of 70 years have a diagnosis of chronic kidney disease according to this threshold[17,18]. Many of these individuals, however, never develop kidney failure or end stage renal disease, and have been inappropriately labeled (overdiagnosed) as having disease[19].

It is important to distinguish pathological aging from physiological decline. Some measures of organ function (such as eGFR) are not calibrated by age or gender, causing overdiagnosis of healthy individuals with disease, which may never manifest or cause harm, and subsequent overtreatment. It is therefore important to clarify what constitutes normal for healthy, aging individuals. To our knowledge, no systematic review has been done to identify and compare the rates of functional decline across organs, and whether there are risk factors/predictors that are in common.

OBJECTIVE

This review aims to determine the average rate of decline of lung function, liver function, pancreatic endocrine function and bone mineral density in healthy individuals with advancing age.

METHODS

Eligibility criteria

Types of studies

This review will consider prospective cohort studies or randomised controlled trials, which employ longitudinal designs (only if they include a control arm that does not receive treatment) with a minimum

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duration of three years and three separate measurements. Studies that report the age-related decline of the specified organ functions will be eligible for inclusion, irrespective of publication status and language of publication.

Types of participants

Studies will be considered eligible for inclusion if they follow a cohort of adults to the age of 65 years or more. Participants who have a known risk factor, medical illness or pre-disease specific to the outcome being studied (i.e. participants with diabetes when investigating pancreatic function decline) will be excluded. Appropriate participants will be included irrespective of sex or ethnicity. Studies including pregnant women or children will be excluded.

Type of exposure

We will include studies involving ageing adults with no known comorbidities. Studies will be eligible for inclusion if they follow a normal cohort. Studies that only followed cohorts with risk factors or known exposures and did not compare them to a normal cohort will be excluded. We plan to assess whether there are certain predictors of decline that organs have in common. Examples of risk factors may include:

- Smoking
- Symptomatic hypertension
- High BMI
- Hyperlipidemia
- Diabetes mellitus
- Alcohol consumption

Types of outcome measures

We will include studies which report annual decline, or repeated measurements of organ function over time, to at least the age of 65 years. Studies should record a minimum of three measurements of organ function. Examples of these parameters include:

- Forced expiratory volume in 1 second (FEV_1) for lung function
- Albumin as a marker of synthetic liver function
- Fasting blood sugar levels for pancreatic endocrine function
- Bone mineral density

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

Electronic searches

We conducted electronic searches of MEDLINE, EMBASE and CINAHL databases from inception through to October 2017, using the search strategy at the end of this document. This was developed with the assistance of an information specialist.

Searching other resources

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Electronic searches were complemented by manual searching through reference lists of studies that were identified for potential inclusion as well as backwards and forward searching.

DATA COLLECTION AND ANALYSIS

Selection of studies

Two authors will independently screen titles and abstracts of all studies identified by the searches for potential inclusion. Prior to commencing screening, a small subset of 50 titles will be screened by the two reviewers as a calibration exercise to check for >80% agreement. After screening, a calibration exercise will be conducted screening the full texts of the studies targeting >80% agreement. The remaining full texts will then be retrieved and reviewed independently by the authors to determine eligibility for inclusion. Disagreements will be resolved by discussion or with another reviewer. If there are multiple reports of the same study, the most recent publication with longest length of follow up will be included.

Data extraction and management

Two authors will independently extract data from the studies using a data extraction form. This form will be piloted using ten studies prior to data extraction as a calibration exercise to check for adequate agreement (>80%) between the reviewers. Data extraction will be performed using Excel and any disagreements will be resolved by discussion or by another reviewer. Extracted measures will include setting and year of the study, duration of the study, population size, ethnicity, baseline age, baseline organ function, organ function measurements, number and frequency of measurements, any known risk factors or exposures, proportion of those exposed, average length of follow up and loss to follow up. A random sample of the extraction will also be cross-checked by a third reviewer. All the measured outcomes (functional parameters) will initially be charted to show how often they are used in studies. A group of geriatricians and primary care physicians will be recruited from Bond University and Gold Coast Hospital and Health Service. Using the modified Delphi approach, these clinicians will be asked to independently rank the organ function parameters that they deem to be the most clinically relevant marker of organ function. The survey will be performed online. The highest ranked outcomes will then be included in the data analysis.

Assessment of risk of bias in included studies

Two authors will independently appraise the quality of the included studies, using the Newcastle Ottawa Scale (NOS) for assessing risk of bias in cohort studies. Disagreements will be resolved by discussion or a third reviewer. Factors that will be assessed include:

- Representativeness of the exposed cohort
- Selection of the non-exposed cohort
- Ascertainment of exposure
- Demonstration that the outcome of interest was not present at start of study
- Comparability of cohorts on the basis of design or analysis
- Assessment of outcome
- Adequate duration of follow up

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- Adequate follow up of cohorts
- Other important biases

Risk of bias for randomised controlled trials will be assessed using the Cochrane Risk of Bias tool which assesses the following domains:

- Random sequence generation
- Allocation concealment
- Blinding of participants and personnel
- Blinding of outcome assessors
- Incomplete outcome data
- Selective reporting
- Other biases

Measures of treatment effect

The data will first be extracted and analysed descriptively using graphs, to determine whether it is appropriate to pool the data. If deemed appropriate, RevMan will be used to pool the data. For continuous outcomes the mean difference (MD) (or standardized mean difference if studies use different measuring scales) and corresponding 95% confidence interval (95% CI) will be calculated. The data will be extracted and reported as an annual percentage decline. The overall rates of decline and corresponding confidence intervals will be presented visually in a forest plot. If the data allow, we will also extract and stratify decade-specific decline rates. If this is not possible, then a descriptive synthesis will be presented.

Subgroup analysis

We plan to re-analyse the data by organ function parameter if more than one marker is deemed appropriate as a useful measure of a certain organ's function (e.g. location of bone mineral density measurement). We will compare decline rates of different ethnicities and sex. As well as this we will separately analyse the data of those develop disease during the course of the study and those who had known risk factors. We will also look for birth cohort effects if the data allow (i.e. cohorts who have suffered deprivation early in life may show more functional decline later in life).

Dealing with missing data

If data were missing from studies published within the last 5 years, we plan to contact authors via email to obtain the individual data set.

Assessment of heterogeneity

Statistical heterogeneity may be assessed by calculating the chi squared score, as well as the I^2 statistic. Studies will be judged to have significant heterogeneity if the P value for the chi squared test was <0.1. If using mixed models, we will report random effects as the measure of heterogeneity. The degree of heterogeneity will be determined by the I^2 as follows (as specified in the Cochrane handbook):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;

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- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If there is considerable heterogeneity within the studies for the outcome, reasons for heterogeneity will be explored and results will not be pooled.

Assessment of reporting biases

If available, outcomes reported in the protocol of the studies will be judged against the final publication to assess for any reporting bias. If there are any discrepancies, these will be reported. If study protocols are not available, the outcomes listed in the methodology of the study will compared to the final reported outcomes in the results. Authors will be contacted if there are any missing data or outcomes.

Data synthesis

Where data are sufficiently similar and are thought to be clinically relevant by a group of geriatricians and primary care physicians, we will pool the study estimates of organ function. A random effects model will be used in the meta-analysis to allow for between study differences.

Sensitivity analysis

Sensitivity analyses will be conducted to check whether heterogeneity in the overall outcomes can be explained by either of the following:

- the presence of low quality studies with high risk of bias (assessed as having one or more domains with a high risk of bias according to the NOS).
- duration of the study or time-points of measurement

DISCUSSION

This review aims to provide an estimate of annual organ function decline across various organs that is part of normal aging in people without symptomatic disease. This will enable clinicians to distinguish age-appropriate laboratory test results from values which represent increased risk of disease. It is more reasonable to assess the health of individuals with reference to others in their age cohorts, not in comparison to healthy young individuals. Determining these 'normal' changes with aging will also avoid the psychological consequences of disease-labelling and side effects of unnecessary drug treatment. Researchers will be able to use this data to plan more longitudinal studies in different cohorts and investigate additional factors that affect changes in organ function. Further research will also be required to determine whether it is possible to regain function and if so, up until what point this is possible once a risk factor is removed.

ABBREVIATIONS

FEV_1 – Forced expiratory volume in 1 second
eGFR - estimated glomerular filtration rate
NOS- Newcastle Ottawa Scale

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DECLARATIONS

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIAL

Not applicable

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING

PG has received funding from the Australian National Health and Medical Research Council (Australia Fellowship No. 527500 and Program Grant No 633003). The funders had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

AUTHORS' CONTRIBUTIONS

ETT, SS and PG were involved in the conception and design of the review. ETT developed the search strategy. ETT drafted the manuscript, and MG, SS, KB and PG contributed to the drafting of the review protocol. All authors approved the final version of the article.

ACKNOWLEDGEMENTS

The authors would like to thank Justin Clark for his assistance with the literature search, as well as Richard Stevens and Ben Feakins for their advice on statistical analysis.

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PUBMED SEARCH STRATEGY

1. ("forced expiratory volume"[tiab] OR FEV[tiab] OR "forced vital capacity"[tiab] OR FVC[tiab] OR spirometry[Mesh] OR spirometry[tiab] OR "lung function"[tiab] OR "pulmonary function"[tiab] OR "Expiratory Flow"[tiab])
   AND
2. ("Aging/ethnology"[Mesh] OR "Aging/physiology"[Mesh] OR “Age-related”[tiab] OR “Age related”[tiab] OR Function[tiab] OR Healthy[tiab])
   AND
3. (Decline[tiab] OR Declines[tiab] OR Declined[tiab] OR Decrease[tiab] OR Decreased[tiab])
   AND
4. ("Middle Aged"[Mesh] OR "Aged"[Mesh] OR Aged[tiab] OR Elderly[tiab] OR Old[tiab] OR Older[tiab])
   AND
5. ("Longitudinal Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR Longitudinal[tiab] OR Trend[tiab] OR Trends[tiab] OR Trajectories[tiab] OR Trajectory[tiab] OR “Follow-up”[tiab] OR “Follow up”[tiab] OR “Rate of”[tiab] OR “Rates of”[tiab])
   AND
6. (Cohort[tiab] OR Observational[tiab] OR Prospective[tiab] OR Compared[tiab] OR Investigated[tiab] OR Evaluating[tiab] OR Analysis[tiab] OR Analyzed[tiab] OR Statistics[tiab] OR Data[tiab] OR Baseline[tiab])
   AND
7. (Humans[Mesh] OR Humans[tiab] OR Human[tiab] OR Population[tiab])

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REFERENCES

1. Mathers C, Stevens G, Mahanani W, Ho J, Fat D, Hogan D. WHO methods and data sources for country-level causes of death 2000-2015. Geneva: Department of Information, Evidence and Research WHO; 2017.
2. Boss G, Seegmiller J. Age-Related Physiological Changes and their Clinical Significance. West J Med 1981;135:434-40.
3. Aalami O, Fang T, Song H, Nacamuli R. Physiological Features of Aging Persons. Arch Surg 2003;138:1068-76.
4. Rodríguez-Rodero S, Fernández-Morera J, Menéndez-Torre E, Calvanese V, Fernández A, Fraga M. Aging Genetics and Aging. Aging and Disease 2011;2:186-95. .
5. Vásárhelyi B, Debreczeni L. Lab test findings in the elderly. J Int Fed Clin Chem 2017;28:328-32.
6. Navaratnarajah A, Jackson S. The physiology of ageing. Medicine 2017;45:6-10.
7. Knudson R, Lebowitz M, Holberg C, Burrows B. Changes in the normal maximal expiratory flow-volume curve with growth and aging. Am Rev Respir Dis 1983;127:725-34.
8. Zaugg M, Lucchinetti E. Respiratory Function in the Elderly. Anesthesiol Clin North America 2000;18:47-58.
9. Vestal R, McGuire E, Tobin J, al e. Aging and ethanol metabolism Clin Pharmacol Ther 1977;21:343-54.
10. Adkins R, Marshall B. Anatomic and physiologic aspects of aging.
. In: Adkins R, Scott H, eds. Surgical Care for the Elderly. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1998:xxi531.
11. Van Tongeren J, Cluysenaer O, Lamers C, De Mulder P, Yap S. Causes of hypoalbuminemia. In: Yap S, Majoor C, van Tongeren J, eds. Clinical Aspects of Albumin. Dordrecht: Springer; 1978.
12. George J, Byth K, Farrell G. Age but not gender selectively affects expression of individual cytochrome P450 proteins in human liver. . Biochem Pharmacol 1995;50:727-30.
13. Loi C, Parker B, Cusack B, Vestal R. Aging and drug interactions. III. Individual and combined effects of cimetidine and cimetidine and ciprofloxacin on theophylline metabolism in healthy male and female nonsmokers. J Pharmacol Exp Ther 1997;280:627-37.
14. McConnell J, Buchanan K, Ardill J, Stout R. Glucose tolerance in the elderly: the role of insulin and its receptor. Eur J Clin Invest 1982;12:55-61.
15. Meigs J, Muller D, Nathan D, Blake D, R A. The natural history of progression from normal glucose tolerance to type 2 diabetes in the Baltimore Longitudinal Study of Aging. Diabetes 2003;52:1475-84.
16. Pathy J, Sinclair A, Morley J, Vellas B. Pathy's Principles and Practice of Geriatric Medicine. Oxford: UK: John Wiley & Sons, Ltd; 2012.
17. Levey A, Stevens L, Coresh J. Conceptual model of CKD: applications and implications. Am J Kidney Dis 2009;53:S4-16.
18. Stevens L, Viswanathan G, Weiner D. CKD and ESRD in the Elderly: Current Prevalence, Future Projections and Clinical Significance. Adv Chronic Kidney Dis 2010;17:293-301.
19. Moynihan R, Glassock R, Doust J. Chronic kidney disease controversy: how expanding definitions are unnecessarily labelling many people as diseased. BMJ 2013;347:f4298.

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Supplementary File 2. Medline Search Strategy, performed 12th February 2019

1. ("forced expiratory volume"[tiab] OR FEV[tiab] OR "forced vital capacity"[tiab] OR FVC[tiab] OR spirometry[Mesh] OR spirometry[tiab] OR "lung function"[tiab] OR "pulmonary function"[tiab] OR "Expiratory Flow"[tiab])
   AND
2. ("Aging/ethnology"[Mesh] OR "Aging/physiology"[Mesh] OR “Age-related”[tiab] OR “Age related”[tiab] OR Function[tiab] OR Healthy[tiab])
   AND
3. (Decline[tiab] OR Declines[tiab] OR Declined[tiab] OR Decrease[tiab] OR Decreased[tiab])
   AND
4. ("Middle Aged"[Mesh] OR "Aged"[Mesh] OR Aged[tiab] OR Elderly[tiab] OR Old[tiab] OR Older[tiab])
   AND
5. ("Longitudinal Studies"[Mesh] OR "Follow-Up Studies"[Mesh] OR Longitudinal[tiab] OR Trend[tiab] OR Trends[tiab] OR Trajectories[tiab] OR Trajectory[tiab] OR “Follow-up”[tiab] OR “Follow up”[tiab] OR “Rate of”[tiab] OR “Rates of”[tiab])
   AND
6. (Cohort[tiab] OR Observational[tiab] OR Prospective[tiab] OR Compared[tiab] OR Investigated[tiab] OR Evaluating[tiab] OR Analysis[tiab] OR Analyzed[tiab] OR Statistics[tiab] OR Data[tiab] OR Baseline[tiab])
   AND
7. (Humans[Mesh] OR Humans[tiab] OR Human[tiab] OR Population[tiab])

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Supplementary File 3. Sample calculations of decline rates for each study

Ahmadi-Abhari 2014

Mean FEV1 decline of people with baseline CRP ≤ 10mg/L who are never smokers

CRP	n	Annual change (multivariable adjusted)
≤ 1	3430	-17.16
1.1 – 3	3012	-18.53
3.1 – 10	1620	=17.15

Mean FEV1 change $= \frac{(3430 \times 17.16) + (3012 \times 18.53) + (1620 \times 17.15)}{(3430 + 3012 + 1620)}$

= - 17.7 ml / year

Mean FVC decline of people with baseline CRP ≤ 10mg/L who are never smokers

CRP	n	Annual change (multivariable adjusted)
≤ 1	3430	-31.57
1.2 – 3	3012	-30.57
3.1 – 10	1620	-30.87

Mean FEV1 change $= \frac{(3430 \times 31.57) + (3012 \times 30.57) + (1620 \times 30.87)}{(3430 + 3012 + 1620)}$

= - 31.1 ml / year

To calculate the standard deviations each group from the given 95% confidence intervals the following formula was used:

$$SD = \sqrt{n} \times \frac{upper\ limit - lower\ limit}{3.92}$$

E.g. The standard deviation of FEV1 decline in the CRP ≤ 1 category was calculated as follows:

$$SD = \sqrt{3430} \times \frac{19.9 - 14.41}{3.92}$$

$$= \sqrt{3430} \times 1.4$$

= 81.99

In this way standard deviations for all of the 3 included groups were calculated for both outcomes

CRP	n	Annual FEV1 change (multivariable adjusted)	Standard deviation
≤ 1	3430	-17.16	81.99
1.3 – 3	3012	-18.53	79.36
3.1 – 10	1620	-17.15	69.23

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CRP	n	Annual FVC change (multivariable adjusted)	Standard deviation
≤ 1	3430	-31.57	122.99
1.4 – 3	3012	-30.57	119.42
3.1 – 10	1620	-30.87	104.00

The combined standard deviation was calculated using the following formula, available from the Cochrane handbook[1] (where only two groups are combined at a time).

$$Combined\ SD_{Group\ 1,2} = \sqrt{\frac{(n_1 - 1)\ {SD_1}^2 + (n_2 - 1)\ {SD_2}^2 + \frac{n_1 n_2}{n_1 + n_2}({m_1}^2 + {m_2}^2 - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}$$

$$= \sqrt{\frac{(3430 - 1)\ 81.99^2 + (3012 - 1)\ 79.36^2 + \frac{3430 \times 3012}{3430 + 3012}(-17.16^2 + -18.53^2 - 2(-17.16 \times -18.53)}{(3430 + 3012 - 1)}}$$

$$= \frac{(23050972.78 + 18963306.91 + 1603.72(637.83 - 635.95))}{6441}$$

$$= 80.77$$

Then the combined values of Group 1 and 2 are treated as one group as follows

SD_1 = 80.77, m_1 = -17.80, n_1= 6442

Group 3 will be assigned to the values of SD_2, m_2 and n_2

$$Combined\ SD_{Group\ 1,2,3} = \sqrt{\frac{(n_1 - 1)\ {SD_1}^2 + (n_2 - 1)\ {SD_2}^2 + \frac{n_1 n_2}{n_1 + n_2}({m_1}^2 + {m_2}^2 - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}$$

$$= \sqrt{\frac{(6442 - 1)\ 80.77^2 + (1620 - 1)\ 69.23^2 + \frac{6442 \times 1620}{6442 + 1620}(-17.80^2 + -17.15^2 - 2(-17.80 \times -17.15)}{(6442 + 1620 - 1)}}$$

$$= \frac{(42019750.07 + 7759531.71 + 1294.47(610.96 - 610.54))}{8061}$$

$$= 78.58$$

The same calculations were carried out for the combined standard deviations of the FVC readings across the 3 CRP groups

Bartholomew 1998

See Table 3 – Female never smokers

FEV1 6 year change from baseline (all ages) = -0.178

Mean FEV1 annual decline $= \frac{0.178}{6}$

= - 30.5ml/year

FVC 6 year change from baseline (all ages) = -0.218

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$= \frac{0.218}{6}$

= - 36.3ml/year

See Table 3 – Male never smokers

FEV1 6 year change from baseline (all ages) = -0.261

Mean FEV1 annual decline $= \frac{-0.261}{6}$

= -43.5ml/year

FVC 6 year change from baseline (all ages) = -0.283

$= \frac{-0.283}{6}$

= 47.2ml/year

Burchfiel 1995

Annual FEV1 decline (ml/year) extracted from Table 2

Male never smokers change from Exam 1-3 = -21.6ml/year

Burrows 1986

Values of FEV1 decline extracted from Figure 3 for both males and females, where in males, height was assumed to be 1.75m and females 1.6m.

Using the formulae provided by the authors to predict ΔFEV1:

Males: $\Delta FEV1 = 21.82 – 0.109Age \times Height^3$

Females: $\Delta FEV1 = 19.79 – 0.205Age \times Height^2$

The relevant values were then derived from the graph and then input into the formulae to produce the following values.

Male

Age	Height (cubed = 5.36)	FEV1 change
25	1.75	7.216*
30	1.75	4.295*
35	1.75	1.374*
40	1.75	-1.547
45	1.75	-4.468
50	1.75	-7.389
55	1.75	-10.309
60	1.75	-13.23
65	1.75	-16.151
70	1.75	-19.072

Mean decline rate: -10.309ml/yr (SD 6.31), where the *figures were not used in the overall decline calculation.

Female

Age	Height (cubed = 5.36)	FEV1 change
25	1.6	6.67*
30	1.6	4.046*

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35	1.6	1.422*
40	1.6	-1.202
45	1.6	-3.826
50	1.6	-6.45
55	1.6	-9.074
60	1.6	-11.698
65	1.6	-14.322
70	1.6	-16.946

Mean decline rate: -9.074 ml/yr (SD 5.668), where the *figures were not used in the overall decline calculation.

Griffith 2001

Rates extracted from Table 4 (random effects model) for FEV1

Females

Mean -0.047L/year (SE 0.0028)

Males

Mean = -0.047 + (-0.0053)

= -0.0523L/year

SE $= \sqrt{(0.0028)^2 + (0.0013)^2}$

= 0.0031

Table 5 for FVC

Females

Mean -0.0656L/year (SE 0.0038)

Males

Mean = -0.0656 + (-0.0128)

= -0.0784L/year

SE $= \sqrt{(0.0038)^2 + (0.0019)^2}$

= 0.0042

Lange 1998

Combined mean (m) of all groups: $= \frac{(m_1 \times n_1) + (m_2 \times n_2) + (m_3 \times n_3)}{n_1 + n_2 + n_3}$

Using values from Table 3 for non-asthmatic non-smoking women and men. The means, no. of subjects and standard deviations were combined for the 20-39 age group, 40-59 group and 60-79 group.

Females

Combined mean $= \frac{(433 \times 5.0) + (1471 \times (-17.7)) + (809 \times (-31.7))}{2713}$

= -18.25ml/year

Group 1 and 2 combined standard deviation

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Combined $SD_{Group1,2}$ $= \sqrt{\frac{(n_1-1)\,SD_1{}^2 + (n_2-1)\,SD_2{}^2 + \frac{n_1 n_2}{n_1+n_2}(m_1{}^2 + m_2{}^2 - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}$

$= \sqrt{\frac{(433-1)\,2.7^2 + (1471-1)\,1.4^2 + \frac{433\times 1471}{433+1471}(5^2 + (-17.7)^2 - 2(5\times -17.7)}{(433+1471-1)}}$

$= \sqrt{\frac{(432)\,2.7^2 + (1470)\,1.4^2 + \frac{636943}{1904}(5^2 + 313.29 - 2(-88.5))}{1903}}$

$= \sqrt{\frac{3149.28 + 2881.2 + 334.529(338.29 - 177)}{1903}}$

$= \sqrt{\frac{6030.48 + 334.529(338.29 - 177)}{1903}}$

$= \sqrt{\frac{6030.48 + 53956.18}{1903}}$

$= \sqrt{\frac{59986.66}{1903}}$

= 5.6144 (combined SD of Group 1,2)

Group 1 and 2 n_1 1904 *m_1-12.538* *SD 5.6144*

Group 3 *n_2 809* *m_2 -31.7* *SD 2.1*

Combined $SD_{Group1,2 \text{ and } 3}$ $= \sqrt{\frac{(n_1-1)\,SD_1{}^2 + (n_2-1)\,SD_2{}^2 + \frac{n_1 n_2}{n_1+n_2}(m_1{}^2 + m_2{}^2 - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}$

$= \sqrt{\frac{(1904-1)\,5.614^2 + (809-1)\,2.1^2 + \frac{1904\times 809}{1904+809}((-12.538)^2 + (-31.7)^2 - 2(397.45))}{(1904+809-1)}}$

$= \sqrt{\frac{(59976.84) + (3563.28) + 567.76(367.19)}{2712}}$

$= \sqrt{\frac{63540.12 + 208475.79}{2712}}$

Combined SD females = 10.015

Males

Combined mean $= \frac{(357\times(-4.6) + (780\times(-24.2)) + (455\times(-37.1))}{1592}$

= -23.49ml/year

Combined $SD_{Group1,2}$ $= \sqrt{\frac{(n_1-1)\,SD_1{}^2 + (n_2-1)\,SD_2{}^2 + \frac{n_1 n_2}{n_1+n_2}(m_1{}^2 + m_2{}^2 - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}$

$= \sqrt{\frac{(357-1)\,4.2^2 + (780-1)\,2.6^2 + \frac{357\times 780}{357+780}((-4.6)^2 + (-24.2)^2 - 2(-4.6\times -24.2)}{(357+780-1)}}$

$= \sqrt{\frac{(356)\,4.2^2 + (779)\,2.6^2 + 244.91(21.16 + 585.64 - 2(111.32))}{(1136)}}$

$= \sqrt{\frac{6279.84 + 5266.04 + 244.91(384.16)}{1136}}$

$= \sqrt{\frac{105630.51}{1136}}$

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= 9.643 (combined SD of Group 1,2)

Group 1 and 2 n_1 1137 m_1-18.046 *SD 9.643*

Group 3 n_2 *455* m_2 *-31.7* *SD 3.7*

Combined $SD_{Group1,2,3}$ $= \sqrt{\frac{(n_1 - 1)\,SD_1{}^2 + (n_2 - 1)\,SD_2{}^2 + \frac{n_1 n_2}{n_1 + n_2}(m_1{}^2 + m_2{}^2 - 2(m_1 m_2)}{(n_1 + n_2 - 1)}}$

$= \sqrt{\frac{(1137 - 1)\,9.643^2 + (455 - 1)\,3.7^2 + \frac{1137 \times 455}{1137 + 445}((-18.046)^2 + (-31.7)^2 - 2(572.06))}{(1137 + 455 - 1)}}$

$= \sqrt{\frac{(105633.74) + (6215.26) + 324.96(186.43))}{1591}}$

$= \sqrt{\frac{111849 + 60582.29}{1591}}$

Combined SD males = 10.41

Liao 2015

FEV1 and FEV1/FVC decline were extracted from Table III (Linear Mixed Model)

Time dependent estimates (SE)

Years after baseline

FEV1 = 25.8 (0.6)

FEV1/FVC = -0.0029 (0.0001)

Luoto 2018

Value for absolute FEV_1 decline for never smokers was extracted from Table 3 (Basic model adjusted for age, sex and smoking status)

FEV_1 absolute decline = -46.4

SD calculated from 95% CI using formula:

$$SD = \sqrt{n} \times \frac{upper\ limit - lower\ limit}{3.92}$$

$$SD = \sqrt{387} \times \frac{\text{-41.7} - \text{-51.2}}{3.92}$$

SD = 47.7

Relative FEV_1 decline was extracted from Table 4 (basic model, non-smoker) = -2.23%/year

SD was calculated using the 95% CI as done for absolute decline values

$$SD = \sqrt{387} \times \frac{\text{-2.00} - \text{-2.46}}{3.92}$$

SD = 2.3

Value for absolute FVC decline for never smokers was extracted from Table 5 (Basic model adjusted for age, sex and smoking status)

FVC absolute decline = -43.7

SD calculated from 95% CI using formula:

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$$SD = \sqrt{n} \times \frac{upper\ limit - lower\ limit}{3.92}$$

$$SD = \sqrt{387} \times \frac{\text{-}37.0 - \text{-}50.4}{3.92}$$

SD = 67.2

Relative FVC decline was extracted from Table 6 (basic model, non-smoker) = -1.68%/year

SD was calculated using the 95% CI as done for absolute decline values

$$SD = \sqrt{387} \times \frac{\text{-}1.46 - \text{-}1.93}{3.92}$$

SD = 2.4

Maselko 2006

PEFR decline extracted from Table 3 (never smokers)

Yearly decline

Men

Time (L/min/year) -8.61 (SE 2.3) P<0.01

Women

Time (L/min/year) -8.58 (SE 1.8) P<0.01

Pearson 1998

Figures of FEV1 decline extracted from Table 1 using the following calculation:

$$Yearly\ decline = \frac{FEV_{last\ visit} - FEV_{first\ visit}}{mean\ follow\ up\ time\ (years)}$$

Men

Yearly decline $= \frac{3.8L - 4.3L}{11.5\ years}$

= 0.0435L/year

Women

Yearly decline $= \frac{2.6L - 2.8L}{5.7\ years}$

= 0.0351L/year

Pelkonen 2001

Figures of 15 year FEV1 decline extracted from Table 1 (Never smokers n=200) = -46.4ml/year (p<0.001)

Figures of 30 year FEV1 decline extracted from Table 1 (Never smokers n=100) = -34.8/year (p<0.001)

Proctor 2006

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PEFR decline calculated from Table 1 using the follow calculation, where EFR is expiratory flow rate.

$$Yearly\ decline\ = \frac{EFR_{Year\ 8} - \ EFR_{Year\ 0}}{8\ years}$$

Men

$$Yearly\ decline\ = \frac{298.36 - \ 390.34}{8\ years}$$

= -11.50L/min/year

Women

$$Yearly\ decline\ = \frac{224.62 - 277.20}{8\ years}$$

= -6.57L/min/year

Sherman 1992

FEV1 Slopes extracted from Table 5, specifically never-smokers who experienced no symptoms (mean [SD] ml/year).

Men 32.8 (29.5) ml/year

Women 27.5 (20.4) ml/year

Triebner 2017

Exact figures of FEV1 and FVC decline for both men and women (never smokers) were obtained by contacting the author.

Graphically represented in Figure 4.

Women

FEV1 decline -22.4ml/year (SD 36.4)

FVC decline -14.1ml/year (SD 42.8)

Wang 2004

5-year FEV1 slope extracted from Table 1, looking at healthy males.

Mean -56ml/year (SD 45)

Xu 1995

Estimates of height-adjusted FEV1 for different ages in both male and females and for different birth cohorts were obtained from the graph in Figure 2.

Time related FEV1 changes were calculated as follows:

Birth after 1946

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Men = $\frac{3800ml - 4100ml}{40 - 25} = \frac{-300ml}{40 - 25}$ = -20ml/year

Women = = $\frac{2800ml - 3000ml}{40 - 25} = \frac{-200ml}{40 - 25}$ = -13.3ml/year

Cohort 1935 – 1946

Men = $\frac{3400ml - 4100ml}{50 - 25} = \frac{-600ml}{25}$ = -24ml/year

Women = $\frac{2500ml - 2930ml}{50 - 25} = \frac{-430ml}{25}$ = -17.2ml/year

Cohort 1923 – 1934

Men = $\frac{2780ml - 3640ml}{65 - 35} = \frac{-860ml}{30}$ = -28.7ml/year

Women = $\frac{2050ml - 2700ml}{65 - 35} = \frac{-650ml}{30}$ = -21.7ml/year

Cohort before 1923

Men = $\frac{2700ml - 3300ml}{65 - 45} = \frac{-600ml}{20}$ = -30ml/year

Women = $\frac{1970ml - 2450ml}{65 - 45} = \frac{-480ml}{20}$ = -24ml/year

Reference

1. The Cochrane Collaboration; 2011 [updated March 2011. Available from: https://handbook-5-1.cochrane.org/chapter_7/table_7_7_a_formulae_for_combining_groups.htm accessed August 3rd 2018.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2,3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4,5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5, Supplementary File 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5,6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary File 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6,7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7,8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8,9

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8,9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7,8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	19, Figure 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	9-19, Table 2,3, Figure 2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	19, Figure 5
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16-19, Figure 2, 3B
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20-23

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PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-25
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25,26

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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