

BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email info.bmjopen@bmj.com

BMJ Open

Risk of all-cause mortality associated with chronic obstructive pulmonary disease and the role of healthy ageing trajectories: A population-based study of middle-aged and older adults.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050947
Article Type:	Original research
Date Submitted by the Author:	08-Mar-2021
Complete List of Authors:	Bayes-Marin, Ivet; Parc Sanitari Sant Joan de Déu, Research, Innovation and Teaching Unit; Universitat de Barcelona Facultat de Medicina Sanchez-Niubo, Albert ; Parc Sanitari Sant Joan de Deu, ; Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) Fernández, Daniel; Polytechnic University of Catalonia, Serra Hünter fellow, Department of Statistics and Operations Research Haro, Josep; Parc Sanitari Sant Joan de Deu, Research, Innovation and Teaching Unit; Centro de Investigación Biomédica en Red de Salud Mental Olaya, Beatriz; Parc Sanitari Sant Joan de Deu, Research, Innovation and Teaching Unit; Centro de Investigación Biomédica en Red de Salud Mental
Keywords:	Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Risk of all-cause mortality associated with chronic obstructive pulmonary disease and the role**
4 **of healthy ageing trajectories: A population-based study of middle-aged and older adults.**
5
6
7
8
9

10 Ivet Bayes-Marin ^{a,b,c}, Albert Sanchez-Niubo ^{a,b}, Daniel Fernández^d, Josep Maria Haro ^{a,b,c}, and
11 Beatriz Olaya ^{a,b}
12
13

14
15 ^aResearch, Innovation and Teaching Unit, Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat,
16 08830 Barcelona, Spain.
17

18
19 ^bCentro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud
20 Carlos III, Madrid 28029, Spain.
21

22
23 ^cDepartment of Medicine, Universitat de Barcelona, Barcelona 08036, Spain.
24

25
26 ^dSerra Húnter fellow, Department of Statistics and Operations Research, Polytechnic University
27 of Catalonia-BarcelonaTech, 08028 Barcelona, Spain.
28
29

30
31
32
33 ***Corresponding author:**

34 Albert Sanchez- Niubo. Research, Innovation and Teaching Unit, Parc Sanitari Sant Joan de Déu,
35 Dr Antoni Pujadas 42, Sant Boi de Llobregat, Barcelona 08830, Spain. E-mail:
36 albert.sanchez@pssjd.org
37
38
39
40
41
42
43

44 **Word count:** 5840
45
46
47

48 **Abstract**

49
50 **Introduction:** Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and
51 mortality worldwide. With a worsening of the disease, there can be an increase of functional
52 ability limitations, limiting exercise performance and self-care. The study of the mortality risk in
53 COPD and its association with health and functioning would allow identifying those vulnerable
54 sectors of the population and the creation of preventive measures and interventions. The aims
55
56
57
58
59
60

1
2
3 were to study the risk of all-cause mortality associated with COPD and healthy ageing
4 trajectories (HAT) in three birth cohorts and to determine the moderating role of HAT in the
5 association between COPD and all-cause mortality. **Methods:** The total sample was 28,857
6 people aged 50+ years from waves 1 to 5 of The Survey of Health, Ageing and Retirement in
7 Europe (SHARE). Analyses were conducted separately in three birth cohorts (>1945, 1936-1945,
8 and ≤ 1935). Latent class growth analysis was used to classify participants into HAT based on
9 their score on the healthy ageing scale. We performed Aalen additive hazards models to explore
10 the associations between COPD, HAT, and mortality. Interactions between COPD and HAT were
11 also explored. **Results:** Three parallel HAT were found in the three birth cohorts ("low",
12 "medium", and "high" healthy ageing). Participants with COPD had an increased mortality risk,
13 but this effect was no longer significant after adjusting for covariates. The "low" HAT was
14 associated with increased mortality risk in the three sub-samples, although this effect was lower
15 after adjustment. The interaction between COPD and HAT was significant only in the ≤ 1935 birth
16 cohort, indicating that those with COPD and a "low" trajectory had a greater risk of mortality.
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Conclusion: The healthy ageing scale may be a suitable tool to identify patients at higher risk in order to mitigate disease burden and improve patient's quality of life.

Keywords: chronic obstructive pulmonary disease (COPD), mortality, healthy ageing, Europe, population-based study

Strengths and limitations of this study

- The analyses were performed in different birth cohorts (>1945, 1936-1945, and ≤ 1935) to assess if there were differences in mortality risks that could be related to societal changes, such as trends in lifestyle behaviors and occupation.
- We used a novel measurement scale of healthy ageing including several variables related to intrinsic capacity and functional ability.

- The calculation of Aalen additive hazards models rather than Cox models allowed the inclusion of time-variant variables in the analyses.
- Due to the high percentage of missings in the age of the diseases diagnosis, we selected the age of the earliest diagnosis of each disease within the five waves.
- For the survival analysis we used the age of the participants instead of the years of the interview, for better interpretation. However, this introduces a problem of left truncation since the age range observed for each participant is different, although we took this into account in the additive regression model.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide[1,2]. COPD is expected to become the third leading cause of death by 2030[3]. The growing burden of COPD is a consequence of the population ageing and the continued use of tobacco, which is considered its main risk factor[4]. Moreover, air pollution has been associated with acute exacerbations of COPD, increased respiratory morbidity and mortality[5].

COPD is characterized by a progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases[6]. With a worsening of the disease, there can be an increase of functional ability limitations in the activities of daily living (ADL), and in the instrumental activities of daily living (IADL), limiting exercise performance and self-care[7–9]. COPD has increasingly been recognized as a multi-component disease, associated with a wide range of physical diseases and psychological disorders[10]. Non-communicable diseases (NCDs) such as hypertension, cardiovascular diseases, diabetes, cancer, and depression commonly co-exist in COPD patients, worsening its progression[1,2,11]. Furthermore, cognitive impairment is common among COPD patients, suggesting that impaired performance in neuropsychological tests might be a predictor of early mortality for people diagnosed with COPD[10].

1
2
3 Despite being a growing public health concern, there is a lack of epidemiological data about the
4 prevalence and distribution of COPD[6,12]. The paucity of information on COPD prevalence and
5 incidence is partly due to differences in the methods used for its diagnosis and classification,
6 often being underestimated[6]. These differences in the assessment methods and definitions
7 have also hampered the comparison of COPD prevalence and impact across countries. Both The
8 Burden of Lung Disease (BOLD) project[4] and the Latin American Project for the Investigation
9 of Obstructive Lung Disease (PLATINO)[13] were developed to map the COPD prevalence using
10 the same methodology in different countries. Those studies were performed in China and
11 Turkey, and five Latin American countries, respectively. Nevertheless, there is a lack of data on
12 the prevalence and distribution of COPD in Europe[2,14]. Additionally, available studies suggest
13 large differences across European countries in terms of prevalence rates of COPD and the
14 associated death rates. In a systematic review, COPD prevalence ranged from 3% in Finnish
15 women to 57% in Italian men and women[15]. Some differences have also been found in COPD-
16 related mortality across European countries and between men and women. Overall, regarding
17 European countries, COPD-related mortality rates appeared to decline in men in most countries
18 from 1995 to 2017, whereas mortality rates due to COPD increased in women from +2% per year
19 in Austria to +4.2% or +4.8% per year in the Czech Republic and Hungary, respectively[16].

20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42 In that sense, a longitudinal integrated dataset that considers different European countries
43 could be particularly useful in the study of the risk of mortality associated with COPD in different
44 European countries. The study of the mortality risk in COPD patients, as well as its association
45 with several variables related to health and functioning, would allow identifying those
46 vulnerable sectors of the population and the creation of preventive measures and interventions
47 in diverse healthcare systems.

48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
841
842
843
844
845
846
847
848
849
850
851
852
853
854
855
856
857
858
859
860
861
862
863
864
865
866
867
868
869
870
871
872
873
874
875
876
877
878
879
880
881
882
883
884
885
886
887
888
889
890
891
892
893
894
895
896
897
898
899
900
901
902
903
904
905
906
907
908
909
910
911
912
913
914
915
916
917
918
919
920
921
922
923
924
925
926
927
928
929
930
931
932
933
934
935
936
937
938
939
940
941
942
943
944
945
946
947
948
949
950
951
952
953
954
955
956
957
958
959
960
961
962
963
964
965
966
967
968
969
970
971
972
973
974
975
976
977
978
979
980
981
982
983
984
985
986
987
988
989
990
991
992
993
994
995
996
997
998
999
1000

Previous studies focused on the association between exercise capacity and mortality among COPD patients, which has been considered one of the best predictors of mortality[17–19].

1
2
3 Measures of exercise capacity include indicators such as body mass index, airflow obstruction,
4
5 dyspnea, handgrip strength, and the sit-to-stand test[20]. Nevertheless, these indicators of
6
7 exercise capacity are just measures of intrinsic capacity that do not capture the individual's
8
9 functional ability over the life-course. In that sense, the functional ability is the result of the
10
11 interaction of the individuals' intrinsic capacity, including physical and mental capacities; and
12
13 their environment, as access to medications, personal and assistive support, or physical
14
15 barriers[21]. Therefore, a measure assessing both intrinsic capacity and functional ability may
16
17 be a better way to capture a person's healthy aging.
18
19

20
21 Several authors advocate for using composite measures as the International Classification of
22
23 Functioning, Disability, and Health to assess COPD patients' complexity, including also functional
24
25 capacity and functional performance[22]. Related to this, the Ageing Trajectories of Health:
26
27 Longitudinal Opportunities and Synergies (ATHLOS) project[23] developed a healthy ageing
28
29 scale[21] using 16 international cohort studies to determine the intrinsic capacity and functional
30
31 ability of the participants allowing comparisons across countries. The healthy ageing scale is
32
33 composed of several domains such as vitality, sensory skills, locomotion/mobility, cognition,
34
35 ADL, and IADL. Thus, this measure includes not only measures of exercise capacity, but also
36
37 functionality that could be affected by the course of COPD disease and impact on the patients'
38
39 quality of life.
40
41
42
43

44
45 The aims of the present paper are: 1) to study the risk of all-cause mortality associated with
46
47 COPD and healthy ageing trajectories (HAT) in three population-based cohorts of middle-aged
48
49 and older adults; 2) to determine the moderating role of HAT in the association between COPD
50
51 and all-cause mortality. We speculated that a HAT characterized by low levels of healthy ageing
52
53 would be significantly associated with an increased risk of mortality in people with COPD,
54
55 whereas individuals with higher levels of healthy ageing and COPD would have a lower risk of
56
57 mortality.
58
59
60

Methods

Study design and Data Collection

The present study used data from five waves of The Survey of Health, Ageing and Retirement in Europe (SHARE)[24]. SHARE is a multidisciplinary, cross-national panel database that contains a broad range of information on health, socioeconomic status, and social networks of European citizens aged 50 and older. The first wave took place in 2004-2005, constituted by more than 22,000 persons born in 1954 and earlier, and the following waves were conducted approximately every two years. The interviewers used computer-assisted personal interviewing (CAPI) to collect most of the data in all waves. Additionally, in waves 1, 2, and 4, self-administered questionnaires were handed out after the CAPI completion. If a respondent passed away during the study, then an end-of-life interview was conducted with a proxy.

The overall individual response rate at baseline was 60.1% and the wave-to-wave retention rate of participants from wave 1 was higher than 55% in all the countries[25]. All participants gave written consent. Ethical approvals for waves from 1 to 3 were granted by the Ethics Committee of the University of Mannheim[24]. For waves 4 and 5, the SHARE projects were reviewed and approved by the Ethics Council of the Max-Planck Society[26]. Further details concerning the study design of SHARE can be found elsewhere[24].

The following countries were included in the present analysis: Denmark, Sweden, Greece, Italy, Spain, Israel, Austria, Belgium, France, Germany, Netherlands, and Switzerland. We excluded those participants who were incorporated in the subsequent waves due to the sample's refreshments ($n=30,816$). The analyses focused on people aged 50 years and older who completed a non-proxy interview at baseline, resulting in an analytical sample of 28,857 respondents.

Patient and public involvement

No patient involved.

Measurements

- *All-cause mortality*

The death of a participant was confirmed by interviewing a proxy-respondent since information on the deceased was not linked to national death registries[25,27]. If confirmed, the date of death was obtained from end-of-life interviews with a proxy respondent[25,27]. Participants were characterized as survivors or censored if they were alive at the end of the study period, and dead if they died during the study period.

Survival time was calculated in years and as follows: 1) from baseline to the reported date of death or the final assessment date for those participants who were alive at the end of 2013; or 2) in the case that a participant reported being diagnosed with COPD at baseline, survival time was calculated from baseline. Besides, for the set of patients who reported a new diagnosis of COPD during the follow-up period, we considered the first time of the observation as the age at which they were newly diagnosed.

- *Chronic obstructive pulmonary disease (COPD)*

Participants reported whether a doctor ever informed them that they had “COPD such as chronic bronchitis or emphysema”. In the present study, we considered the first age in which a participant reported having been diagnosed with COPD instead of considering the presence/absence of COPD at baseline because the participant might be diagnosed in the subsequent waves. Therefore, COPD diagnosis was treated as a time-variant variable.

- *Healthy ageing scale*

We used an international scale of healthy ageing measurement developed by the ATHLOS consortium[21,28]. This scale used items about intrinsic capacity and functional ability based on

1
2
3 the World Mental Health's (WHO) concept of healthy ageing[29]. The healthy ageing scale
4 covers different domains, such as vitality, sensory skills, locomotion/mobility, cognition, ADL,
5 and IADL. Thirty-nine study-specific variables were harmonised into dichotomous items
6 indicating the presence or absence of difficulties (see Supplementary Table 1). Final scores were
7 estimated for all individuals and converted to *T*-scores with a mean of 50 and a standard
8 deviation of 10. In our study, we applied latent class growth analysis (LCGA)[30] to identify
9 longitudinal trajectories according to the healthy ageing scale score across the waves and
10 classify the participants into those trajectories.
11
12
13
14
15
16
17
18
19

- 20 • *Covariates*

21
22 Demographic variables included sex (male/female), age (in years), level of education (less than
23 primary, primary, secondary, and tertiary), marital status (single, married or currently
24 cohabiting, separated or divorced, and widowed), and quintiles of household wealth (first
25 quintile indicating lowest level).
26
27
28
29
30
31
32

33
34 Lifestyles and health behaviors included ever smoked and practice of vigorous physical activity
35 during the last two weeks and were coded as *yes* or *no*. The following self-reported diagnoses
36 of NCDs different from COPD were included: diabetes, hypertension, joint disorders (arthritis,
37 rheumatism, or osteoarthritis), asthma, myocardial infarction, and stroke. Similar to COPD, we
38 selected the age of the earliest diagnosis of each NCD across the five waves, considering them
39 as time-variant variables.
40
41
42
43
44
45
46
47

48 Depression was assessed with the EURO-D 12-item scale, which was developed and validated
49 for the EURODEP studies to measure depressive symptoms across European countries
50 accounting for regional differences[31,32]. The EURO-D score ranges from 0 to 12, with higher
51 scores meaning higher levels of depression, being 4 or greater than the proposed cut-off score
52 that has been selected to create a dichotomous depression variable (*yes/no*)[31].
53
54
55
56
57
58
59
60

1
2
3 Finally, we grouped the countries into 3 European regions according to the World Health
4 Organization (WHO) and the United Nations Statistical Division (UNSD) regional
5 classification[33,34]. Thus, Northern Europe was constituted by Denmark and Sweden, Western
6 Europe included Austria, Belgium, France, Germany, Israel, the Netherlands, and Switzerland,
7 and Southern Europe included Spain, Italy, and Greece.
8
9

10 11 12 13 14 15 *Statistical Analyses*

16
17
18 We divided the sample into three groups according to the year of birth of the participants and
19 keeping proportional sample sizes. The first group ($n=9,866$) was composed of those participants
20 who were born after 1945 (the youngest participants: aged 50+), the second group ($n=9,254$)
21 comprised participants born between 1936 and 1945 (ages from 58 to 70 years old), and the
22 third one ($n=9,739$) encompassed individuals who were born in 1935 or earlier (the oldest
23 participants: from 69 to 104 years old). Analyses were independently conducted in these three
24 birth cohorts.
25
26
27
28
29
30
31
32
33

34
35 Latent class growth analysis (LCGA) was used to classify individuals into trajectories based on
36 their score on the healthy ageing scale[30]. The number of trajectories was determined by
37 analyzing group models from 1 to 5 trajectories. The optimal model was selected according to
38 the Bayesian information criterion, where the lowest value indicates the better fit[35,36], and
39 the sample size of the trajectory group; a sample size lower than 5% was considered insufficient
40 to identify classes[36].
41
42
43
44
45
46
47
48

49 To avoid the assumption of proportionality of the Cox regression hazards, we conducted an
50 Aalen additive hazards modeling approach, which explores the associations between COPD and
51 time to death[37,38]. These models can provide a better picture of how the effects of covariates
52 develop over time without assuming the proportional risk hypothesis as in the Cox regression
53 models[39]. Parameters of these models are arbitrary cumulative regression functions that
54 represent the cumulative excess risk at each unit of time and are useful to assess changes over
55
56
57
58
59
60

1
2
3 time graphically[40]. Confidence intervals above zero for a concrete age indicate a significant
4 risk, below zero indicate a protective effect, and confidence intervals including zero show a non-
5 significant risk[41]. Models were adjusted for sex, age, marital status, level of education,
6 household wealth, region, vigorous physical activity, tobacco consumption, HAT, depression,
7 and presence of NCDs, all as time-varying covariates. The interaction between COPD and HAT
8 was also assessed. Age was used as the time measure. Participants who were alive at the end of
9 the study period or in their final assessment were censored. In the modeling process, we also
10 took into account that the data were left-truncated because we considered the first interview
11 as the time of diagnosis in the case of the participants who had been diagnosed by an NCD
12 before baseline. All analyses were performed using R Version 4.0.3.[42]. Statistical significance
13 was set at $p < 0.05$.

28 Results

29 We identified three HAT in each of the three birth cohorts according to lower BIC and the sample
30 sizes not lower than 5% (Supplementary Table 2 and Supplementary Figure 1). Although in the
31 oldest birth cohort 4 trajectories met the selection criteria, we decided to select a three-
32 trajectory model to facilitate comparison between the three cohorts. In all birth cohorts, the
33 trajectories were parallel. The first trajectory group included individuals with the highest scores
34 on the healthy ageing scale and the third those with the worse scores. We named each trajectory
35 group as “high”, “medium”, and “low”, respectively.

36 Table 1 shows the characteristics of participants. Those participants of the oldest group (born
37 ≤ 1935) showed a higher prevalence of COPD (12.50%), followed by those born between 1935
38 and 1945 (9.57%), ($p < 0.001$). The oldest group presented lower proportions of the “high” HAT
39 (31.60%), compared with the other two birth cohorts ($p < 0.001$). Finally, the proportion of deaths
40 increased with age, being lower in the > 1945 (2.07%) and higher in the ≤ 1935 sub-sample
41 (16.90%) ($p < 0.001$).

Table 1. Main characteristics of the sample broken down by year of birth

Characteristics	Years of birth cohort			p value ¹
	≤1935 (N=9738)	1936-1945 (N=9254)	>1945 (N=9865)	
Female, n (%)	5407 (55.50)	4879 (52.70)	5382 (54.60)	<0.001
Age, mean (SD)	74.40 (5.94)	61.30 (2.95)	52.10 (2.58)	<0.001
Marital status, n (%)				<0.001
Single	452 (4.64)	468 (5.06)	638 (6.47)	
Married	5832 (59.90)	7343 (79.30)	8051 (81.60)	
Divorced	338 (3.47)	603 (6.52)	950 (9.63)	
Widowed	3646 (37.40)	1203 (13.00)	531 (5.38)	
Education level, n (%)				<0.001
Less than primary	994 (10.20)	417 (4.51)	246 (2.49)	
Primary	3895 (40.00)	2513 (27.20)	1604 (16.30)	
Secondary	3734 (38.30)	4570 (49.40)	5520 (56.00)	
Tertiary	1115 (11.40)	1754 (19.00)	2495 (25.30)	
Wealth quintiles, n (%)				<0.001
1 st (worst)	1798 (18.50)	801 (8.66)	687 (6.96)	
2 nd	2479 (25.50)	1380 (14.90)	960 (9.73)	
3 rd	2185 (22.40)	1895 (20.50)	1481 (15.00)	
4 th	1721 (17.70)	2247 (24.30)	2494 (25.30)	
5 th (best)	1555 (16.00)	2931 (31.70)	4243 (43.00)	
Region, n (%)				0.049
Northern Europe	1557 (16.00)	1483 (16.00)	1473 (14.90)	
Western Europe	4842 (49.70)	4676 (50.50)	5090 (51.60)	
Southern Europe	3339 (34.30)	3095 (33.40)	3302 (33.50)	
Healthy ageing trajectories, n (%)				<0.001
High	3073 (31.60)	4620 (49.90)	5962 (60.40)	
Medium	4713 (48.40)	3491 (37.70)	3050 (30.90)	
Low	1952 (20.00)	1143 (12.40)	853 (8.65)	
Physical activity, n (%)	4934 (50.70)	7107 (76.80)	8283 (84.00)	<0.001
Ever smoked, n (%)	3910 (40.20)	4572 (49.40)	5543 (56.20)	<0.001
Diseases, n (%)				
Diabetes	1821 (18.70)	1628 (17.60)	1132 (11.50)	<0.001
Hypertension	5334 (54.80)	4647 (50.20)	3500 (35.50)	<0.001
Joint disorders	3914 (40.20)	3018 (32.60)	2407 (24.40)	<0.001
Asthma	703 (7.22)	550 (5.94)	497 (5.04)	<0.001
COPD	1214 (12.50)	886 (9.57)	622 (6.31)	<0.001
Myocardial infarction	3022 (31.00)	1751 (18.90)	957 (9.70)	<0.001
Stroke	1119 (11.50)	565 (6.11)	332 (3.37)	<0.001
Depression	4340 (44.60)	3387 (36.60)	3444 (34.90)	<0.001
Death, n (%)	1642 (16.90)	451 (4.87)	204 (2.07)	<0.001

Note. Household income was divided into 5 quintiles (the first indicating the lowest income). Marital status “married” category included “currently married or cohabiting”, and “divorced” included “divorced or separated”. Abbreviations: COPD, chronic obstructive pulmonary disease. ¹Based on T-tests for numerical variables and Chi-square tests for categorical variables.

1
2
3
4
5 Three Aalen regression models were conducted: one with only the variable COPD, the second
6
7 with only the variable of HAT, and the third with COPD and the HAT adjusted for covariates. The
8
9 estimated cumulative coefficients of the first and second model are presented in Supplementary
10
11 Figure 2, and those from the third model are presented in Figure 1, according to the >1945,
12
13 1936-1945, and ≤ 1935 sub-samples, respectively. In the first model, COPD diagnosis had a
14
15 significant risk on mortality in the three birth cohort groups: from 74 years old onwards in the
16
17 ≤ 1935 sub-sample, from 65 years old onwards in the other two sub-samples (see Supplementary
18
19 Figure 2). In the second model, regarding the HAT, those individuals classified in “low”
20
21 trajectories had a significant risk of mortality: in the ≤ 1935 sub-sample there was a significant
22
23 risk of death from 76 to 94 years, and from 97 to 98; in the 1936-1945 sub-sample from 63
24
25 onwards; and in the >1945 sub-sample from 60 onwards. Those following a “medium” HAT had
26
27 a significant risk of death in the ≤ 1935 sub-sample intermittently from 76 to 86 years and at 98
28
29 years; in the 1936-1945 sub-sample from 65 onwards; and in the >1945 sub-sample from 62
30
31 onwards (see Supplementary Figure 2).
32
33
34
35
36

37 Figure 1 shows the estimated cumulative coefficients calculated from the third model (including
38
39 all variables) for each birth cohort. In this model, although the risk effect of COPD increases
40
41 across age, it was rather non-significant (only a small effect in the ≤ 1935 sub-sample around 76
42
43 and 77 years old). In the case of the HAT, “low” trajectories were associated with a higher risk
44
45 of mortality in the case of the ≤ 1935 sub-sample (from 88 to 90). There was a significant
46
47 mortality risk in the 1936-1945 and the >1945 birth cohorts (from 71 onwards and 60 onwards,
48
49 respectively). “Medium” HAT had only a significant effect in the 1936-1945 sub-sample, from 74
50
51 onwards. The interaction between COPD and HAT was assessed in the third model. A significant
52
53 effect was only found in the model with the ≤ 1935 sub-sample. The interaction showed that
54
55 there was a significant effect (higher risk of death) for participants with COPD and a “low” HAT,
56
57 with the highest risk of death at the age of 75 and from 81 to 87.
58
59
60

1
2
3 Completed and detailed results of the fitting of Aalen's additive regression models are presented
4
5 in Supplementary Figure 3.
6
7
8
9

10 Discussion

11
12
13 We analysed the association of COPD with the risk of mortality and the moderating role of HAT
14 in the SHARE study, a population-based cohort of middle-aged and older adults from 12
15 European countries who were followed up for 9 years. With the aim of accounting for potential
16 cohort effects, we analysed the results separately in three groups: those born after 1945 (aged
17 50+), born between 1936 and 1945 (ages from 58 to 70 years old), and born in 1935 or earlier
18 (ages from 69 to 104 years old).
19
20
21
22
23
24
25
26

27 Our findings show that COPD increased the risk of mortality in the three birth cohorts. However,
28 this association was no longer significant after adjusting for demographic and economic
29 variables, presence of other NCDs and depression, and HAT. In line with previous research, the
30 study of mortality in COPD patients is quite cumbersome, and multiple variables may play a role
31 in this association. For example, lung cancer and COPD mortality were assessed including several
32 variables (residential characteristics, marital status, education, health insurance, and family
33 income) in a research study based on The National Longitudinal Mortality Study in the United
34 States[43]. They found that COPD mortality rates were highest among 65 to 74 years old, in
35 males and non-Hispanic whites[43]. The results concerning the periods are consistent with those
36 we found before adjustment, suggesting the existence of a period of increased risk of mortality
37 in COPD patients. In another study based on The National Mortality Database of Statistics
38 Canada, the mortality related to COPD varied by age, sex, birth cohort, and the province[44]. In
39 that study, the mortality risk attributed to COPD decreased in male and female cohorts born
40 after 1920 to 1924, whereas between 1971 and 1983 the mortality ratios were stable[44]. Thus,
41 performing the analyses considering different birth cohorts seems to be appropriate, since
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 exposure to risk factors for COPD such as tobacco consumption or occupational pollution might
4
5 greatly vary across birth cohorts. Moreover, previous studies on the risk of COPD mortality have
6
7 reported differences in terms of age, sex, birth cohort, location, household income, education,
8
9 and marital status[43–46]. Thus, the study of mortality associated with COPD needs to account
10
11 for the potential confounding effects of these risk factors.
12
13

14
15 One potential confounder is the region of residence, as indicated in previous studies[47].
16
17 Despite not being the focus of our study, we identify that living in Western or Southern Europe
18
19 had a protective effect on the risk of all-cause mortality, compared to Northern Europe
20
21 (Denmark and Sweden). Similarly, Blanco et al (2017), found a lower mean COPD prevalence in
22
23 Southern Europe (10.8%) compared to Northern Europe (11,5%), although variations in terms
24
25 of COPD prevalence were also found among countries of the same European region[12]. In
26
27 Northern Europe, it was higher in Denmark (ranging from 12% to 25%) than in Sweden (ranging
28
29 from 2% to 20%); whereas in Southern Europe, Italy showed higher prevalence (ranging from
30
31 12% to 23%), than in Spain (from 7 to 10%)[12]. The greater COPD prevalence and its associated
32
33 mortality risk in Denmark could be a consequence of a very high smoking prevalence in the past
34
35 5 decades, resulting in the highest COPD prevalence in the western world[48]. This
36
37 heterogeneity among countries and regions might suggest the need for a better understanding
38
39 of the underlying mechanisms.
40
41
42
43

44
45 Regarding the HAT, our results seem to confirm that participants (from different birth cohorts)
46
47 with “low” and “medium” HAT (i.e, worse health status) have a higher risk of mortality,
48
49 compared to those classified into “high” HAT. This effect remains after adjusting for covariates
50
51 although in the case of the “medium” trajectories only a significant effect was found in the 1936-
52
53 1945 birth cohort (constituted by people aged 58 to 70 years old). According to our results, “low”
54
55 trajectories seem to discriminate in a better way a poorer health status and to predict mortality,
56
57 even after adjusting for confounders. Previous studies examined the connection between
58
59
60

1
2
3 healthy ageing and mortality, albeit using different indicators[49,50]. In a South Brazilian
4 population-based cohort, researchers differentiated between normal ageing and successful
5 ageing (defined as a very good state of health, a complete absence of functional disability and
6 mood changes, and no cognitive impairment)[49]. They detected that successful agers had lower
7 mortality rates, and the normal agers had a higher risk for mortality[49]. These results may be
8 extrapolated to our “low” and “high” HAT, being the last the equivalent to “successful ageing”.
9
10 Another study used The Healthy Ageing Index (HAI) as a summary measure of physiologic
11 aging[50], composed of markers of cardiovascular, lung, cognitive, metabolic, and kidney
12 function. In that study, HAI scores tended to increase with age (meaning worse healthy ageing)
13 and predicted mortality from a given time-point[50]. Hence, composite measures of ageing
14 seem to be powerful tools to predict mortality and to identify individuals at a higher risk.
15
16

17
18 One of the main results from our study is that the association between COPD and risk of
19 mortality depended upon the HAT of the oldest participants (i.e., born ≤ 1935). Individuals with
20 COPD and a “low” trajectory of healthy ageing were more likely to die at the age of 75 years old
21 and from 81 to 87, compared with people with COPD and a “medium” or “high” HAT. The healthy
22 ageing scale covers several domains (vitality, sensory skills, mobility, cognition, and ADL/IADL)
23 and could be negatively affected in those patients with worse COPD symptoms[7–10]. The fact
24 that these results were found only in the oldest sub-sample may be related to the course of the
25 disease since COPD is a progressive disease and exacerbations and hospitalizations are
26 particularly common among older individuals[51]. Our results point out temporary spaces where
27 older COPD patients with a “low” HAT are at higher risk of mortality. Thus, future efforts should
28 be concentrated on those aged 75 years old and from 81 to 87.
29
30

31
32 To the best of our knowledge, few studies have analysed the relationship between health status
33 in COPD patients. These studies were based on self-reported perceived health status assessed
34 through the SF-12 questionnaire, which is a generic instrument to evaluate physical and mental
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 health[52,53]. The main finding in one of these studies, that used data from the BOLD project,
4
5 was that COPD severity was an important determinant of health status (more severity linked to
6
7 poorer health status)[52]. Although these studies considered the health status of people with
8
9 COPD, we have not found any study that used a composite measure of healthy ageing as we
10
11 have done. An integrated measure assessing intrinsic capacity and functional ability could be a
12
13 useful tool in daily clinical practice for patient prognosis, as well as a mortality predictor, and for
14
15 the creation of future public health strategies addressing COPD patients' needs[21]. While it is
16
17 true that other composite tools to predict COPD mortality are available (such as St George's
18
19 Respiratory Questionnaire[54], or the BODE index[55]), the healthy ageing scale is a
20
21 comprehensive tool that could be applied not only to COPD patients but also to patients with
22
23 multimorbidity.
24
25
26
27

28 *Strengths and limitations*

29
30 These findings should be interpreted in light of the following limitations. Firstly, the presence or
31
32 absence of COPD and NCDs was based on self-reported diagnostics, thus they might be affected
33
34 by measurement errors. Nevertheless, some authors sustain self-reported diagnostics as a well-
35
36 established method for the measurement of NCDs in population-based studies[56]. Secondly,
37
38 we did some assumptions in terms of age of diagnosis. Due to the high percentage of
39
40 missingness (48%) in the age of the NCD diagnosis, we selected the age of the earliest diagnosis
41
42 of each NCD within the five waves. That is, we coded the age of the participant in the wave
43
44 he/she reported the first time having some of the included diseases. Despite being an
45
46 assumption, there are only two years between each wave in the SHARE study. Thus, we believe
47
48 that there is not a huge impact on our conclusions. Thirdly, we split the sample into three birth
49
50 cohorts when performing the analyses, and we reported the mortality risk in each group. By
51
52 doing so, we captured potential cohort effects which people from different birth cohorts can be
53
54 influenced by different exposure to COPD-related risk factors that contribute differently to
55
56 mortality, as the different trends in smoking prevalence. For each birth cohort, the survival
57
58
59
60

1
2
3 analysis can be focused according to the years of the interview or according to the age of the
4 participants. We finally decided to do it according to the age of the participants because working
5 with time-varying variables and without the assumption of proportional risks, the fluctuations
6 in mortality risk according to age could be better interpreted. However, this introduces a
7 problem of left truncation since the age range observed for each participant is different,
8 although we took this into account in the additive regression model. Fourthly, another issue is
9 that the age range observed for each birth cohort is also different so that the excess cumulative
10 risk curve starts at the first observed age. Therefore, the bias of the healthy participant in the
11 first wave of the study means that in the first ages of observation there is no significant excess
12 risk.
13
14
15
16
17
18
19
20
21
22
23
24
25

26 Alongside these limitations, this study had a number of strengths. Firstly, the analyses were
27 performed in different birth cohorts (>1945, 1936-1945, and ≤1935) to assess if there were
28 differences in mortality risks that could be related to societal changes, such as trends in lifestyle
29 behaviours and occupation. Secondly, we used a novel measurement scale of healthy ageing
30 including several variables related to intrinsic capacity and functional ability. Compared with the
31 use of different indicators of health separately, we believe that using an integrated and reliable
32 measure of health status is a powerful tool to predict the mortality risk of the participants.
33 Thirdly, the calculation of Aalen additive hazards models rather than Cox models allowed the
34 inclusion of time-variant variables in the analyses.
35
36
37
38
39
40
41
42
43
44
45
46

47 **Conclusion**

48 COPD is a costly and preventable disease that has large-scale implications for patients' quality
49 of life and society in general[57,58]. Our findings suggest that the association between COPD
50 and risk of mortality in the general population of middle-aged and older adults might be
51 explained by the presence of other risk factors. However, for older people with COPD (i.e., aged
52 69 or older), having a poor trajectory of healthy ageing might compromise their survival. Especial
53
54
55
56
57
58
59
60

1
2
3 attention should be paid to these patients, with the healthy ageing scale as a potential suitable
4
5 tool to do identify older patients with COPD at high risk of mortality[20].
6
7

8 **Competing interests**

9
10 The authors declare no conflict of interest.
11
12

13 **Patient consent for publication**

14
15 Not required.
16
17

18
19 **Data sharing statement:** The original data of the Survey of Health, Ageing and Retirement in
20 Europe – SHARE is available on the official website (<http://www.share-project.org/home0.html>).
21
22

23 R codes for harmonizing the healthy ageing scale is available on
24
25 <https://athlos.pssjd.org/study/share-hs>.
26
27
28
29

30 **Funding**

31
32 This work was supported by the five-year Ageing Trajectories of Health: Longitudinal
33 Opportunities and Synergies (ATHLOS) project. The ATHLOS project has received funding from
34 the European Union's Horizon 2020 research and innovation program under grant agreement
35 No 635316. BO's work is supported by the Miguel Servet program (CP20/00040), funded by
36 Instituto de Salud Carlos III and co-funded by European Union (ERDF/ESF, "Investing in your
37 future"). DF's work has been supported by Marsden grant E2987-3648 administrated by the
38 Royal Society of New Zealand) and by grant 2017 SGR 622 (GRBIO) administrated by the
39 Departament d'Economia i Coneixement de la Generalitat de Catalunya (Spain).
40
41
42
43
44
45
46
47
48
49

50 **Acknowledgments**

51
52 The SHARE study is funded by the European Commission through FP5 (QLK6-CT-2001-00360),
53 FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-
54 2006-028812) and FP7 (SHARE-PREP: N°211909, SHARE-LEAP: N°227822, SHARE M4: N°261982).
55
56
57
58
59
60 Additional funding from the German Ministry of Education and Research, the Max Planck Society

1
2
3 for the Advancement of Science, the U.S. National Institute on Aging (U01_AG09740-13S2,
4 P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11,
5
6 OGHA_04-064, HHSN271201300071C) and from various national funding sources is gratefully
7
8 acknowledged (see www.share-project.org).
9
10
11
12

13 **Author contributions**

14
15 **IB:** Participated in the database management, drafted the paper, carried out the statistical
16
17 analyses and worked on the interpretation of data. She also gave final approval of the version
18
19 to be published and agreed to be accountable for all aspects of the work in ensuring that
20
21 questions related to the accuracy or integrity of any part of the work are appropriately
22
23 investigated and resolved; **AS:** Participated in the study design, database management, carried
24
25 out the statistical analyses, gave statistical support and critical revision of the paper. He also
26
27 gave final approval of the version to be published and agreed to be accountable for all aspects
28
29 of the work in ensuring that questions related to the accuracy or integrity of any part of the work
30
31 are appropriately investigated and resolved; **DF:** Participated in the statistical support and
32
33 critical revision of the paper. He also gave final approval of the version to be published and
34
35 agreed to be accountable for all aspects of the work in ensuring that questions related to the
36
37 accuracy or integrity of any part of the work are appropriately investigated and resolved; **JMH:**
38
39 Participated in the acquisition of data, and critical revision of the paper. He also gave final
40
41 approval of the version to be published and agreed to be accountable for all aspects of the work
42
43 in ensuring that questions related to the accuracy or integrity of any part of the work are
44
45 appropriately investigated and resolved; **BO:** Participated in the critical revision of the paper.
46
47 She also gave final approval of the version to be published and agreed to be accountable for all
48
49 aspects of the work in ensuring that questions related to the accuracy or integrity of any part of
50
51 the work are appropriately investigated and resolved.
52
53
54
55
56
57

58 **References**

59
60 1 Miniati M, Monti S, Pavlickova I, *et al.* Survival in COPD: impact of lung dysfunction and

- comorbidities. *Med* 2014;**93**:e76. doi:10.1097/MD.000000000000076
- 2 Okely JA, Shaheen SO, Weiss A, *et al.* Wellbeing and chronic lung disease incidence: the
3 Survey of Health, Ageing and Retirement in Europe. *PLoS One* 2017;**12**:e0181320.
4 doi:10.1371/journal.pone.0181320
- 5
6
7
8
9 3 World Health Organization. World Health Statistics 2008. 2008.
10 https://www.who.int/whosis/whostat/EN_WHS08_Full.pdf?ua=1 (accessed 20 May
11 2020).
- 12
13 4 Buist AS, McBurnie MA, Vollmer WM, *et al.* International variation in the prevalence of
14 COPD (The BOLD Study): a population-based prevalence study. *Lancet* 2007;**370**:741–
15 50. doi:10.1016/S0140-6736(07)61377-4
- 16
17 5 Duan R-R, Hao K, Yang T. Air pollution and chronic obstructive pulmonary disease.
18 *Chronic Dis Transl Med* 2020;**6**:260–9. doi:10.1016/j.cdtm.2020.05.004
- 19
20 6 Rosenberg SR, Kalhan R, Mannino DM. Epidemiology of chronic obstructive pulmonary
21 disease: prevalence, morbidity, mortality, and risk factors. *Semin Respir Crit Care Med*
22 2015;**36**:457–69. doi:10.1055/s-0035-1555607
- 23
24 7 Bourbeau J. Activities of Life: the COPD patient. *COPD* 2009;**6**:192–200.
25 doi:10.1080/15412550902902638
- 26
27 8 Barusso MS, Gianjeppe-Santos J, Basso-Vanelli RP, *et al.* Limitation of activities of daily
28 living and quality of life based on COPD combined classification. *Respir Care*
29 2015;**60**:388–98. doi:10.4187/RESPCARE.03202
- 30
31 9 Medina-Mirapeix F, Bernabeu-Mora R, Piedad Sánchez-Martínez M, *et al.* Mobility
32 limitations related to reduced pulmonary function among aging people with chronic
33 obstructive pulmonary disease. *PLoS One* 2018;**13**:e0196152.
34 doi:10.1371/journal.pone.0196152
- 35
36 10 Dodd JW. Lung disease as a determinant of cognitive decline and dementia. *Alzheimer's*
37 *Res Ther* 2015;**7**:1–8. doi:10.1186/s13195-015-0116-3
- 38
39 11 Eroglu SA, Gunen H, Yakar HI, *et al.* Influence of comorbidities in long-term survival of
40 chronic obstructive pulmonary disease patients. *J Thorac Dis* 2019;**11**:1379–86.
41 doi:10.21037/jtd.2019.03.78
- 42
43 12 Blanco I, Diego I, Bueno P, *et al.* Geographical distribution of COPD prevalence in
44 Europe, estimated by an inverse distance weighting interpolation technique. *Int J Chron*
45 *Obs Pulmon Dis* 2017;**13**:57–67. doi:10.2147/COPD.S150853
- 46
47 13 Menezes AMB, Perez-Padilla R, Jardim JRB, *et al.* Chronic obstructive pulmonary disease
48 in five Latin American cities (the PLATINO study): A prevalence study. *Lancet*
49 2005;**366**:1875–81. doi:10.1016/S0140-6736(05)67632-5
- 50
51 14 Blanco I, Diego I, Bueno P, *et al.* Geographical distribution of COPD prevalence in
52 Europe, estimated by an inverse distance weighting interpolation technique. *Int J Chron*
53 *Obs Pulmon Dis* 2017;**13**:57–67. doi:10.2147/COPD.S150853
- 54
55 15 Nowak D, Berger K, Lippert B, *et al.* Epidemiology and health economics of COPD across
56 Europe: A critical analysis. *Treat. Respir. Med.* 2005;**4**:381–95. doi:10.2165/00151829-
57 200504060-00003
- 58
59 16 Lortet-Tieulent J, Soerjomataram I, López-Campos JL, *et al.* International trends in COPD
60 mortality, 1995-2017. *Eur Respir J* 2019;**54**:1901791. doi:10.1183/13993003.01791-

- 2019
- 17 Pinto-Plata VM, Cote C, Cabral H, *et al.* The 6-min walk distance: Change over time and value as a predictor of survival in severe COPD. *Eur Respir J* 2004;**23**:28–33. doi:10.1183/09031936.03.00034603
 - 18 Spruit MA, Polkey MI, Celli B, *et al.* Predicting Outcomes from 6-Minute Walk Distance in Chronic Obstructive Pulmonary Disease. *J Am Med Dir Assoc* 2012;**13**:291–7. doi:10.1016/j.jamda.2011.06.009
 - 19 Puhan MA, Garcia-Aymerich J, Frey M, *et al.* Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 2009;**374**:704–11. doi:10.1016/S0140-6736(09)61301-5
 - 20 Puhan MA, Siebeling L, Zoller M, *et al.* Simple functional performance tests and mortality in COPD. *Eur Respir J* 2013;**42**:956–63. doi:10.1183/09031936.00131612
 - 21 Sanchez-Niubo A, Forero CG, Wu Y-T, *et al.* Development of a common scale for measuring healthy ageing across the world: results from the ATHLOS consortium. *Int J Epidemiol* 2020;**dyaa236**:1–13. doi:10.1093/ije/dyaa236
 - 22 Bui KL, Nyberg A, Maltais F, *et al.* Functional tests in chronic obstructive pulmonary disease, Part 1: Clinical relevance and links to the international classification of functioning, disability, and health. In: *Annals of the American Thoracic Society*. American Thoracic Society 2017. 778–84. doi:10.1513/AnnalsATS.201609-733AS
 - 23 Sanchez-Niubo A, Egea-Cortés L, Olaya B, *et al.* Cohort profile: the ageing trajectories of health - longitudinal opportunities and synergies (ATHLOS) project. *Int J Epidemiol* 2019;**48**:1052-1053i. doi:org/10.1093/ije/dyz077
 - 24 Börsch-Supan A, Brandt M, Hunkler C, *et al.* Data resource profile: The survey of health, ageing and retirement in europe (SHARE). *Int J Epidemiol* 2013;**42**:992–1001. doi:10.1093/ije/dyt088
 - 25 Bergmann, Michael; Kneip, Thorsten; De Luca, Giuseppe; Scherpenzeel A. Survey Participation in the Survey of Health, Ageing and Retirement in Europe (SHARE), Wave 1-6. Based on Release 6.0.0 (March 2017). Munich: Munich Center for the Economics of Aging (MEA): 2017.
 - 26 Wolfrum R. Opinion of the ethics council of the Max Planck society on the “SHARE” project. 2016.http://www.share-project.org/fileadmin/pdf_documentation/SHARE_ethics_approvals.pdf
 - 27 Bergmann, M. Kneip, T., De Luca, G., & Scherpenzeel A. Survey participation in the Survey of Health, Ageing and Retirement in Europe (SHARE), Wave 1-7. Based on Release 7.0.0. Munich: SHARE-ERIC: 2019.
 - 28 Sanchez-Niubo A, Egea-Cortés L, Olaya B, *et al.* Cohort Profile: The Ageing Trajectories of Health - Longitudinal Opportunities and Synergies (ATHLOS) project. *Int J Epidemiol* 2019;**48**:1052-1053I. doi:10.1093/ije/dyz077
 - 29 World Health Organization. World report on ageing and health 2015. 2015.<https://www.who.int/ageing/events/world-report-2015-launch/en/> (accessed 27 Jul 2020).
 - 30 Berlin KS, Parra GR, Williams NA. An Introduction to Latent Variable Mixture Modeling (Part 2): Longitudinal Latent Class Growth Analysis and Growth Mixture Models. *J*

- 1
2
3 *Pediatr Psychol* 2014;**39**:188–203. doi:10.1093/jpepsy/jst085
4
5 31 Reischies F, Lobo A, Turrina C, *et al.* Development of the EURO–D scale – a European
6 Union initiative to compare symptoms of depression in 14 European centres. *Br J*
7 *Psychiatry* 2008;**174**:330–8. doi:10.1192/bjp.174.4.330
8
9 32 Copeland JRM, Beekman ATF, Dewey ME, *et al.* Depression in Europe. Geographical
10 distribution among older people. *Br J Psychiatry* 1999;**174**:312–21.
11 doi:10.1192/bjp.174.4.312
12
13 33 WHO. Country groupings.
14 https://www.who.int/quantifying_ehimpacts/global/ebdcountgroup/en/ (7 February
15 2019, date last accessed)
16
17 34 United Nations Statistical Division (UNSD). Countries or areas/geographical regions.
18 <https://unstats.un.org/unsd/methodology/m49/> (7 February 2019, date last accessed)
19
20 35 Tein JY, Coxe S, Cham H. Statistical power to detect the correct number of classes in
21 latent profile analysis. *Struct Equ Model* 2013;**20**:640–57.
22 doi:10.1080/10705511.2013.824781
23
24 36 Nylund-Gibson K, Choi AY. Ten frequently asked questions about latent class analysis.
25 *Transl Issues Psychol Sci* 2018;**4**:440–61. doi:10.1037/tps0000176
26
27 37 Aalen O. A Model for Nonparametric Regression Analysis of Counting Processes.
28 Springer, New York, NY 1980. 1–25. doi:10.1007/978-1-4615-7397-5_1
29
30 38 Aalen OO. A linear regression model for the analysis of life times. *Stat Med* 1989;**8**:907–
31 25. doi:10.1002/sim.4780080803
32
33 39 O. O. Aalen; O. Borgan; H. K. Gjessing. *Survival and event history analysis: a process*
34 *point of view*. Springer. New York: 2008.
35
36 40 Xie X, Strickler HD, Xue X. Additive hazard regression models: An application to the
37 natural history of human papillomavirus. *Comput. Math. Methods Med.* 2013;**2013**.
38 doi:10.1155/2013/796270
39
40 41 Aalen OO, Scheike TH. Aalen's Additive Regression Model. In: *Encyclopedia of*
41 *Biostatistics*. Chichester, UK: : John Wiley & Sons, Ltd 2005.
42 doi:10.1002/0470011815.b2a11002
43
44 42 Team RC. R: A language and environment for statistical computing.
45 2020.<https://www.r-project.org/>
46
47 43 Lewis DR, Clegg LX, Johnson NJ. Lung disease mortality in the United States: the
48 National Longitudinal Mortality Study. *Int J Tuberc Lung Dis* 2009;**13**:1008–
49 14./pmc/articles/PMC2765862/?report=abstract (accessed 4 Feb 2021).
50
51 44 Manfreda J, Mao Y, Litven W. Morbidity and mortality from chronic obstructive
52 pulmonary disease. *Am Rev Respir Dis* 1989;**140**:16–26.
53 doi:10.1164/ajrccm/140.3_pt_2.s19
54
55 45 Ntritsos G, Franek J, Belbasis L, *et al.* Gender-specific estimates of COPD prevalence: a
56 systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2018;**13**:1507–14.
57 doi:10.2147/COPD.S146390
58
59 46 Hummer RA, Hernandez EM. The effect of educational attainment on adult mortality in
60 the United States. *Popul Bull* 2013;**68**:1–

- 1
2
3 16.<http://www.ncbi.nlm.nih.gov/pubmed/25995521> (accessed 9 Dec 2020).
4
5 47 OECD/European Union. Mortality from respiratory diseases. In: OECD Publishing, ed.
6 *Health at a Glance: Europe 2018: State of Health in the EU Cycle*. Paris/European Union,
7 Brussels: 2018. doi:https://doi.org/10.1787/health_glance_eur-2018-en
8
9 48 Lange P, Tøttenborg SS, Sorknæs AD, *et al*. Danish register of chronic obstructive
10 pulmonary disease. *Clin Epidemiol* 2016;**8**:673–8. doi:10.2147/CLEP.S99489
11
12 49 Camozzato AL, Godinho C, Chaves MLF. Effect of successful aging on mortality in older
13 individuals: the PALA study. *Dement e Neuropsychol* 2014;**8**:182–6. doi:10.1590/S1980-
14 57642014DN82000015
15
16 50 O’Connell MDL, Marron MM, Boudreau RM, *et al*. Mortality in relation to changes in a
17 healthy aging index: the Health, Aging, and Body Composition Study. *Journals Gerontol -*
18 *Ser A Biol Sci Med Sci* 2019;**74**:726–32. doi:10.1093/gerona/gy114
19
20 51 Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease
21 heterogeneity. *Chest* 2002;**121**:121–6. doi:10.1378/chest.121.5_suppl.121S
22
23 52 Janson C, Marks G, Buist S, *et al*. The impact of COPD on health status: Findings from
24 the BOLD study. *Eur Respir J* 2013;**42**:1472–83. doi:10.1183/09031936.00153712
25
26 53 López Varela MV, Montes de Oca M, Halbert R, *et al*. Comorbidities and Health Status in
27 Individuals With and Without COPD in Five Latin American Cities: The PLATINO Study.
28 *Arch Bronconeumol* 2013;**49**:468–74. doi:10.1016/j.arbr.2013.09.009
29
30 54 Jones PW, Quirk FH, Baveystock CM. The St George’s Respiratory Questionnaire. *Respir*
31 *Med* 1991;**85**:25–31. doi:10.1016/S0954-6111(06)80166-6
32
33 55 Celli BR, Cote CG, Marin JM, *et al*. The Body-Mass Index, Airflow Obstruction, Dyspnea,
34 and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. *N Engl J Med*
35 2004;**350**:1005–12. doi:10.1056/nejmoa021322
36
37 56 Huntley AL, Johnson R, Purdy S, *et al*. Measures of multimorbidity and morbidity
38 burden for use in primary care and community settings: a systematic review and guide.
39 *Ann Fam Med* 2012;**10**:134–41. doi:10.1370/afm.1363
40
41 57 Chapmann KR, Mannino DM, Soriano JB, *et al*. Epidemiology and costs of chronic
42 obstructive pulmonary disease. *Eur. Respir. J.* 2006;**27**:188–207.
43 doi:10.1183/09031936.06.00024505
44
45 58 Quaderi SA, Hurst JR. The unmet global burden of COPD. *Glob. Heal. Epidemiol.*
46 *Genomics.* 2018;**3**:1–3. doi:10.1017/ghg.2018.1
47
48
49
50
51
52
53
54
55
56
57
58
59
60

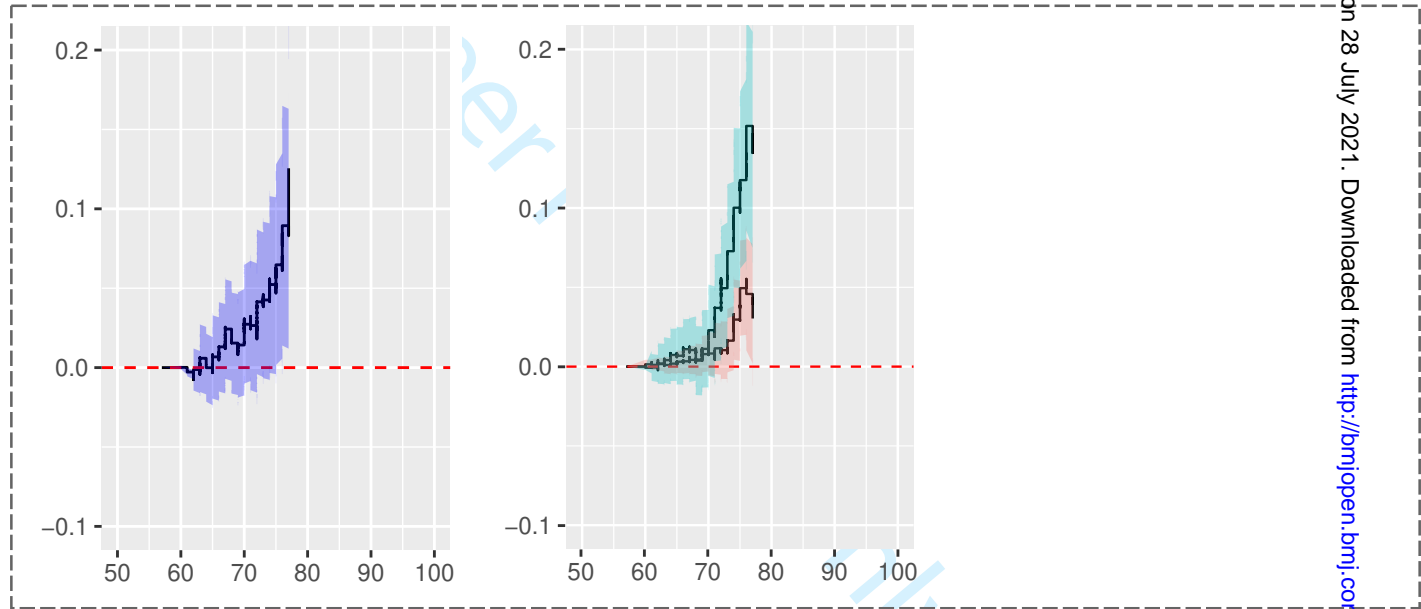
Models adjusted by sex, education, income, wealth, marital status, region, depression, diabetes, hypertension, joint disorders, asthma, myocardial infarction, and stroke:

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

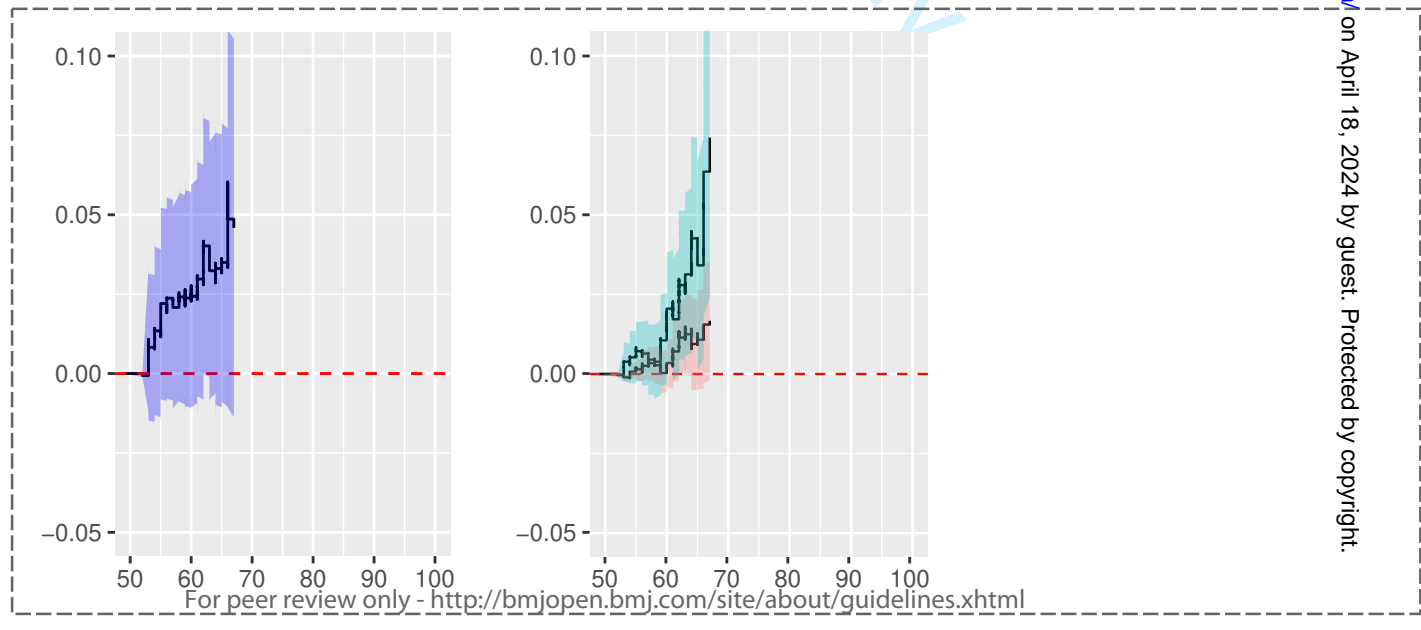


Birth Cohort
≤1935

23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40



41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Open: first published as 10.1136/bmjopen-2021-0250947 on 28 July 2021. Downloaded from <http://bmjopen.bmj.com/> on April 18, 2024 by guest. Protected by copyright.

Supplemental material

Supplementary Table 1. Harmonised items of the healthy ageing scale in the SHARE study

ATHLOS harmonized variables		SHARE	
Memory	Self-reported ratings of memory at the time of the interview	Label	A4-B3 Memory self-rating
		Values	1 = None; 2 = Mild; 3 = Moderate; 4 = Severe; 5 = Extreme
		Harmonisation	1 = Absence; 2-5 = Presence
Immediate recall	Immediate recall of common nouns from a list	Label	ten words list learning first trial total
		Values	Continuous Variable 0-10
		Harmonisation	<=25% into Presence >25% into Absence
Delayed recall	Test that assesses delayed recall using the common nouns from the list previously employed for measuring Immediate recall	Label	ten words list learning delayed recall total
		Values	Continuous Variable 0-10
		Harmonisation	<=25% into Presence >25% into Absence
Verbal fluency†	Test that assesses verbal (semantic) fluency	Label	verbal fluency score
		Values	Continuous Variable 0-88
		Harmonisation	<=25% into Presence >25% into Absence
Orientation in time	Difficulties for orientation in time, evaluated by a set of questions about the date and day of the week	Label	orientation to date, month, year and day of week
		Values	0-3 = bad; 4 = good
		Harmonisation	4 = Absence; 0-3 = Presence
Numeracy		Label	cf012_ : Chance disease 10 perc. of 1000 cf013_ : Half price [of a 300 Euro sofa] cf014_ : 6000 is two-thirds what is total price cf015_ : Amount in the savings account [on 2000 Euros after 2 years of 10% interest]
		Values	All: 1 = correct answer: 100; 2 = wrong answer: 10; 3 = wrong answer: 90; 4 = wrong answer: 900; 97 = wrong answer: Other answer keep 1 into 1; recode -1, 2, 3, 4, 5, 6 and 97 into 0
		Harmonisation	All 1 = Absence; Some 0 = Presence
Sleeping	Sleeping problems	Label	sleep (part of EURO-D)
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Pain	It measures if the participant experiences some degree of pain or if the participant does not present any pain at all	Label	bothered by: pain in back, knees, hips or other joint
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Energy	Self-reported high level of energy experienced at the time of the interview	Label	fatigue
		Values	1 = Yes; 5 = No
		Harmonisation	5 = Absence; 1 = Presence
		Label	bothered by: incontinence

Urine incontinence	It measures if the participant has experienced loss of urine (or has used any special device for urine leakage)	Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Near vision	Difficulties for near vision	Label	eyesight reading
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor
		Harmonisation	1-3 = Absence; 4-5 = Presence
Far vision	Difficulties for far vision	Label	eyesight distance
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor
		Harmonisation	1-3 = Absence; 4-5 = Presence
Eyesight	Difficulties in eye sight using glasses or corrective lens as usual	Label	Is your eyesight (using glasses or contact lens if you use them)
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor; 6 = registered or legally blind
		Harmonisation	1-3 = Absence; 4-6 = Presence
Hearing in general	It measures if the participant experiences some difficulty for hearing (i.e., hearing someone talking on the other side of the room in a normal voice) or not, using a hearing aid as usual	Label	hearing
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor
		Harmonisation	1-3 = Absence; 4-5 = Presence
Hearing in a conversation	It measures if the participant experiences some difficulty (including total disability) for following a conversation (i.e., if there is a background noise, or several people talking) or not, using a hearing aid as usual	Label	hearing with one person
		Values	1 = Yes; 5 = No
		Harmonisation	1 = Absence; 0 = Presence
Stooping, kneeling or crouching	Difficulty for stooping, kneeling or crouching	Label	difficulties: stooping, kneeling, crouching
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Lifting or carrying weights	Difficulty for lifting or carrying weights	Label	difficulties: lifting or carrying weights over 5 kilos
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Climbing stairs	Difficulty for climbing stairs	Label	difficulties: climbing one flight of stairs
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Getting up	Difficulty for getting up from sitting down	Label	difficulties: getting up from chair
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Walking	Difficulty for walking by yourself and without using any special equipment	Label	difficulties: walking 100 metres
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Pulling or pushing	Difficulty for pulling or pushing large objects	Label	difficulties: pulling or pushing large objects
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Sitting	Difficulty for sitting for long periods	Label	difficulties: sitting two hours
		Values	0 = Not selected; 1 = Selected

		Harmonisation	0 = Absence; 1 = Presence
Reaching or extending arms	Difficulty for reaching / extending arms	Label	difficulties: reaching or extending arms above shoulder
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Walking speed	It is measured assessing the time that is taken to walk a distance	Label	walking speed
		Values	Continuous
		Harmonisation	<=25% into Presence >25% into Absence
Dizziness	Dizziness problems when walking on a level surface	Label	bothered by: dizziness, faints or blackouts
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Picking up	Difficulty for picking up things with fingers, e.g. picking up a coin	Label	difficulties: picking up a small coin from a table
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Getting in or out of bed	Difficulty for getting in or out of bed	Label	difficulties: getting in or out of bed
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Bathing or showering	Difficulties for bathing or showering	Label	difficulties: bathing or showering
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Getting dressed	Difficulty for getting dressed	Label	difficulties: dressing, including shoes and socks
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Moving around the home	Difficulty for moving around the home	Label	difficulties: walking across a room
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Toilet	Difficulties for using the toilet	Label	difficulties: using the toilet, incl getting up or down
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Eating	Difficulties for eating	Label	difficulties: eating, cutting up food
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Housework	Difficulties for doing housework	Label	difficulties: doing work around the house or garden
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Shopping	Difficulties for shopping groceries	Label	difficulties: shopping for groceries
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Meals	Difficulties in preparing meals	Label	difficulties: preparing a hot meal
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Map	Difficulties for using a map	Label	difficulties: using a map in a strange place
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Money	Difficulties for managing money, bills, or expenses	Label	difficulties: managing money
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Medications	Difficulties for taking medications	Label	difficulties: taking medications

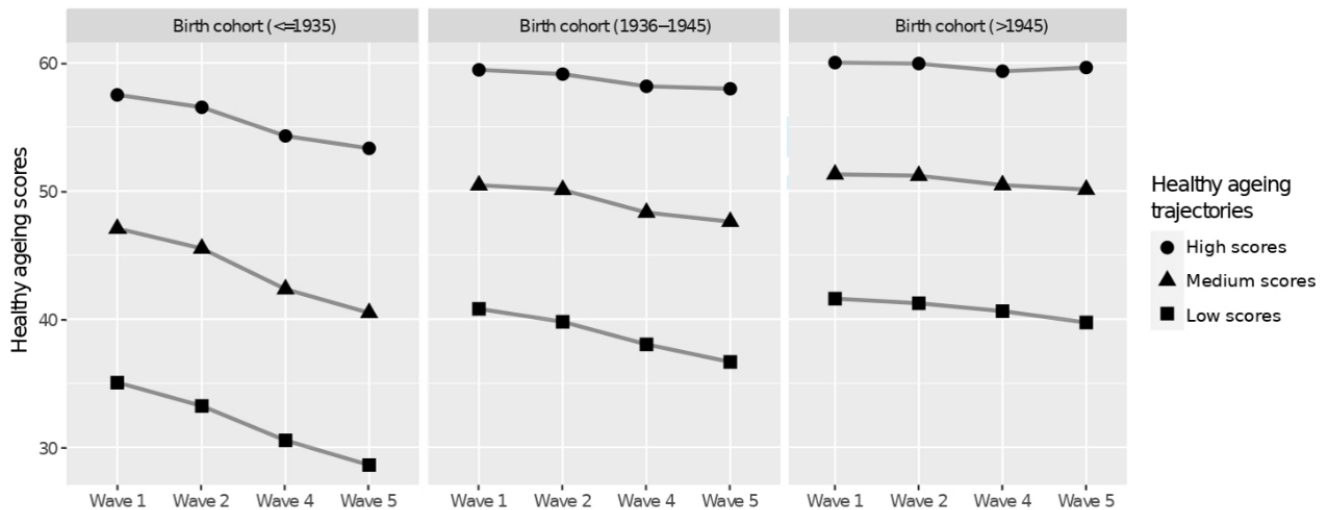
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
		Label	difficulties: telephone calls
Telephone	Difficulties for using telephone	Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence

For peer review only

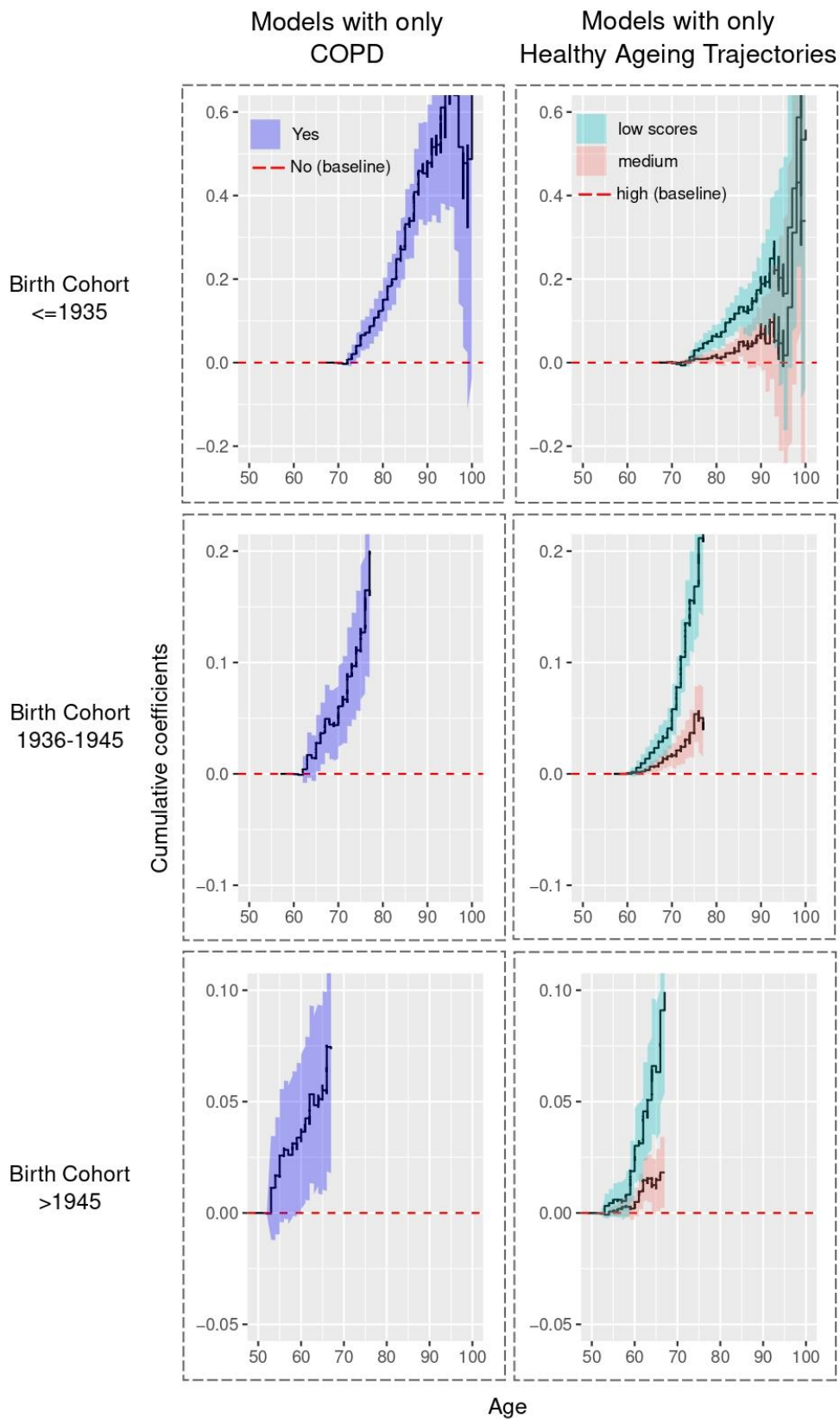
Supplementary Table 2. Results from the latent class growth analysis models for the three birth cohorts

≤1935								
No. of classes	Loglik	npm	BIC	% class 1	% class 2	% class 3	% class 4	% class 5
1	-83923.67	3	167875.0	100.00				
2	-80924.65	6	161904.6	51.39	48.60			
3	-79920.76	9	159924.4	20.21	31.38	48.39		
4	-79545.29	12	159201.1	7.37	32.59	23.22	36.80	
5	-79429.36	15	158996.8	31.64	23.08	1.31	7.19	36.76
1936 – 1945								
No. of classes	Loglik	npm	BIC	% class 1	% class 2	% class 3	% class 4	% class 5
1	-86218.80	3	172465.1	100.00				
2	-82811.31	6	165677.6	66.84	33.15			
3	-81877.93	9	163838.3	49.72	12.44	37.83		
4	-81611.24	12	163332.3	43.55	35.79	2.38	18.26	
5	-81540.03	15	163217.4	33.21	12.13	24.67	28.00	1.97
>1945								
No. of classes	Loglik	npm	BIC	% class 1	% class 2	% class 3	% class 4	% class 5
1	-89325.74	3	178679.1	100.00				
2	-85721.95	6	171499.2	23.37	76.62			
3	-84856.16	9	169795.3	8.75	30.81	60.43		
4	-84608.23	12	169327.1	30.97	53.19	13.34	2.47	
5	-84607.84	15	169354.0	2.39	13.17	32.36	52.02	0.02

Supplementary Figure 1. Trajectories of healthy ageing among birth cohorts



Supplementary Figure 2. Estimates of cumulative excess of risk of COPD and healthy ageing trajectories, separately by using the Aalen's additive regression



Supplementary Figure 3.

Figure 3.1. Estimates of cumulative excess risk of covariates from the Aalen's additive regression model by >1945 birth cohort sub-sample.

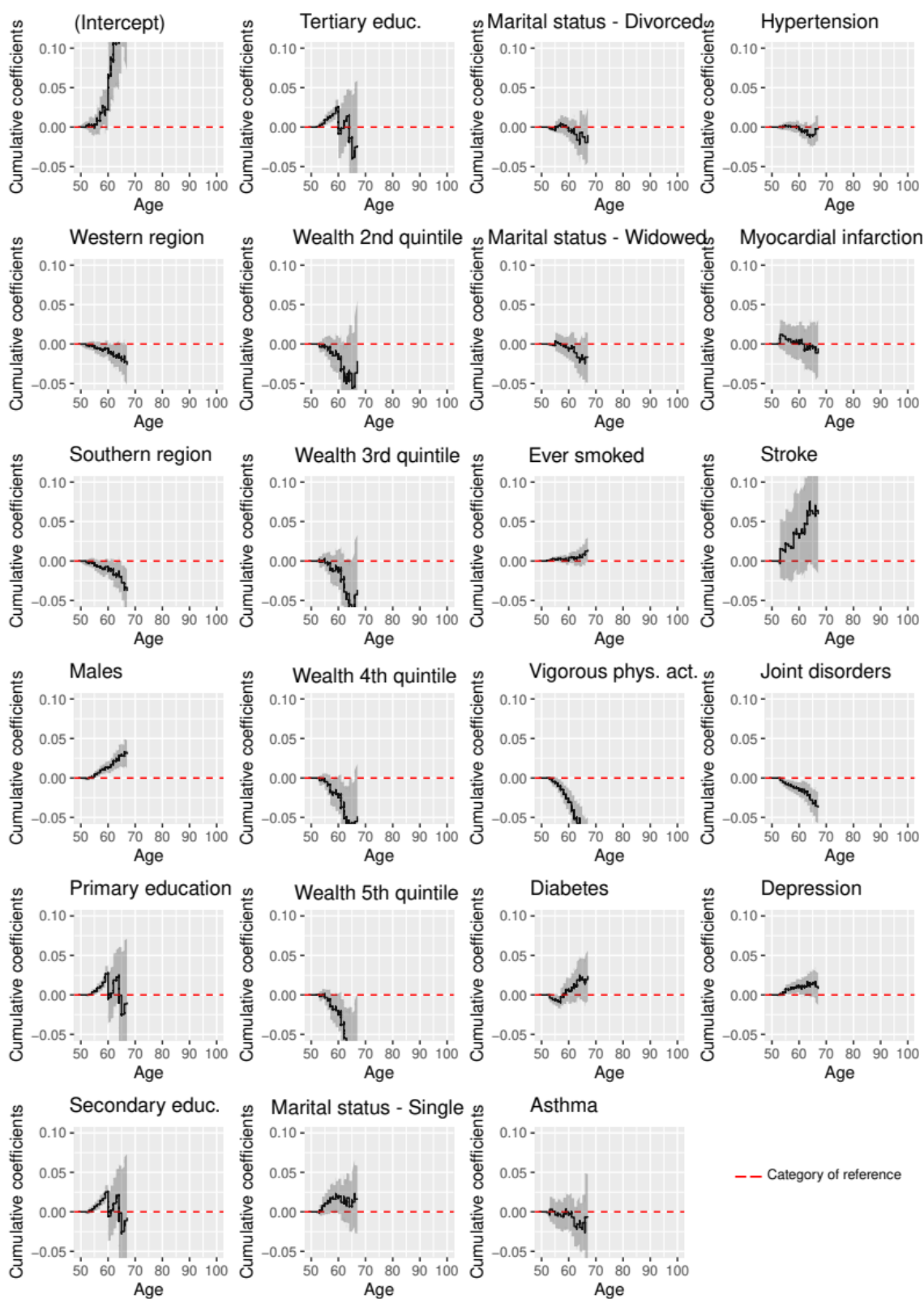


Figure 3.2. Estimates of cumulative excess risk of covariates from the Aalen's additive regression model by 1936-1945 birth cohort sub-sample.

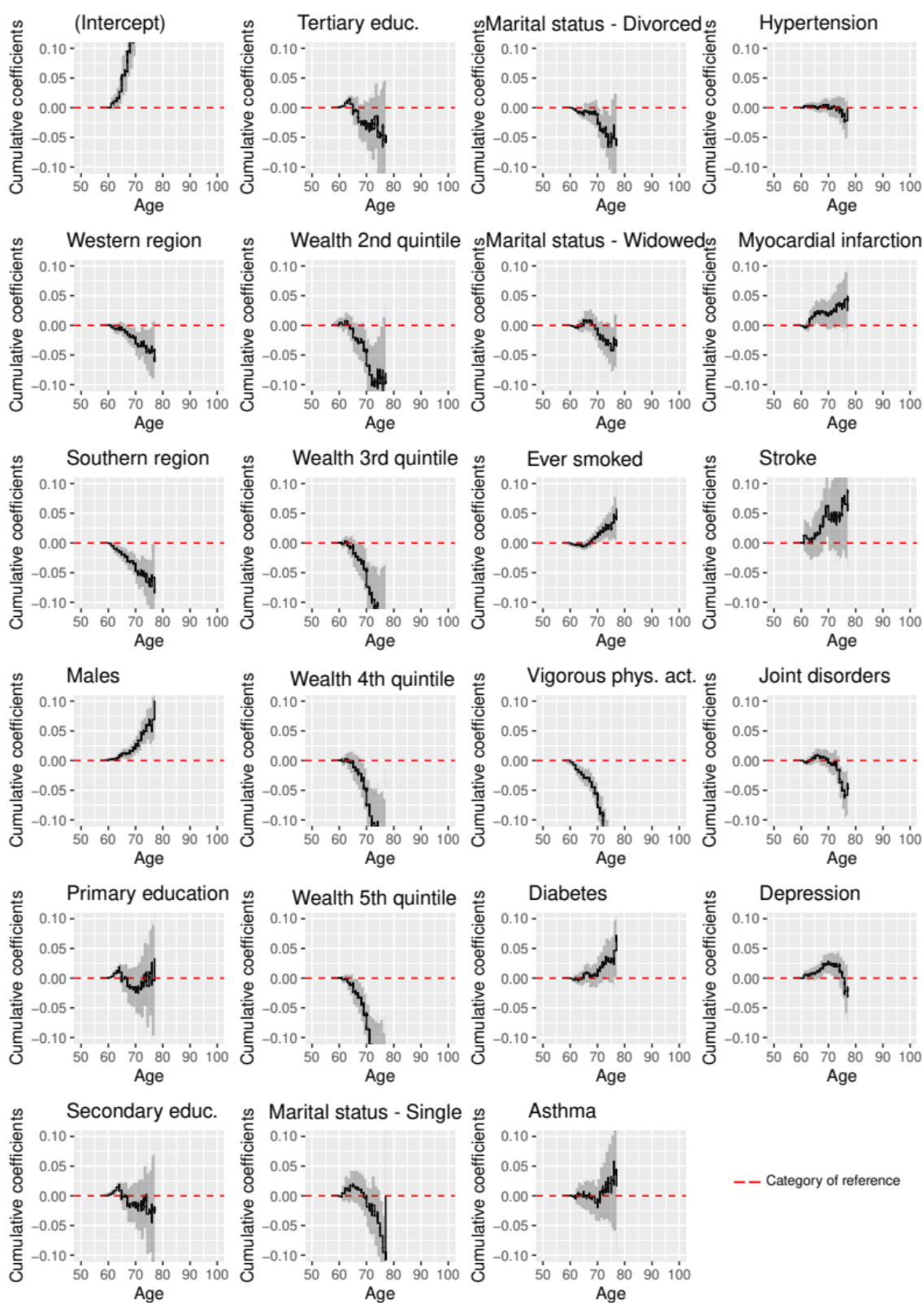
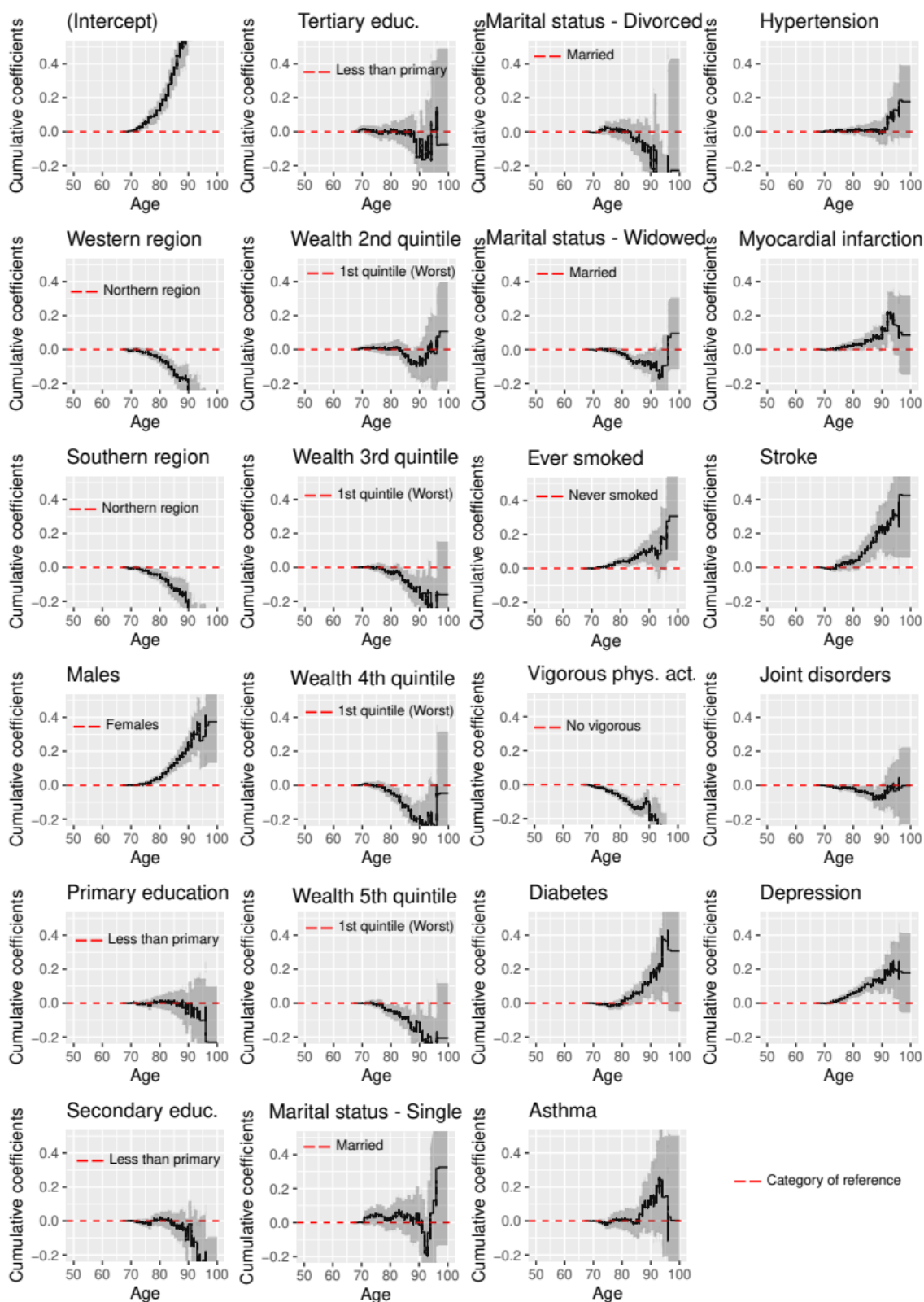


Figure 3.3. Estimates of cumulative excess risk of covariates from the Aalen’s additive regression model by ≤ 1935 birth cohort sub-sample.



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7-10
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6-7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4				
5				
6				
7				
8				
9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplemental material
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	17-18
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-18
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
20				
21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
23				
24				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Risk of all-cause mortality associated with chronic obstructive pulmonary disease and the role of healthy ageing trajectories: A population-based study of middle-aged and older adults.

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-050947.R1
Article Type:	Original research
Date Submitted by the Author:	09-Jun-2021
Complete List of Authors:	Bayes-Marin, Iveta; Parc Sanitari Sant Joan de Déu, Research, Innovation and Teaching Unit; Universitat de Barcelona Facultat de Medicina Sanchez-Niubo, Albert ; Parc Sanitari Sant Joan de Deu, ; Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) Fernández, Daniel; Polytechnic University of Catalonia, Serra Hünter fellow, Department of Statistics and Operations Research Haro, Josep; Parc Sanitari Sant Joan de Deu, Research, Innovation and Teaching Unit; Centro de Investigación Biomédica en Red de Salud Mental Olaya, Beatriz; Parc Sanitari Sant Joan de Deu, Research, Innovation and Teaching Unit; Centro de Investigación Biomédica en Red de Salud Mental
Primary Subject Heading:	Epidemiology
Secondary Subject Heading:	Public health, Respiratory medicine
Keywords:	Chronic airways disease < THORACIC MEDICINE, EPIDEMIOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1
2
3 **Risk of all-cause mortality associated with chronic obstructive pulmonary disease and the**
4 **role of healthy ageing trajectories: A population-based study of middle-aged and older**
5 **adults.**
6
7
8
9

10
11
12 Ivet Bayes-Marin ^{a,b,c}, Albert Sanchez-Niubo ^{a,b}, Daniel Fernández^d, Josep Maria Haro ^{a,b,c}, and
13
14 Beatriz Olaya ^{a,b}
15

16
17 ^aResearch, Innovation and Teaching Unit, Parc Sanitari Sant Joan de Déu, Sant Boi de
18
19 Llobregat, 08830 Barcelona, Spain.
20

21
22 ^bCentro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Instituto de Salud
23
24 Carlos III, Madrid 28029, Spain.
25

26
27 ^cDepartment of Medicine, Universitat de Barcelona, Barcelona 08036, Spain.
28

29
30 ^dSerra Húnter fellow, Department of Statistics and Operations Research, Polytechnic
31
32 University of Catalonia-BarcelonaTech, 08028 Barcelona, Spain.
33
34

35 ***Corresponding author:**
36

37 Albert Sanchez-Niubo. Research, Innovation and Teaching Unit, Parc Sanitari Sant Joan de Déu,
38
39 Dr Antoni Pujadas 42, Sant Boi de Llobregat, Barcelona 08830, Spain. E-mail:
40
41 albert.sanchez@pssjd.org
42
43
44
45

46 **Word count:** 5840
47
48
49

50 **Abstract**
51

52 **Objectives:** The aims were to study the risk of all-cause mortality associated with chronic
53
54 obstructive pulmonary disease (COPD) and healthy ageing trajectories (HAT) in three birth
55
56 cohorts and to determine the moderating role of HAT in the association between COPD and
57
58 all-cause mortality. **Design:** prospective cohort study. **Setting:** Data from waves 1 to 5 of The
59
60

1
2
3 Survey of Health, Ageing and Retirement in Europe (SHARE). **Participants:** The total sample
4 was 28,857 community-dwelling individuals aged 50+ years. **Main outcome:** All-cause
5 mortality associated with COPD and HAT adjusting for covariates. We performed Aalen
6 additive hazards models to explore these associations. Interactions between COPD and HAT
7 were also explored. Analyses were conducted separately in three birth cohorts (>1945, 1936-
8 1945, and ≤1935). Latent class growth analysis was used to classify participants into HAT.
9
10
11
12
13
14
15
16 **Results:** Three parallel HAT were found in the three birth cohorts (“low”, “medium”, and
17 “high” healthy ageing). Participants with COPD had an increased mortality risk, but this effect
18 was no longer significant after adjusting for covariates. The “low” HAT was associated with
19 increased mortality risk in the three sub-samples, although this effect was lower after
20 adjustment. The interaction between COPD and HAT was significant only in the ≤1935 birth
21 cohort, indicating that those with COPD and a “low” trajectory had a greater risk of mortality.
22
23
24
25
26
27
28
29
30 **Conclusions:** The healthy ageing scale may be a suitable tool to identify patients at higher risk
31 to mitigate disease burden and improve patients’ quality of life.
32
33

34
35 **Keywords:** chronic obstructive pulmonary disease (COPD), mortality, healthy ageing, Europe,
36 population-based study
37
38
39

40 **Strengths and limitations of this study**

- 41
42
43 • The analyses were performed in different birth cohorts (>1945, 1936-1945, and ≤1935)
44 to assess differences in mortality risks related to societal changes, such as lifestyle
45 behaviours and occupation trends.
46
47
- 48
49 • We used a novel measurement scale of healthy ageing including intrinsic capacity and
50 functional ability variables.
51
52
- 53
54 • The calculation of Aalen additive hazards models rather than Cox models allowed the
55 inclusion of time-variant variables in the analyses.
56
57
58
59
60

- Due to the high percentage of missingness in the age of the diagnosis of the diseases, we selected the age of the earliest diagnosis of each disease within the five waves.
- For the survival analysis we used the age of the participants instead of the years of the interview for better interpretation. However, this introduces a problem of left truncation since the age range observed for each participant is different, although we took this into account in the additive regression model.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide(1,2). COPD is expected to become the third leading cause of death by 2030(3). The growing burden of COPD is a consequence of population ageing and the continued use of tobacco, which is considered its main risk factor(4). Moreover, air pollution has been associated with acute exacerbations of COPD, increased respiratory morbidity and mortality(5).

COPD is characterised by a progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases(6). With a worsening of the disease, there can be an increase of functional ability limitations in the activities of daily living (ADL), and in the instrumental activities of daily living (IADL), limiting exercise performance and self-care(7–9). COPD has increasingly been recognised as a multi-component disease, associated with a wide range of physical diseases and psychological disorders(10). Non-communicable diseases (NCDs) such as hypertension, cardiovascular diseases, diabetes, cancer, and depression commonly co-exist in COPD patients, worsening its progression(1,2,11). Furthermore, cognitive impairment is common among COPD patients, suggesting that impaired performance in neuropsychological tests might be a predictor of early mortality for people diagnosed with COPD(10).

1
2
3 Despite being a growing public health concern, there is a lack of epidemiological data about
4 the prevalence and distribution of COPD(6,12). The paucity of information on COPD prevalence
5 and incidence is partly due to differences in the methods used for its diagnosis and
6 classification, often being underestimated(6). These differences in the assessment methods
7 and definitions have also hampered the comparison of COPD prevalence and impact across
8 countries. Both The Burden of Lung Disease (BOLD) project(4) and the Latin American Project
9 for the Investigation of Obstructive Lung Disease (PLATINO)(13) were developed to map the
10 COPD prevalence using the same methodology in different countries. Those studies were
11 performed in China and Turkey, and five Latin American countries, respectively. Nevertheless,
12 there is a lack of integrated and updated estimates of COPD prevalence, similar to BOLD and
13 PLATINO initiatives, and information regarding patient's quality of life impact and associated
14 mortality in Europe(2,14). Additionally, available studies suggest large differences across
15 European countries regarding prevalence rates of COPD and the associated death rates(15,16).
16 In a systematic review, COPD prevalence ranged from 3% in Finnish women to 57% in Italian
17 men and women(15). Some differences have also been found in COPD-related mortality across
18 European countries and between men and women(16). Overall, regarding European countries,
19 COPD-related mortality rates appeared to decline in men in most countries from 1995 to 2017,
20 whereas mortality rates due to COPD increased in women from +2% per year in Austria to
21 +4.2% or +4.8% per year in the Czech Republic and Hungary, respectively(16).
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46 In that sense, an integrated longitudinal dataset that considers different European countries
47 could be particularly useful in studying the risk of mortality associated with COPD in different
48 European countries. In particular, using a cross-national panel database may prevent possible
49 heterogeneities arising from differences in survey methodologies, diagnostic criteria, and
50 population structure(17). The study of the mortality risk in COPD patients, and its association
51 with several variables related to health and functioning would allow identifying those
52
53
54
55
56
57
58
59
60

1
2
3 vulnerable sectors of the population and creating of preventive measures and interventions in
4
5 diverse healthcare systems.
6
7

8 Previous studies focused on the association between exercise capacity and mortality among
9
10 COPD patients, which has been considered one of the best predictors of mortality(18–20).
11
12 Measures of exercise capacity include indicators such as body mass index, airflow obstruction,
13
14 dyspnea, handgrip strength, and the sit-to-stand test(21). Nevertheless, these indicators of
15
16 exercise capacity are just measures of intrinsic capacity that do not capture the individual's
17
18 functional ability over the life course. In that sense, the functional ability results from the
19
20 interaction of the individuals' intrinsic capacity, including physical and mental capacities, and
21
22 their environment, as access to medications, personal and assistive support, or physical
23
24 barriers(22). Therefore, a measure assessing both intrinsic capacity and functional ability may
25
26 be a better way to capture a person's healthy ageing.
27
28
29

30
31 Several authors advocate for using composite measures as the International Classification of
32
33 Functioning, Disability, and Health to assess COPD patients' complexity, including also
34
35 functional capacity and functional performance(23). Related to this, the Ageing Trajectories of
36
37 Health: Longitudinal Opportunities and Synergies (ATHLOS) project(24) developed a healthy
38
39 ageing scale(22) using 16 international cohort studies to determine the intrinsic capacity and
40
41 functional ability of the participants allowing comparisons across countries. The healthy ageing
42
43 scale comprises several domains such as vitality, sensory skills, locomotion/mobility, cognition,
44
45 ADL, and IADL. Thus, this measure includes measures of exercise capacity and functionality
46
47 that could be affected by the course of COPD disease and impact on the patients' quality of
48
49 life.
50
51
52

53
54 The aims of the present paper are: 1) to study the risk of all-cause mortality associated with
55
56 COPD and healthy ageing trajectories (HAT) in three population-based cohorts of middle-aged
57
58 and older adults; 2) to determine the moderating role of HAT in the association between COPD
59
60

1
2
3 and all-cause mortality. We speculated that a HAT characterised by low levels of healthy
4 ageing would be significantly associated with an increased risk of mortality in people with
5 COPD. In contrast, individuals with higher levels of healthy ageing and COPD would have a
6
7 lower risk of mortality.
8
9
10

11 12 **Methods**

13 14 *Study design and Data Collection*

15
16
17
18 The present study used data from five waves of The Survey of Health, Ageing and Retirement
19 in Europe (SHARE)(25). SHARE is a multidisciplinary, cross-national panel database that
20 contains a broad range of information on health, socioeconomic status, and social networks of
21 European citizens aged 50 and older. The first wave took place in 2004-2005, constituted by
22 more than 22,000 persons born in 1954 and earlier, and the following waves were conducted
23 approximately every two years. The interviewers used computer-assisted personal
24 interviewing (CAPI) to collect most of the data in all waves. Additionally, in waves 1, 2, and 4,
25 self-administered questionnaires were handed out after the CAPI completion. If a respondent
26 passed away during the study, then an end-of-life interview was conducted with a proxy.
27
28
29
30
31
32
33
34
35
36
37
38

39
40 The overall individual response rate at baseline was 60.1%, and the wave-to-wave retention
41 rate of participants from wave 1 was higher than 55% in all the countries(26). All participants
42 gave written consent. Ethical approvals for waves from 1 to 3 were granted by the Ethics
43 Committee of the University of Mannheim(25). For waves 4 and 5, the SHARE projects were
44 reviewed and approved by the Ethics Council of the Max-Planck Society(27). Further details
45 concerning the study design of SHARE can be found elsewhere(25).
46
47
48
49
50
51
52

53
54 The following countries were included in the present analysis: Denmark, Sweden, Greece, Italy,
55 Spain, Israel, Austria, Belgium, France, Germany, Netherlands, and Switzerland. We excluded
56 participants incorporated in the subsequent waves due to the sample's refreshments
57
58
59
60

1
2
3 (n=30,816). The analyses focused on people aged 50 years and older who completed a non-
4 proxy interview at baseline, resulting in an analytical sample of 28,857 respondents.
5
6
7

8 *Patient and public involvement*

9

10 No patient involved.
11
12

13 *Measurements*

- 14 • *All-cause mortality*

15
16
17
18
19 The death of a participant was confirmed by interviewing a proxy-respondent since
20 information on the deceased was not linked to national death registries(26,28). If confirmed,
21 the date of death was obtained from end-of-life interviews with a proxy respondent(26,28).
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
Participants were characterised as survivors or censored if they were alive at the end of the
study period, and dead if they died during the study period.

Survival time was calculated in years and as follows: 1) from baseline to the reported date of
death or the final assessment date for those participants who were alive at the end of 2013; or
2) in the case that a participant reported being diagnosed with COPD at baseline, survival time
was calculated from baseline. Besides, for the set of patients who reported a new diagnosis of
COPD during the follow-up period, we considered the first time of the observation as the age
at which they were newly diagnosed.

- *Chronic obstructive pulmonary disease (COPD)*

Participants reported whether a doctor ever informed them that they had “COPD such as
chronic bronchitis or emphysema”. In the present study, we considered the first age in which a
participant reported having been diagnosed with COPD instead of considering the
presence/absence of COPD at baseline because the participant might be diagnosed in the
subsequent waves. Therefore, COPD diagnosis was treated as a time-variant variable.

- *Healthy ageing scale*

1
2
3 We used an international scale of healthy ageing measurement developed by the ATHLOS
4 consortium(22,29). This scale used items about intrinsic capacity and functional ability based
5 on the World Mental Health's (WHO) concept of healthy ageing(30). The healthy ageing scale
6 covers different domains, such as vitality, sensory skills, locomotion/mobility, cognition, ADL,
7 and IADL. Thirty-nine study-specific variables were harmonised into dichotomous items
8 indicating the presence or absence of difficulties (see Supplementary Table 1). Final scores
9 were estimated for all individuals and converted to *T*-scores with a mean of 50 and a standard
10 deviation of 10. We applied latent class growth analysis (LCGA)(31) to identify longitudinal
11 trajectories according to the healthy ageing scale score across the waves and classify the
12 participants into those trajectories.

- 23 • *Covariates*

24
25 Demographic variables included sex (male/female), age (in years), level of education (less than
26 primary, primary, secondary, and tertiary), marital status (single, married or currently
27 cohabiting, separated or divorced, and widowed), and quintiles of household wealth (first
28 quintile indicating lowest level).

29
30 Lifestyles and health behaviours included ever smoked and practice of vigorous physical
31 activity during the last two weeks and were coded as *yes* or *no*. The following self-reported
32 diagnoses of NCDs different from COPD were included: diabetes, hypertension, joint disorders
33 (arthritis, rheumatism, or osteoarthritis), asthma, myocardial infarction, and stroke. Similar to
34 COPD, we selected the age of the earliest diagnosis of each NCD across the five waves,
35 considering them as time-variant variables.

36
37 Depression was assessed with the EURO-D 12-item scale, which was developed and validated
38 for the EURODEP studies to measure depressive symptoms across European countries,
39 accounting for regional differences(32,33). The EURO-D score ranges from 0 to 12, with higher
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 scores meaning higher levels of depression, being four or greater than the proposed cut-off
4
5 score that has been selected to create a dichotomous depression variable (yes/no)(32).
6
7

8 Finally, we grouped the countries into three European regions according to the World Health
9
10 Organization (WHO) and the United Nations Statistical Division (UNSD) regional
11
12 classification(34,35). Thus, Northern Europe was constituted by Denmark and Sweden;
13
14 Western Europe included Austria, Belgium, France, Germany, Israel, the Netherlands; and
15
16 Switzerland, and Southern Europe included Spain, Italy, and Greece.
17
18

19 20 *Statistical Analyses*

21
22
23 We divided the sample into three groups according to the participants' birth year and kept
24
25 proportional sample sizes. The first group ($n=9,866$) was composed of those participants who
26
27 were born after 1945 (the youngest participants: aged 50+), the second group ($n=9,254$)
28
29 comprised participants born between 1936 and 1945 (ages from 58 to 70 years old), and the
30
31 third one ($n=9,739$) encompassed individuals who were born in 1935 or earlier (the oldest
32
33 participants: from 69 to 104 years old). Analyses were independently conducted in these three
34
35 birth cohorts.
36
37
38

39
40 Latent class growth analysis (LCGA) was used to classify individuals into trajectories based on
41
42 their score on the healthy ageing scale(31). The number of trajectories was determined by
43
44 analysing group models from 1 to 5 trajectories. According to the Bayesian information
45
46 criterion, the optimal model was selected. The lowest value indicates the better fit(36,37) and
47
48 the sample size of the trajectory group. In addition, a sample size lower than 5% was
49
50 considered insufficient to identify classes(37).
51
52
53

54 To analyse the associations between COPD and time to death, we conducted an Aalen additive
55
56 hazards modelling approach, avoiding the assumption of proportionality of the Cox regression
57
58 hazards (38,39). These models can provide a better picture of how the effects of covariates
59
60

1
2
3 develop over time without assuming the proportional risk hypothesis as in the Cox regression
4 models(40). Parameters of these models are arbitrary cumulative regression functions that
5 represent the cumulative excess risk at each unit of time and are useful to assess changes over
6 time graphically(41). Confidence intervals above zero for a concrete age indicate a significant
7 risk, below zero indicate a protective effect, and confidence intervals including zero show a
8 non-significant risk(42). Models were adjusted for sex, age, marital status, level of education,
9 household wealth, region, vigorous physical activity, tobacco consumption, HAT, depression,
10 and presence of NCDs, all as time-varying covariates. The interaction between COPD and HAT
11 was also assessed. Age was used as the time measure. Participants who were alive at the end
12 of the study period or in their final assessment were censored. In the modeling process, data
13 were left-truncated because we considered the first interview as the time of diagnosis in the
14 participants whom and NCD had been diagnosed before baseline. All analyses were performed
15 using R Version 4.0.3.(43). Statistical significance was set at $p<0.05$.

32 Results

33 We identified three HAT in each of the three birth cohorts according to lower BIC and the
34 sample sizes not lower than 5% (Supplementary Table 2 and Supplementary Figure 1).
35 Although four trajectories met the selection criteria in the oldest birth cohort, we decided to
36 select a three-trajectory model to facilitate comparison between the three cohorts. In all birth
37 cohorts, the trajectories were parallel. The first trajectory group included individuals with the
38 highest scores on the healthy ageing scale and the third with the worse scores. We named
39 each trajectory group as “high”, “medium”, and “low”, respectively.

40 Table 1 shows the characteristics of participants. Those participants of the oldest group (born
41 ≤ 1935) showed a higher prevalence of COPD (12.50%), followed by those born between 1935
42 and 1945 (9.57%), ($p<0.001$). The oldest group presented lower proportions of the “high” HAT
43 (31.60%) compared with the other two birth cohorts ($p<0.001$). Finally, the proportion of
44

deaths increased with age, being lower in the >1945 (2.07%) and higher in the ≤1935 sub-sample (16.90%) ($p<0.001$).

Table 1. Main characteristics of the sample broken down by year of birth

Characteristics	Years of birth cohort			<i>p</i> value ¹
	≤1935 (N=9738)	1936-1945 (N=9254)	>1945 (N=9865)	
Female, n (%)	5407 (55.50)	4879 (52.70)	5382 (54.60)	<0.001
Age, mean (SD)	74.40 (5.94)	61.30 (2.95)	52.10 (2.58)	<0.001
Marital status, n (%)				<0.001
Single	452 (4.64)	468 (5.06)	638 (6.47)	
Married	5832 (59.90)	7343 (79.30)	8051 (81.60)	
Divorced	338 (3.47)	603 (6.52)	950 (9.63)	
Widowed	3646 (37.40)	1203 (13.00)	531 (5.38)	
Education level, n (%)				<0.001
Less than primary	994 (10.20)	417 (4.51)	246 (2.49)	
Primary	3895 (40.00)	2513 (27.20)	1604 (16.30)	
Secondary	3734 (38.30)	4570 (49.40)	5520 (56.00)	
Tertiary	1115 (11.40)	1754 (19.00)	2495 (25.30)	
Wealth quintiles, n (%)				<0.001
1 st (worst)	1798 (18.50)	801 (8.66)	687 (6.96)	
2 nd	2479 (25.50)	1380 (14.90)	960 (9.73)	
3 rd	2185 (22.40)	1895 (20.50)	1481 (15.00)	
4 th	1721 (17.70)	2247 (24.30)	2494 (25.30)	
5 th (best)	1555 (16.00)	2931 (31.70)	4243 (43.00)	
Region, n (%)				0.049
Northern Europe	1557 (16.00)	1483 (16.00)	1473 (14.90)	
Western Europe	4842 (49.70)	4676 (50.50)	5090 (51.60)	
Southern Europe	3339 (34.30)	3095 (33.40)	3302 (33.50)	
Healthy ageing trajectories, n (%)				<0.001
High	3073 (31.60)	4620 (49.90)	5962 (60.40)	
Medium	4713 (48.40)	3491 (37.70)	3050 (30.90)	
Low	1952 (20.00)	1143 (12.40)	853 (8.65)	
Physical activity, n (%)	4934 (50.70)	7107 (76.80)	8283 (84.00)	<0.001
Ever smoked, n (%)	3910 (40.20)	4572 (49.40)	5543 (56.20)	<0.001
Diseases, n (%)				
Diabetes	1821 (18.70)	1628 (17.60)	1132 (11.50)	<0.001
Hypertension	5334 (54.80)	4647 (50.20)	3500 (35.50)	<0.001
Joint disorders	3914 (40.20)	3018 (32.60)	2407 (24.40)	<0.001
Asthma	703 (7.22)	550 (5.94)	497 (5.04)	<0.001
COPD	1214 (12.50)	886 (9.57)	622 (6.31)	<0.001
Myocardial infarction	3022 (31.00)	1751 (18.90)	957 (9.70)	<0.001

Stroke	1119 (11.50)	565 (6.11)	332 (3.37)	<0.001
Depression	4340 (44.60)	3387 (36.60)	3444 (34.90)	<0.001
Death, n (%)	1642 (16.90)	451 (4.87)	204 (2.07)	<0.001

Note. Household income was divided into 5 quintiles (the first indicating the lowest income). Marital status "married" category included "currently married or cohabiting", and "divorced" included "divorced or separated". Abbreviations: COPD, chronic obstructive pulmonary disease. ¹Based on T-tests for numerical variables and Chi-square tests for categorical variables.

Three Aalen regression models were conducted: one with only the variable COPD, the second with only the HAT variable, and the third with COPD and the HAT adjusted for covariates. The estimated cumulative coefficients of the first and second model are presented in Supplementary Figure 2, and those from the third model are presented in Figure 1, according to the >1945, 1936-1945, and ≤1935 sub-samples, respectively. In the first model, COPD diagnosis had a significant risk on mortality in the three birth cohort groups: from 74 years old onwards in the ≤1935 sub-sample, from 65 years old onwards in the other two sub-samples (see Supplementary Figure 2). In the second model, regarding the HAT, those individuals classified in "low" trajectories had a significant risk of mortality: in the ≤1935 sub-sample, there was a significant risk of death from 76 to 94 years, and from 97 to 98; in the 1936-1945 sub-sample from 63 onwards; and in the >1945 sub-sample from 60 onwards. Those following a "medium" HAT had a significant risk of death in the ≤1935 sub-sample intermittently from 76 to 86 years and at 98 years; in the 1936-1945 sub-sample from 65 onwards; and in the >1945 sub-sample from 62 onwards (see Supplementary Figure 2).

Figure 1 shows the estimated cumulative coefficients calculated from the third model (including all variables) for each birth cohort. In this model, although the risk effect of COPD increases across age, it was rather non-significant (only a small effect in the ≤1935 sub-sample around 76 and 77 years old). In the case of the HAT, "low" trajectories were associated with a higher risk of mortality in the case of the ≤1935 sub-sample (from 88 to 90). There was a significant mortality risk in the 1936-1945 and the >1945 birth cohorts (from 71 onwards and 60 onwards, respectively). "Medium" HAT had only a significant effect in the 1936-1945 sub-

1
2
3 sample, from 74 onwards. The interaction between COPD and HAT was assessed in the third
4
5 model. A significant effect was only found in the model with the ≤ 1935 sub-sample. The
6
7 interaction showed a significant effect (higher risk of death) for participants with COPD and a
8
9 “low” HAT, with the highest risk of death at the age of 75 and from 81 to 87.

10
11
12 Completed and detailed results of the fitting of Aalen’s additive regression models are
13
14 presented in Supplementary Figure 3.

15 16 17 18 19 20 **Discussion**

21
22
23 We analysed the association of COPD with the risk of mortality and the moderating role of HAT
24
25 in the SHARE study, a population-based cohort of middle-aged and older adults from 12
26
27 European countries who were followed up for nine years. To account for potential cohort
28
29 effects, we analysed the results separately in three groups: those born after 1945 (aged 50+),
30
31 born between 1936 and 1945 (ages from 58 to 70 years old), and born in 1935 or earlier (ages
32
33 from 69 to 104 years old).

34
35
36
37 Our findings show that COPD increased the risk of mortality in the three birth cohorts.
38
39 However, this association was no longer significant after adjusting for demographic and
40
41 economic variables, presence of other NCDs and depression, and HAT. In line with previous
42
43 research, the study of mortality in COPD patients is quite cumbersome, and multiple variables
44
45 may play a role in this association. For example, lung cancer and COPD mortality were
46
47 assessed, including several variables (residential characteristics, marital status, education,
48
49 health insurance, and family income) in a research study based on The National Longitudinal
50
51 Mortality Study in the United States(44). They found that COPD mortality rates were highest
52
53 among 65 to 74 years old, in males and non-Hispanic whites(44). The results concerning the
54
55 periods are consistent with those we found before adjustment, suggesting the existence of a
56
57 period of increased risk of mortality in COPD patients. In another study based on The National
58
59
60

1
2
3 Mortality Database of Statistics Canada, the mortality related to COPD varied by age, sex, birth
4 cohort, and the province(45). In that study, the mortality risk attributed to COPD decreased in
5 male and female cohorts born after 1920 to 1924, whereas between 1971 and 1983 the
6 mortality ratios were stable(45). Thus, performing the analyses considering different birth
7 cohorts seems appropriate since exposure to risk factors for COPD such as tobacco
8 consumption or occupational pollution might greatly vary across birth cohorts. Moreover,
9 previous studies on the risk of COPD mortality have reported differences in age, sex, birth
10 cohort, location, household income, education, and marital status(44–47). Thus, the study of
11 mortality associated with COPD needs to account for the potential confounding effects of
12 these risk factors.
13
14

15
16 One potential confounder is the region of residence, as indicated in previous studies(48).
17 Despite not being the focus of our study, we identify that living in Western or Southern Europe
18 had a protective effect on the risk of all-cause mortality, compared to Northern Europe
19 (Denmark and Sweden). Similarly, Blanco et al. (2017) found a lower mean COPD prevalence in
20 Southern Europe (10.8%) compared to Northern Europe (11.5%). However, variations in COPD
21 prevalence were also found among countries of the same European region(12). In Northern
22 Europe, it was higher in Denmark (ranging from 12% to 25%) than in Sweden (ranging from 2%
23 to 20%); whereas in Southern Europe, Italy showed higher prevalence (ranging from 12% to
24 23%), than in Spain (from 7 to 10%)(12). The greater COPD prevalence and its associated
25 mortality risk in Denmark could be a consequence of a very high smoking prevalence in the
26 past five decades, resulting in the highest COPD prevalence in the western world(49). This
27 heterogeneity among countries and regions might suggest the need for a better understanding
28 of the underlying mechanisms.
29
30

31
32 Regarding the HAT, our results seem to confirm that participants (from different birth cohorts)
33 with “low” and “medium” HAT (i.e., worse health status) have a higher risk of mortality
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 compared to those classified into “high” HAT. This effect remains after adjusting for covariates,
4
5 although in the case of the “medium” trajectories, only a significant effect was found in the
6
7 1936-1945 birth cohort (constituted by people aged 58 to 70 years old). According to our
8
9 results, “low” trajectories seem to discriminate a poorer health status in a better way and to
10
11 predict mortality, even after adjusting for confounders. Previous studies examined the
12
13 connection between healthy ageing and mortality, albeit using different indicators(50,51). In a
14
15 South Brazilian population-based cohort, researchers differentiated between normal ageing
16
17 and successful ageing (defined as a good state of health, a complete absence of functional
18
19 disability and mood changes, and no cognitive impairment)(50). They detected that successful
20
21 agers had lower mortality rates, and the normal agers had a higher risk for mortality(50).
22
23 These results may be extrapolated to our “low” and “high” HAT, being the last the equivalent
24
25 to “successful ageing”. Another study used The Healthy Ageing Index (HAI) as a summary
26
27 measure of physiologic ageing(51), composed of cardiovascular, lung, cognitive, metabolic, and
28
29 kidney function markers. In that study, HAI scores tended to increase with age (meaning worse
30
31 healthy ageing) and predicted mortality from a given time-point(51). Hence, composite
32
33 measures of ageing seem to be powerful tools to predict mortality and identify individuals at a
34
35 higher risk.
36
37
38
39
40
41

42 One of the main results from our study is that the association between COPD and risk of
43
44 mortality depended upon the HAT of the oldest participants (i.e., born ≤ 1935). Individuals with
45
46 COPD and a “low” trajectory of healthy ageing were more likely to die at the age of 75 years
47
48 old and from 81 to 87, compared with people with COPD and a “medium” or “high” HAT. The
49
50 healthy ageing scale covers several domains (vitality, sensory skills, mobility, cognition, and
51
52 ADL/IADL) and could negatively affect those patients with worse COPD symptoms(7–10). The
53
54 fact that these results were found only in the oldest sub-sample may be related to the course
55
56 of the disease since COPD is a progressive disease, and exacerbations and hospitalisations are
57
58 particularly common among older individuals(52). Our results point out temporary spaces
59
60

1
2
3 where older COPD patients with a “low” HAT are at higher risk of mortality. Thus, future
4
5 efforts should be concentrated on those aged 75 years old and from 81 to 87.
6
7

8 Few studies have analysed the relationship between health status in COPD patients to the best
9
10 of our knowledge. These studies were based on self-reported perceived health status assessed
11
12 through the SF-12 questionnaire, a generic instrument to evaluate physical and mental
13
14 health(53,54). The main finding in one of these studies that used data from the BOLD project
15
16 was that COPD severity was an important determinant of health status (more severity linked to
17
18 poorer health status)(53). Although these studies considered the health status of people with
19
20 COPD, we have not found any study that used a composite measure of healthy ageing as we
21
22 have done. An integrated measure assessing intrinsic capacity and functional ability could be a
23
24 useful tool in daily clinical practice for patient prognosis, as well as a mortality predictor, and
25
26 for the creation of future public health strategies addressing COPD patients’ needs(22). While
27
28 it is true that other composite tools to predict COPD mortality are available (such as St
29
30 George’s Respiratory Questionnaire(55), or the BODE index(56)), the healthy ageing scale is a
31
32 comprehensive tool that could be applied not only to COPD patients but also to patients with
33
34 multimorbidity.
35
36
37
38
39

40 *Strengths and limitations*

41
42 These findings should be interpreted in light of the following limitations. Firstly, the presence
43
44 or absence of COPD and NCDs was based on self-reported diagnostics. Thus they might be
45
46 affected by measurement errors. Nevertheless, some authors sustain self-reported diagnostics
47
48 as a well-established method for measuring NCDs in population-based studies(57). Secondly,
49
50 we made some assumptions in terms of age of diagnosis. Due to the high percentage of
51
52 missingness (48%) in the age of the first NCD diagnosis, we selected the age of the earliest
53
54 diagnosis of each NCD within the five waves. That is, we coded the age of the participant in the
55
56 wave he/she reported the first time having some of the included diseases. Despite being an
57
58
59
60

1
2
3 assumption, there are only two years between each wave in the SHARE study. Thus, we believe
4 that there is not a significant impact on our conclusions. Thirdly, we split the sample into three
5 birth cohorts when performing the analyses, and we reported the mortality risk in each group.
6
7 By doing so, we captured potential cohort effects which people from different birth cohorts
8 can be influenced by different exposure to COPD-related risk factors that contribute differently
9 to mortality, as the different trends in smoking prevalence. For each birth cohort, the survival
10 analysis can be focused according to the years of the interview or according to the age of the
11 participants. We finally decided to do it according to the age of the participants because
12 working with time-varying variables and without the assumption of proportional risks, the
13 fluctuations in mortality risk according to age could be better interpreted. However, this
14 introduces a problem of left truncation since the age range observed for each participant is
15 different, although we took this into account in the additive regression model. Fourthly,
16 another issue is that the age range observed for each birth cohort is also different so that the
17 excess cumulative risk curve starts at the first observed age. Therefore, the bias of the healthy
18 participant in the first wave of the study means that there is no significant excess risk in the
19 first ages of observation. Fifthly, we considered several variables that could affect mortality in
20 COPD patients, such as the presence of other NCDs, ever smoked, the practice of vigorous
21 physical activity and the role of healthy ageing trajectories on mortality risk. However, other
22 known factors with cumulative effects on COPD, such as long-term smoking and physical
23 activity or lung function data (52), were not available in the study. Thus we could not control
24 for their potential confounding effect. Alongside these limitations, this study had some
25 strengths. Firstly, the analyses were performed in different birth cohorts (>1945, 1936-1945,
26 and ≤ 1935) to assess differences in mortality risks related to societal changes, such as lifestyle
27 behaviours and occupation trends. Secondly, we used a novel measurement scale of healthy
28 ageing, including intrinsic capacity and functional ability variables. Compared with the use of
29 different health indicators separately, we believe that using an integrated and reliable
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 measure of health status is a powerful tool to predict the mortality risk of the participants.

4
5 Thirdly, the calculation of Aalen additive hazards models rather than Cox models allowed the
6
7 inclusion of time-variant variables in the analyses.
8
9

10 **Conclusion**

11
12 COPD is a costly and preventable disease that has large-scale implications for patients' quality
13
14 of life and society in general(58,59). Our findings suggest that the association between COPD
15
16 and the risk of mortality in the general population of middle-aged and older adults might be
17
18 explained by the presence of other risk factors. However, for older people with COPD (i.e.,
19
20 aged 69 or older), having a poor trajectory of healthy ageing might compromise their survival.
21
22 Especial attention should be paid to these patients, with the healthy ageing scale as a suitable
23
24 tool identifying older patients with COPD at high risk of mortality(21).
25
26
27
28

29 **Competing interests**

30 The authors declare no conflict of interest.

31 **Ethics statements**

32 **Patient consent for publication**

33 Not required.

34 **Ethics approval**

35
36 Ethical approvals for waves from 1 to 3 were granted by the Ethics Committee of the
37
38 University of Mannheim. For waves 4 and 5, the SHARE projects were reviewed and approved
39
40 by the Ethics Council of the Max-Planck Society. All data were anonymised and EHR
41
42 confidentially was respected in accordance with national and international law.
43
44
45
46
47
48

49 **Data sharing statement:** The original data of the Survey of Health, Ageing and Retirement in
50
51 Europe – SHARE is available on the official website ([http://www.share-](http://www.share-project.org/home0.html)
52
53 [project.org/home0.html](http://www.share-project.org/home0.html)). R codes for harmonising the healthy ageing scale is available on
54
55 <https://athlos.pssjd.org/study/share-hs>.
56
57
58
59
60

Funding

This work was supported by the five-year Ageing Trajectories of Health: Longitudinal Opportunities and Synergies (ATHLOS) project. The ATHLOS project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 635316. BO's work is supported by the Miguel Servet Program (CP20/00040), funded by Instituto de Salud Carlos III and co-funded by European Union (ERDF/ESF, "Investing in your future"). DF's work has been supported by Marsden grant E2987-3648 administered by the Royal Society of New Zealand) and by grant 2017 SGR 622 (GRBIO) administered by the Departament d'Economia i Coneixement de la Generalitat de Catalunya (Spain).

Acknowledgements

The SHARE study is funded by the European Commission through FP5 (QLK6-CT-2001-00360), FP6 (SHARE-I3: RII-CT-2006-062193, COMPARE: CIT5-CT-2005-028857, SHARELIFE: CIT4-CT-2006-028812) and FP7 (SHARE-PREP: N°211909, SHARE-LEAP: N°227822, SHARE M4: N°261982). Additional funding from the German Ministry of Education and Research, the Max Planck Society for the Advancement of Science, the U.S. National Institute on Aging (U01_AG09740-13S2, P01_AG005842, P01_AG08291, P30_AG12815, R21_AG025169, Y1-AG-4553-01, IAG_BSR06-11, OGHA_04-064, HHSN271201300071C) and from various national funding sources is gratefully acknowledged (see www.share-project.org).

Author contributions

IB: Participated in database management, drafted the paper, carried out the statistical analyses and worked on the interpretation of data. She also gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; **AS:** Participated in the study design, database management, carried out the statistical analyses, gave statistical support and critical revision of the paper. He also gave final approval of the version to be published and agreed to be accountable for all aspects

1
2
3 of the work in ensuring that questions related to the accuracy or integrity of any part of the
4
5 work are appropriately investigated and resolved; **DF:** Participated in the statistical support
6
7 and critical revision of the paper. He also gave final approval of the version to be published and
8
9 agreed to be accountable for all aspects of the work in ensuring that questions related to the
10
11 accuracy or integrity of any part of the work are appropriately investigated and resolved; **JMH:**
12
13 Participated in the acquisition of data, and critical revision of the paper. He also gave final
14
15 approval of the version to be published and agreed to be accountable for all aspects of the
16
17 work in ensuring that questions related to the accuracy or integrity of any part of the work are
18
19 appropriately investigated and resolved; **BO:** Participated in the critical revision of the paper.
20
21 She also gave final approval of the version to be published and agreed to be accountable for all
22
23 aspects of the work in ensuring that questions related to the accuracy or integrity of any part
24
25 of the work are appropriately investigated and resolved.
26
27
28
29
30

31 **References**

- 32 1. Miniati M, Monti S, Pavlickova I, Bottai M. Survival in COPD: impact of lung dysfunction
33 and comorbidities. *Med*. 2014;93(12):e76.
- 34 2. Okely JA, Shaheen SO, Weiss A, Gale CR. Wellbeing and chronic lung disease incidence:
35 the Survey of Health, Ageing and Retirement in Europe. Leroyer C, editor. *PLoS One*
36 [Internet]. 2017 Jul 20 [cited 2020 May 19];12(7):e0181320. Available from:
37 <https://dx.plos.org/10.1371/journal.pone.0181320>
- 38 3. World Health Organization. World Health Statistics 2008 [Internet]. 2008 [cited 2020
39 May 20]. Available from:
40 https://www.who.int/whosis/whostat/EN_WHS08_Full.pdf?ua=1
- 41 4. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al.
42 International variation in the prevalence of COPD (The BOLD Study): a population-based
43 prevalence study. *Lancet*. 2007 Sep 1;370(9589):741–50.
- 44 5. Duan R-R, Hao K, Yang T. Air pollution and chronic obstructive pulmonary disease.
45 *Chronic Dis Transl Med*. 2020 Dec 1;6(4):260–9.
- 46 6. Rosenberg SR, Kalhan R, Mannino DM. Epidemiology of chronic obstructive pulmonary
47 disease: prevalence, morbidity, mortality, and risk factors. *Semin Respir Crit Care Med*.
48 2015 Aug 5;36(4):457–69.
- 49 7. Bourbeau J. Activities of Life: the COPD patient. *COPD*. 2009;6(3):192–200.
- 50 8. Barusso MS, Gianjeppe-Santos J, Basso-Vanelli RP, Regueiro EM, Panin JC, Lorenzo VAP
51 Di. Limitation of activities of daily living and quality of life based on COPD combined
52 classification. *Respir Care*. 2015 Mar 1;60(3):388–98.
- 53
54
55
56
57
58
59
60

- 1
2
3 9. Medina-Mirapeix F, Bernabeu-Mora R, Piedad Sánchez-Martínez M, Montilla-Herrador
4 J, Bernabeu-Mora M, Escolar-Reina P. Mobility limitations related to reduced
5 pulmonary function among aging people with chronic obstructive pulmonary disease.
6 *PLoS One*. 2018 May 1;13(5):e0196152.
- 7
8 10. Dodd JW. Lung disease as a determinant of cognitive decline and dementia. *Alzheimer's*
9 *Res Ther*. 2015;7(1):1–8.
- 10
11 11. Eroglu SA, Gunen H, Yakar HI, Yildiz E, Kavaz M, Duman D. Influence of comorbidities in
12 long-term survival of chronic obstructive pulmonary disease patients. *J Thorac Dis*. 2019
13 Apr 1;11(4):1379–86.
- 14
15 12. Blanco I, Diego I, Bueno P, Fernández E, Casas-Maldonado F, Esquinas C, et al.
16 Geographical distribution of COPD prevalence in Europe, estimated by an inverse
17 distance weighting interpolation technique. *Int J Chron Obs Pulmon Dis [Internet]*. 2017
18 [cited 2020 Dec 9];13:57–67. Available from:
19 /pmc/articles/PMC5743112/?report=abstract
- 20
21 13. Menezes AMB, Perez-Padilla R, Jardim JRB, Muiño A, Lopez MV, Valdivia G, et al.
22 Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO
23 study): A prevalence study. *Lancet*. 2005 Nov 26;366(9500):1875–81.
- 24
25 14. Blanco I, Diego I, Bueno P, Fernández E, Casas-Maldonado F, Esquinas C, et al.
26 Geographical distribution of COPD prevalence in Europe, estimated by an inverse
27 distance weighting interpolation technique. *Int J Chron Obs Pulmon Dis*. 2017;13:57–
28 67.
- 29
30 15. Nowak D, Berger K, Lippert B, Kilgert K, Caeser M, Sandtmann R. Epidemiology and
31 health economics of COPD across Europe: A critical analysis. Vol. 4, *Treatments in*
32 *Respiratory Medicine*. *Treat Respir Med*; 2005. p. 381–95.
- 33
34 16. Lortet-Tieulent J, Soerjomataram I, López-Campos JL, Coebergh JW, Ancochea J, Soriano
35 JB. International trends in COPD mortality, 1995-2017. *Eur Respir J*. 2019 Dec
36 1;54(6):1901791.
- 37
38 17. Davies Adeloye, Stephen Chua, Chinwei Lee, Catriona Basquill, Angeliki Papan, Evropi
39 Theodoratou, Harish Nair, Danijela Gasevic, Devi Sridhar, Harry Campbell, Kit Yee Chan,
40 Aziz Sheikh, Igor Rudan and GHERG (GHERG). Global and regional estimates of COPD
41 prevalence: Systematic review and meta-analysis. *J Glob Health*. 2015;5(2):020415.
- 42
43 18. Pinto-Plata VM, Cote C, Cabral H, Taylor J, Celli BR. The 6-min walk distance: Change
44 over time and value as a predictor of survival in severe COPD. *Eur Respir J [Internet]*.
45 2004 Jan [cited 2021 Jan 8];23(1):28–33. Available from:
46 <https://pubmed.ncbi.nlm.nih.gov/14738227/>
- 47
48 19. Spruit MA, Polkey MI, Celli B, Edwards LD, Watkins ML, Pinto-Plata V, et al. Predicting
49 Outcomes from 6-Minute Walk Distance in Chronic Obstructive Pulmonary Disease. *J*
50 *Am Med Dir Assoc [Internet]*. 2012 [cited 2021 Jan 8];13(3):291–7. Available from:
51 <https://pubmed.ncbi.nlm.nih.gov/21778120/>
- 52
53 20. Puhan MA, Garcia-Aymerich J, Frey M, ter Riet G, Antó JM, Agustí AG, et al. Expansion
54 of the prognostic assessment of patients with chronic obstructive pulmonary disease:
55 the updated BODE index and the ADO index. *Lancet [Internet]*. 2009 Sep 4 [cited 2021
56 Jan 8];374(9691):704–11. Available from: <https://pubmed.ncbi.nlm.nih.gov/19716962/>
- 57
58 21. Puhan MA, Siebeling L, Zoller M, Muggensturm P, Riet G Ter. Simple functional
59
60

- 1
2
3 performance tests and mortality in COPD. *Eur Respir J* [Internet]. 2013 Oct 1 [cited 2021
4 Jan 8];42(4):956–63. Available from: <http://ow.ly/mxrPx>
5
- 6 22. Sanchez-Niubo A, Forero CG, Wu Y-T, Giné-Vázquez I, Prina M, De La Fuente J, et al.
7 Development of a common scale for measuring healthy ageing across the world: results
8 from the ATHLOS consortium. *Int J Epidemiol* [Internet]. 2020 Dec 4 [cited 2020 Dec
9 5];49(6):1–13. Available from: [https://academic.oup.com/ije/advance-](https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa236/6020095)
10 [article/doi/10.1093/ije/dyaa236/6020095](https://academic.oup.com/ije/advance-article/doi/10.1093/ije/dyaa236/6020095)
11
- 12 23. Bui KL, Nyberg A, Maltais F, Saey D. Functional tests in chronic obstructive pulmonary
13 disease, Part 1: Clinical relevance and links to the international classification of
14 functioning, disability, and health. In: *Annals of the American Thoracic Society*
15 [Internet]. American Thoracic Society; 2017 [cited 2021 Jan 8]. p. 778–84. Available
16 from: <http://www.atsjournals.org/doi/10.1513/AnnalsATS.201609-733AS>
17
- 18 24. Sanchez-Niubo A, Egea-Cortés L, Olaya B, Caballero FF, Ayuso-Mateos JL, Prina M, et al.
19 Cohort profile: the ageing trajectories of health - longitudinal opportunities and
20 synergies (ATHLOS) project. *Int J Epidemiol*. 2019;48(4):1052-1053i.
21
- 22 25. Börsch-Supan A, Brandt M, Hunkler C, Kneip T, Korbmacher J, Malter F, et al. Data
23 resource profile: The survey of health, ageing and retirement in europe (SHARE). *Int J*
24 *Epidemiol*. 2013;42(4):992–1001.
25
- 26 26. Bergmann, Michael; Kneip, Thorsten; De Luca, Giuseppe; Scherpenzeel A. Survey
27 Participation in the Survey of Health, Ageing and Retirement in Europe (SHARE), Wave
28 1-6. Based on Release 6.0.0 (March 2017). Munich: Munich Center for the Economics of
29 Aging (MEA); 2017.
30
- 31 27. Wolfrum R. Opinion of the ethics council of the Max Planck society on the “SHARE”
32 project [Internet]. 2016. Available from: [http://www.share-](http://www.share-project.org/fileadmin/pdf_documentation/SHARE_ethics_approvals.pdf)
33 [project.org/fileadmin/pdf_documentation/SHARE_ethics_approvals.pdf](http://www.share-project.org/fileadmin/pdf_documentation/SHARE_ethics_approvals.pdf)
34
- 35 28. Bergmann, M. Kneip, T., De Luca, G., & Scherpenzeel A. Survey participation in the
36 Survey of Health, Ageing and Retirement in Europe (SHARE), Wave 1-7. Based on
37 Release 7.0.0. Munich: SHARE-ERIC; 2019.
38
- 39 29. Sanchez-Niubo A, Egea-Cortés L, Olaya B, Caballero FF, Ayuso-Mateos JL, Prina M, et al.
40 Cohort Profile: The Ageing Trajectories of Health - Longitudinal Opportunities and
41 Synergies (ATHLOS) project. *Int J Epidemiol*. 2019 Aug 1;48(4):1052-1053i.
42
- 43 30. World Health Organization. World report on ageing and health 2015 [Internet]. 2015
44 [cited 2020 Jul 27]. Available from: [https://www.who.int/ageing/events/world-report-](https://www.who.int/ageing/events/world-report-2015-launch/en/)
45 [2015-launch/en/](https://www.who.int/ageing/events/world-report-2015-launch/en/)
46
- 47 31. Berlin KS, Parra GR, Williams NA. An Introduction to Latent Variable Mixture Modeling
48 (Part 2): Longitudinal Latent Class Growth Analysis and Growth Mixture Models. *J*
49 *Pediatr Psychol*. 2014 Mar 1;39(2):188–203.
50
- 51 32. Reischies F, Lobo A, Turrina C, Jonker C, Fuhrer R, Fichter M, et al. Development of the
52 EURO-D scale – a European Union initiative to compare symptoms of depression in 14
53 European centres. *Br J Psychiatry*. 2008;174(04):330–8.
54
- 55 33. Copeland JRM, Beekman ATF, Dewey ME, Hooijer C, Jordan A, Lawlor BA, et al.
56 Depression in Europe. Geographical distribution among older people. *Br J Psychiatry*
57 [Internet]. 1999 [cited 2020 Dec 2];174(APR.):312–21. Available from:
58 <https://pubmed.ncbi.nlm.nih.gov/10533550/>
59
60

- 1
- 2
- 3 34. WHO. Country groupings [Internet]. Available from:
4 https://www.who.int/quantifying_ehimpacts/global/ebdcountgroup/en/ (7 February
5 2019, date last accessed)
6
- 7 35. United Nations Statistical Division (UNSD). Countries or areas/geographical regions
8 [Internet]. Available from: <https://unstats.un.org/unsd/methodology/m49/> (7 February
9 2019, date last accessed)
10
- 11 36. Tein JY, Coxe S, Cham H. Statistical power to detect the correct number of classes in
12 latent profile analysis. *Struct Equ Model*. 2013;20(4):640–57.
13
- 14 37. Nylund-Gibson K, Choi AY. Ten frequently asked questions about latent class analysis.
15 *Transl Issues Psychol Sci*. 2018;4(4):440–61.
16
- 17 38. Aalen O. A Model for Nonparametric Regression Analysis of Counting Processes. In
18 Springer, New York, NY; 1980 [cited 2020 Dec 5]. p. 1–25. Available from:
19 https://link.springer.com/chapter/10.1007/978-1-4615-7397-5_1
20
- 21 39. Aalen OO. A linear regression model for the analysis of life times. *Stat Med* [Internet].
22 1989 [cited 2020 Dec 5];8(8):907–25. Available from:
23 <https://pubmed.ncbi.nlm.nih.gov/2678347/>
24
- 25 40. O. O. Aalen; O. Borgan; H. K. Gjessing. *Survival and event history analysis: a process
26 point of view*. Springer. New York; 2008.
27
- 28 41. Xie X, Strickler HD, Xue X. Additive hazard regression models: An application to the
29 natural history of human papillomavirus. Vol. 2013, *Computational and Mathematical
30 Methods in Medicine*. 2013.
31
- 32 42. Aalen OO, Scheike TH. Aalen’s Additive Regression Model. In: *Encyclopedia of
33 Biostatistics* [Internet]. Chichester, UK: John Wiley & Sons, Ltd; 2005 [cited 2021 Feb 2].
34 Available from: <http://doi.wiley.com/10.1002/0470011815.b2a11002>
35
- 36 43. Team RC. R: A language and environment for statistical computing [Internet]. Vienna,
37 Austria: R Foundation for Statistical Computing; 2020. Available from: [https://www.r-
38 project.org/](https://www.r-project.org/)
39
- 40 44. Lewis DR, Clegg LX, Johnson NJ. Lung disease mortality in the United States: the
41 National Longitudinal Mortality Study. *Int J Tuberc Lung Dis* [Internet]. 2009 Aug [cited
42 2021 Feb 4];13(8):1008–14. Available from:
43 </pmc/articles/PMC2765862/?report=abstract>
44
- 45 45. Manfreda J, Mao Y, Litven W. Morbidity and mortality from chronic obstructive
46 pulmonary disease. *Am Rev Respir Dis* [Internet]. 1989 [cited 2021 Jan 20];140(3):16–
47 26. Available from: <https://pubmed.ncbi.nlm.nih.gov/2782756/>
48
- 49 46. Ntritsos G, Franek J, Belbasis L, Christou MA, Markozannes G, Altman P, et al. Gender-
50 specific estimates of COPD prevalence: a systematic review and meta-analysis. *Int J
51 Chron Obstruct Pulmon Dis* [Internet]. 2018 May 10 [cited 2020 Dec 9];13:1507–14.
52 Available from: </pmc/articles/PMC5953270/?report=abstract>
53
- 54 47. Hummer RA, Hernandez EM. The effect of educational attainment on adult mortality in
55 the United States. *Popul Bull* [Internet]. 2013 Jun [cited 2020 Dec 9];68(1):1–16.
56 Available from: <http://www.ncbi.nlm.nih.gov/pubmed/25995521>
57
- 58 48. OECD/European Union. Mortality from respiratory diseases. In: OECD Publishing, editor.
59 *Health at a Glance: Europe 2018: State of Health in the EU Cycle*. Paris/European Union,
60

- Brussels; 2018.
49. Lange P, Tøttenborg SS, Sorknæs AD, Andersen JS, Sjøgaard M, Nielsen H, et al. Danish register of chronic obstructive pulmonary disease. *Clin Epidemiol* [Internet]. 2016 Oct 25 [cited 2020 Dec 9];8:673–8. Available from: [/pmc/articles/PMC5094652/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/29733331/)
 50. Camozzato AL, Godinho C, Chaves MLF. Effect of successful aging on mortality in older individuals: the PALA study. *Dement e Neuropsychol* [Internet]. 2014 [cited 2021 Feb 4];8(2):182–6. Available from: [/pmc/articles/PMC5619127/?report=abstract](https://pubmed.ncbi.nlm.nih.gov/12010839/)
 51. O’Connell MDL, Marron MM, Boudreau RM, Canney M, Sanders JL, Kenny RA, et al. Mortality in relation to changes in a healthy aging index: the Health, Aging, and Body Composition Study. *Journals Gerontol - Ser A Biol Sci Med Sci* [Internet]. 2019 May 1 [cited 2021 Feb 4];74(5):726–32. Available from: <https://pubmed.ncbi.nlm.nih.gov/29733331/>
 52. Mannino DM. COPD: epidemiology, prevalence, morbidity and mortality, and disease heterogeneity. *Chest* [Internet]. 2002 [cited 2021 Feb 4];121(5):121–6. Available from: <https://pubmed.ncbi.nlm.nih.gov/12010839/>
 53. Janson C, Marks G, Buist S, Gnatiuc L, Gislason T, McBurnie MA, et al. The impact of COPD on health status: Findings from the BOLD study. *Eur Respir J* [Internet]. 2013 Dec 1 [cited 2021 Feb 4];42(6):1472–83. Available from: <http://ow.ly/p1clxwww.erj.ersjournals.com>
 54. López Varela MV, Montes de Oca M, Halbert R, Muiño A, Tálamo C, Pérez-Padilla R, et al. Comorbidities and Health Status in Individuals With and Without COPD in Five Latin American Cities: The PLATINO Study. *Arch Bronconeumol* [Internet]. 2013 Nov 1 [cited 2021 Feb 4];49(11):468–74. Available from: <https://www.archbronconeumol.org/en-comorbidities-health-status-in-individuals-articulo-S1579212913001729>
 55. Jones PW, Quirk FH, Baveystock CM. The St George’s Respiratory Questionnaire. *Respir Med* [Internet]. 1991 [cited 2021 Jan 20];85:25–31. Available from: <https://pubmed.ncbi.nlm.nih.gov/1759018/>
 56. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, et al. The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease. *N Engl J Med* [Internet]. 2004 Mar 4 [cited 2021 Jan 20];350(10):1005–12. Available from: <https://pubmed.ncbi.nlm.nih.gov/14999112/>
 57. Huntley AL, Johnson R, Purdy S, Valderas JM, Salisbury C. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. *Ann Fam Med* [Internet]. 2012;10(2):134–41. Available from: <https://www.samsungrecycle.co.uk/>
 58. Chapmann KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ, et al. Epidemiology and costs of chronic obstructive pulmonary disease [Internet]. Vol. 27, *European Respiratory Journal*. European Respiratory Society; 2006 [cited 2020 Dec 9]. p. 188–207. Available from: <https://erj.ersjournals.com/content/27/1/188>
 59. Quaderi SA, Hurst JR. The unmet global burden of COPD [Internet]. Vol. 3, *Global Health, Epidemiology and Genomics*. Cambridge University Press; 2018 [cited 2020 Dec 9]. p. 1–3. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5921960/>

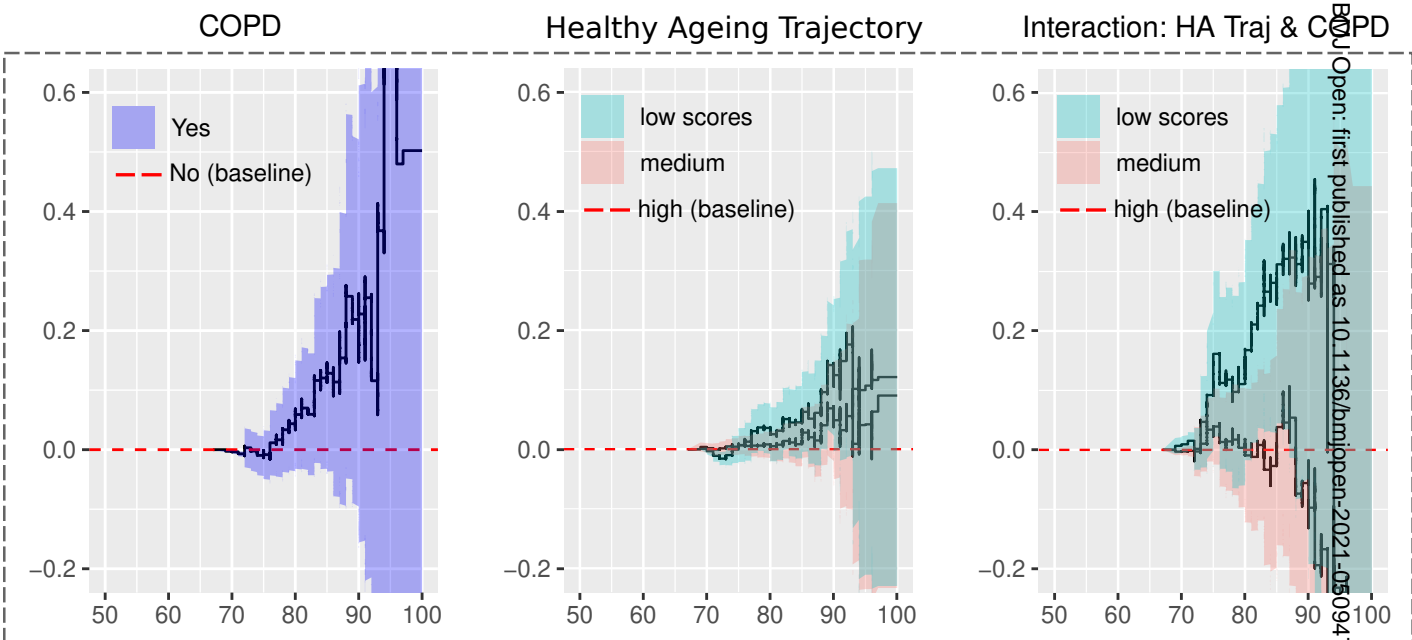
1
2
3
4
5
6
7
8 **Figure 1.** Cumulative excess risk of mortality associated with COPD, HAT by birth cohort and
9 their interaction in the oldest birth cohort.

10
11 **Note:** All models were adjusted by sex, education, wealth, marital status, region, depression,
12 diabetes, hypertension, joint disorders, asthma, myocardial infarction, and stroke.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

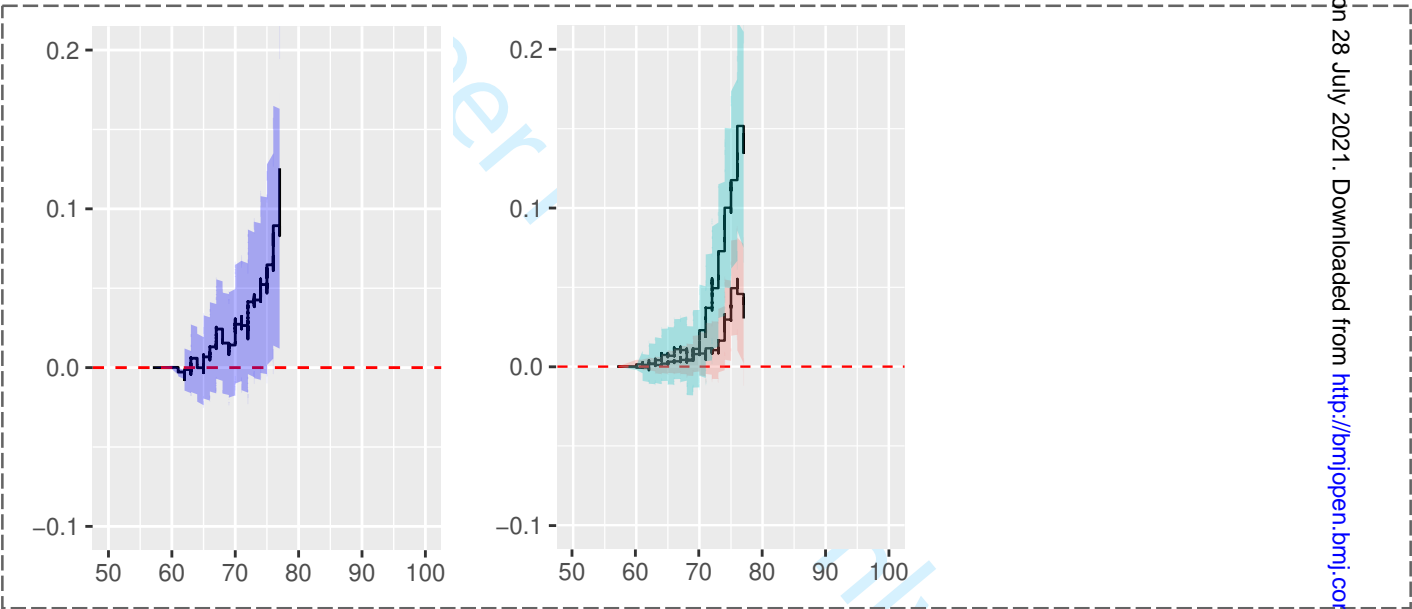
For peer review only

Models adjusted by sex, education, income, wealth, marital status, region, depression, diabetes, hypertension, joint disorders, asthma, myocardial infarction, and stroke:

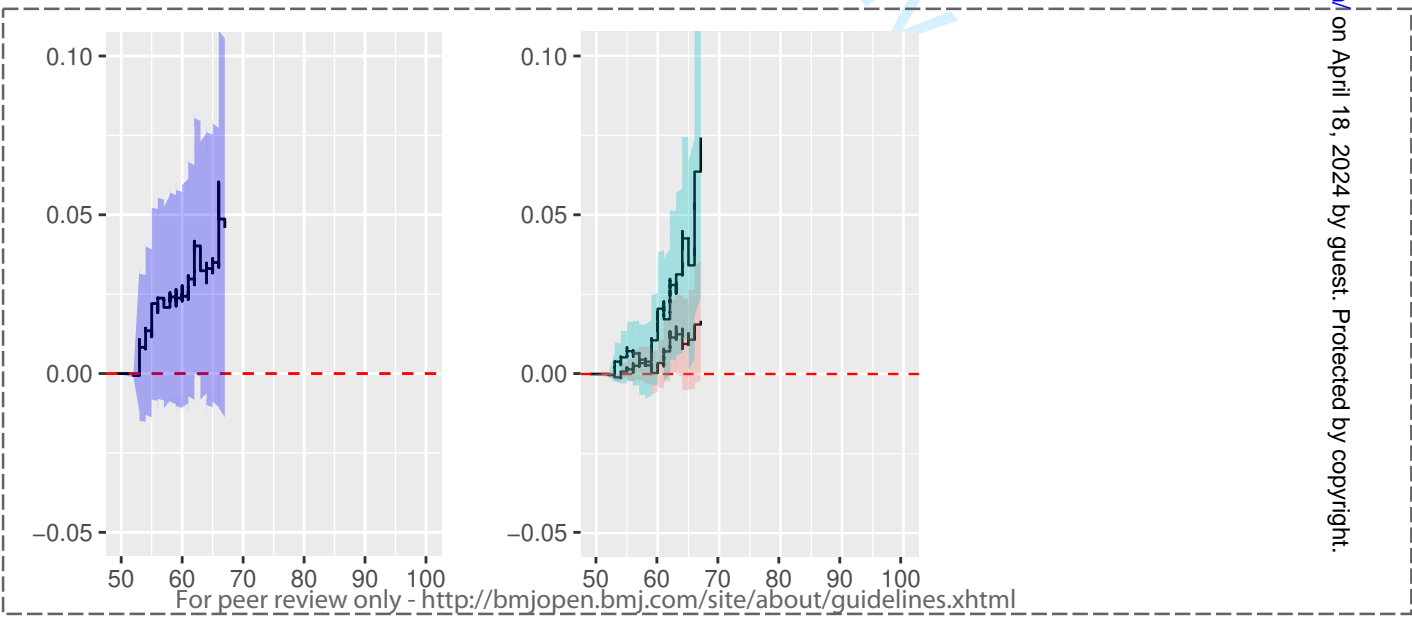
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22



23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41



42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60



Open: first published as 10.1136/bmjopen-2021-0250947 on 28 July 2021. Downloaded from <http://bmjopen.bmj.com/> on April 18, 2024 by guest. Protected by copyright.

Supplemental material

Supplementary Table 1. Harmonised items of the healthy ageing scale in the SHARE study

ATHLOS harmonized variables		SHARE	
Memory	Self-reported ratings of memory at the time of the interview	Label	A4-B3 Memory self-rating
		Values	1 = None; 2 = Mild; 3 = Moderate; 4 = Severe; 5 = Extreme
		Harmonisation	1 = Absence; 2-5 = Presence
Immediate recall	Immediate recall of common nouns from a list	Label	ten words list learning first trial total
		Values	Continuous Variable 0-10
		Harmonisation	<=25% into Presence >25% into Absence
Delayed recall	Test that assesses delayed recall using the common nouns from the list previously employed for measuring Immediate recall	Label	ten words list learning delayed recall total
		Values	Continuous Variable 0-10
		Harmonisation	<=25% into Presence >25% into Absence
Verbal fluency†	Test that assesses verbal (semantic) fluency	Label	verbal fluency score
		Values	Continuous Variable 0-88
		Harmonisation	<=25% into Presence >25% into Absence
Orientation in time	Difficulties for orientation in time, evaluated by a set of questions about the date and day of the week	Label	orientation to date, month, year and day of week
		Values	0-3 = bad; 4 = good
		Harmonisation	4 = Absence; 0-3 = Presence
Numeracy		Label	cf012_ : Chance disease 10 perc. of 1000 cf013_ : Half price [of a 300 Euro sofa] cf014_ : 6000 is two-thirds what is total price cf015_ : Amount in the savings account [on 2000 Euros after 2 years of 10% interest]
		Values	All: 1 = correct answer: 100; 2 = wrong answer: 10; 3 = wrong answer: 90; 4 = wrong answer: 900; 97 = wrong answer: Other answer keep 1 into 1; recode -1, 2, 3, 4, 5, 6 and 97 into 0
		Harmonisation	All 1 = Absence; Some 0 = Presence
Sleeping	Sleeping problems	Label	sleep (part of EURO-D)
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Pain	It measures if the participant experiences some degree of pain or if the participant does not present any pain at all	Label	bothered by: pain in back, knees, hips or other joint
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Energy	Self-reported high level of energy experienced at the time of the interview	Label	fatigue
		Values	1 = Yes; 5 = No
		Harmonisation	5 = Absence; 1 = Presence
		Label	bothered by: incontinence

Urine incontinence	It measures if the participant has experienced loss of urine (or has used any special device for urine leakage)	Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Near vision	Difficulties for near vision	Label	eyesight reading
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor
		Harmonisation	1-3 = Absence; 4-5 = Presence
Far vision	Difficulties for far vision	Label	eyesight distance
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor
		Harmonisation	1-3 = Absence; 4-5 = Presence
Eyesight	Difficulties in eye sight using glasses or corrective lens as usual	Label	Is your eyesight (using glasses or contact lens if you use them)
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor; 6 = registered or legally blind
		Harmonisation	1-3 = Absence; 4-6 = Presence
Hearing in general	It measures if the participant experiences some difficulty for hearing (i.e., hearing someone talking on the other side of the room in a normal voice) or not, using a hearing aid as usual	Label	hearing
		Values	1 = excellent; 2 = very good; 3 = good; 4 = fair; 5 = poor
		Harmonisation	1-3 = Absence; 4-5 = Presence
Hearing in a conversation	It measures if the participant experiences some difficulty (including total disability) for following a conversation (i.e., if there is a background noise, or several people talking) or not, using a hearing aid as usual	Label	hearing with one person
		Values	1 = Yes; 5 = No
		Harmonisation	1 = Absence; 0 = Presence
Stooping, kneeling or crouching	Difficulty for stooping, kneeling or crouching	Label	difficulties: stooping, kneeling, crouching
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Lifting or carrying weights	Difficulty for lifting or carrying weights	Label	difficulties: lifting or carrying weights over 5 kilos
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Climbing stairs	Difficulty for climbing stairs	Label	difficulties: climbing one flight of stairs
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Getting up	Difficulty for getting up from sitting down	Label	difficulties: getting up from chair
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Walking	Difficulty for walking by yourself and without using any special equipment	Label	difficulties: walking 100 metres
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Pulling or pushing	Difficulty for pulling or pushing large objects	Label	difficulties: pulling or pushing large objects
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Sitting	Difficulty for sitting for long periods	Label	difficulties: sitting two hours
		Values	0 = Not selected; 1 = Selected

		Harmonisation	0 = Absence; 1 = Presence
Reaching or extending arms	Difficulty for reaching / extending arms	Label	difficulties: reaching or extending arms above shoulder
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Walking speed	It is measured assessing the time that is taken to walk a distance	Label	walking speed
		Values	Continuous
		Harmonisation	<=25% into Presence >25% into Absence
Dizziness	Dizziness problems when walking on a level surface	Label	bothered by: dizziness, faints or blackouts
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Picking up	Difficulty for picking up things with fingers, e.g. picking up a coin	Label	difficulties: picking up a small coin from a table
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Getting in or out of bed	Difficulty for getting in or out of bed	Label	difficulties: getting in or out of bed
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Bathing or showering	Difficulties for bathing or showering	Label	difficulties: bathing or showering
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Getting dressed	Difficulty for getting dressed	Label	difficulties: dressing, including shoes and socks
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Moving around the home	Difficulty for moving around the home	Label	difficulties: walking across a room
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Toilet	Difficulties for using the toilet	Label	difficulties: using the toilet, incl getting up or down
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Eating	Difficulties for eating	Label	difficulties: eating, cutting up food
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Housework	Difficulties for doing housework	Label	difficulties: doing work around the house or garden
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Shopping	Difficulties for shopping groceries	Label	difficulties: shopping for groceries
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Meals	Difficulties in preparing meals	Label	difficulties: preparing a hot meal
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Map	Difficulties for using a map	Label	difficulties: using a map in a strange place
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Money	Difficulties for managing money, bills, or expenses	Label	difficulties: managing money
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
Medications	Difficulties for taking medications	Label	difficulties: taking medications

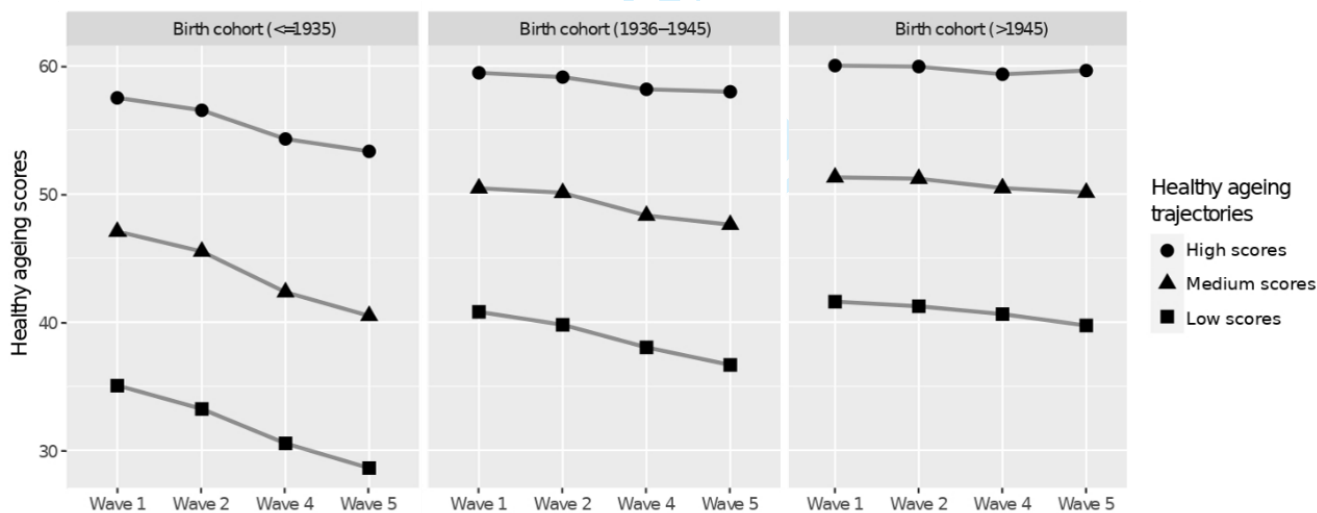
		Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence
		Label	difficulties: telephone calls
Telephone	Difficulties for using telephone	Values	0 = Not selected; 1 = Selected
		Harmonisation	0 = Absence; 1 = Presence

For peer review only

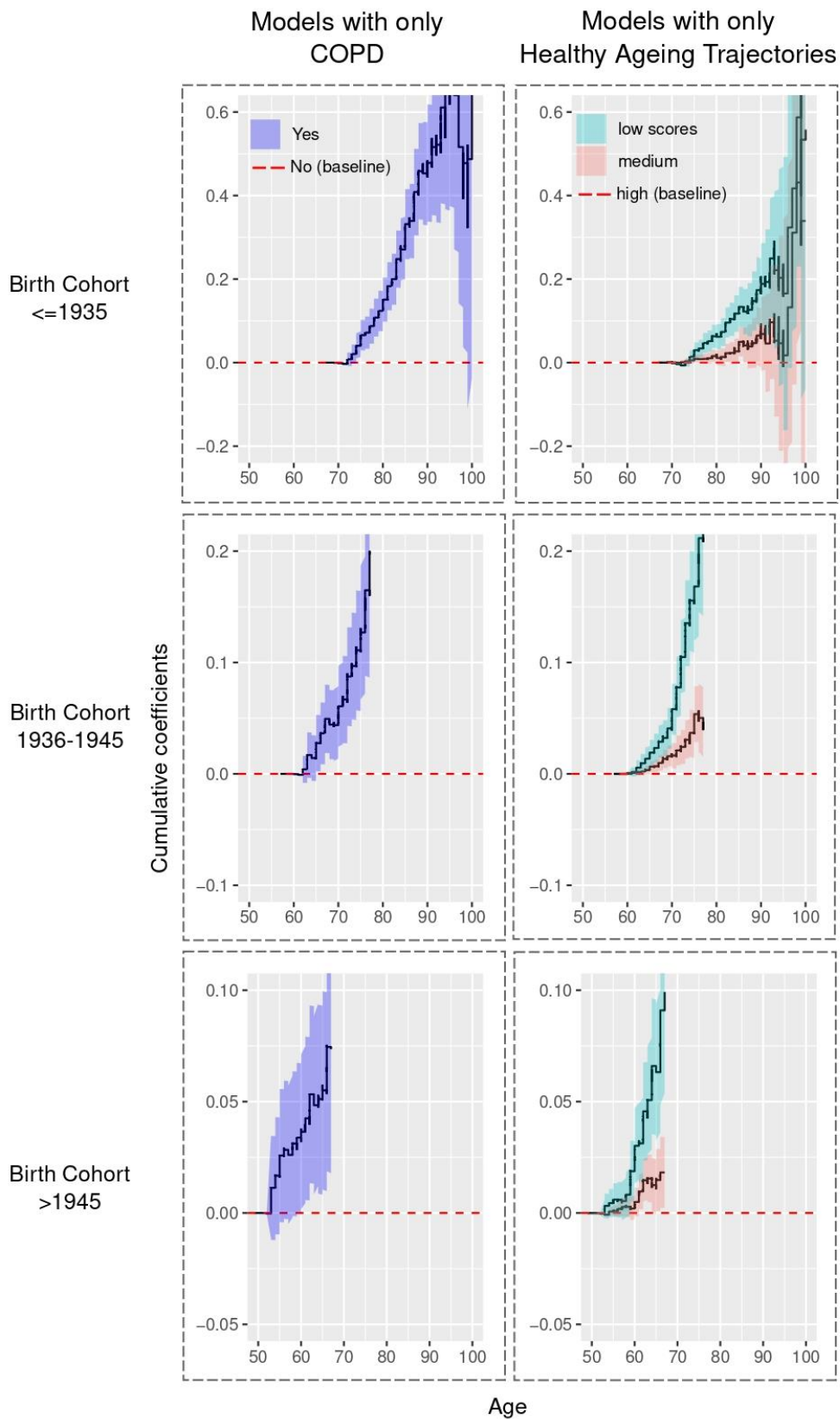
Supplementary Table 2. Results from the latent class growth analysis models for the three birth cohorts

≤1935								
No. of classes	Loglik	npm	BIC	% class 1	% class 2	% class 3	% class 4	% class 5
1	-83923.67	3	167875.0	100.00				
2	-80924.65	6	161904.6	51.39	48.60			
3	-79920.76	9	159924.4	20.21	31.38	48.39		
4	-79545.29	12	159201.1	7.37	32.59	23.22	36.80	
5	-79429.36	15	158996.8	31.64	23.08	1.31	7.19	36.76
1936 – 1945								
No. of classes	Loglik	npm	BIC	% class 1	% class 2	% class 3	% class 4	% class 5
1	-86218.80	3	172465.1	100.00				
2	-82811.31	6	165677.6	66.84	33.15			
3	-81877.93	9	163838.3	49.72	12.44	37.83		
4	-81611.24	12	163332.3	43.55	35.79	2.38	18.26	
5	-81540.03	15	163217.4	33.21	12.13	24.67	28.00	1.97
>1945								
No. of classes	Loglik	npm	BIC	% class 1	% class 2	% class 3	% class 4	% class 5
1	-89325.74	3	178679.1	100.00				
2	-85721.95	6	171499.2	23.37	76.62			
3	-84856.16	9	169795.3	8.75	30.81	60.43		
4	-84608.23	12	169327.1	30.97	53.19	13.34	2.47	
5	-84607.84	15	169354.0	2.39	13.17	32.36	52.02	0.02

Supplementary Figure 1. Trajectories of healthy ageing among birth cohorts



Supplementary Figure 2. Estimates of cumulative excess of risk of COPD and healthy ageing trajectories, separately by using the Aalen’s additive regression



Supplementary Figure 3.

Figure 3.1. Estimates of cumulative excess risk of covariates from the Aalen's additive regression model by >1945 birth cohort sub-sample.

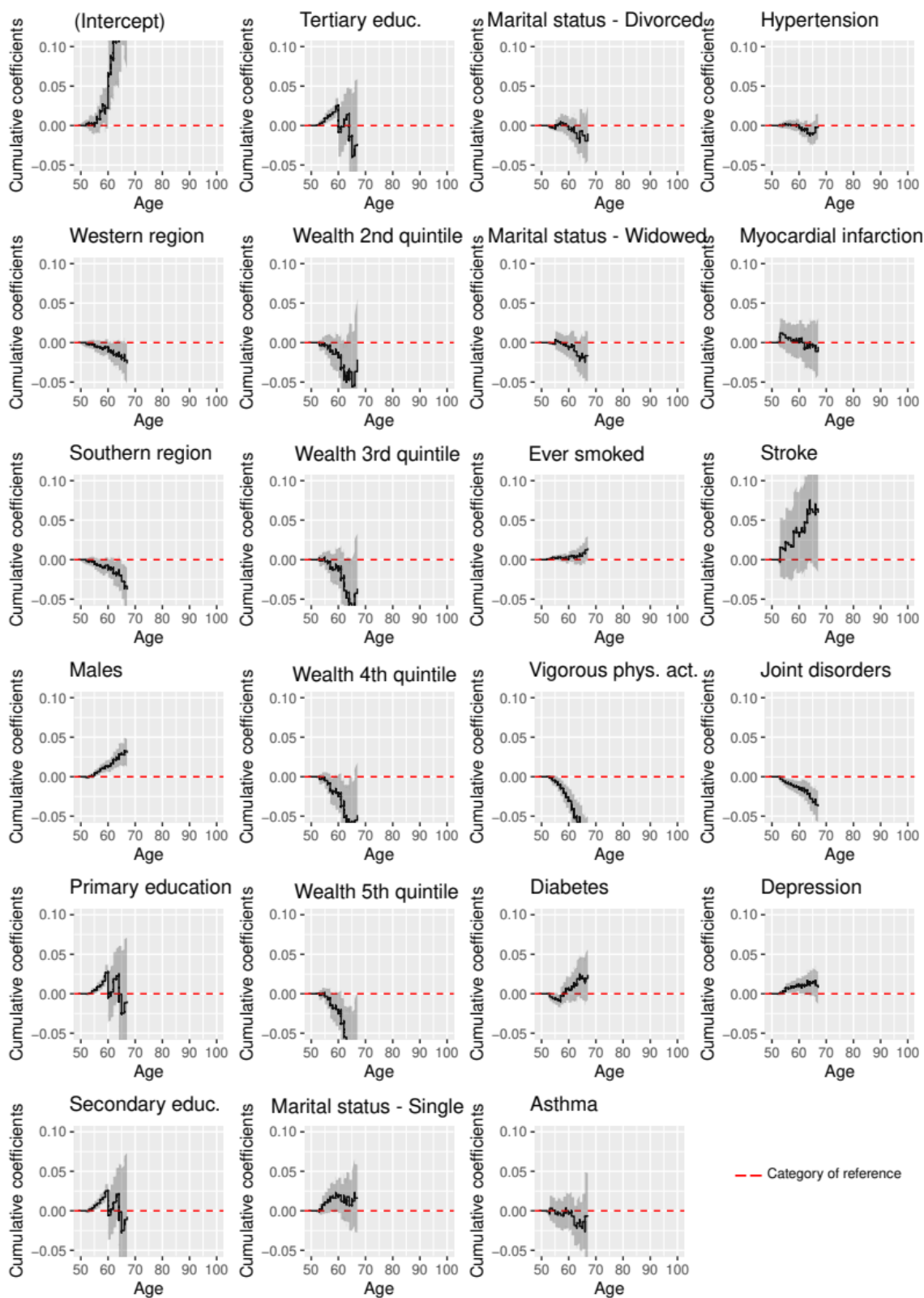


Figure 3.2. Estimates of cumulative excess risk of covariates from the Aalen’s additive regression model by 1936-1945 birth cohort sub-sample.

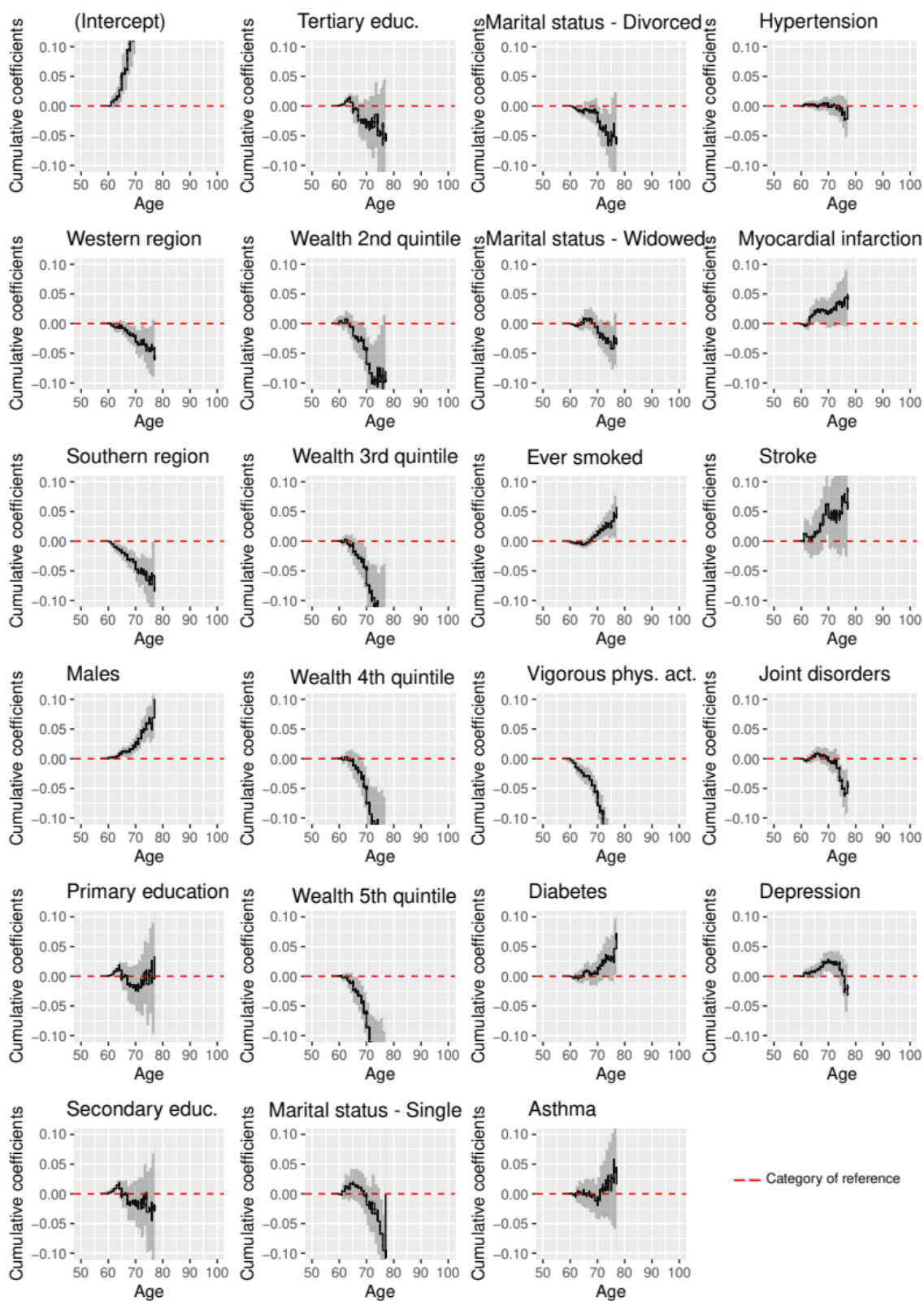
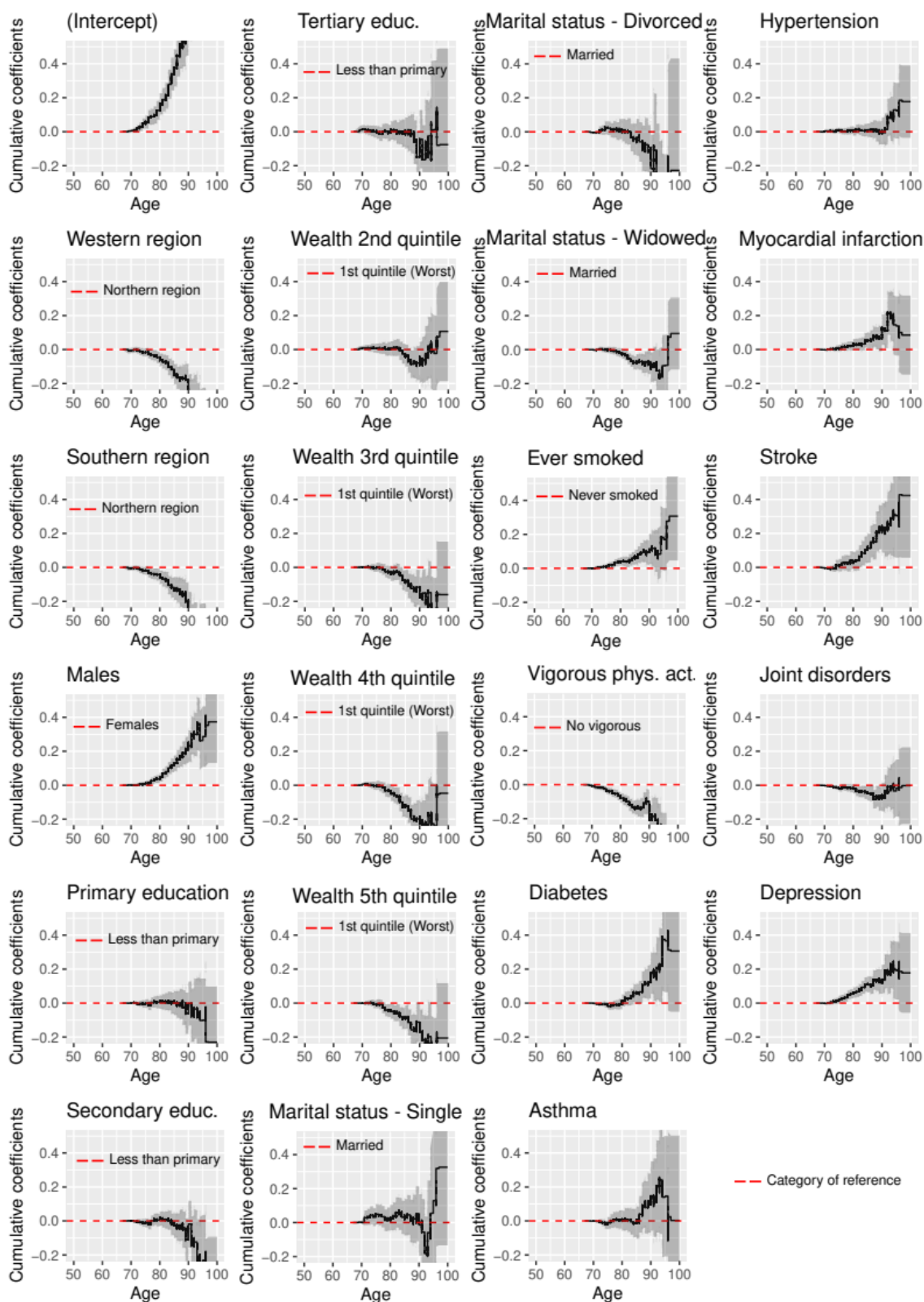


Figure 3.3. Estimates of cumulative excess risk of covariates from the Aalen’s additive regression model by ≤ 1935 birth cohort sub-sample.



STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-6
Objectives	3	State specific objectives, including any prespecified hypotheses	5-6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-9
Bias	9	Describe any efforts to address potential sources of bias	7-10
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	9-10
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	6-7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	10-11
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
4				
5				
6				
7				
8				
9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplemental material
10				
11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	17-18
14	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
15				
16	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-18
17				
18				
19	Generalisability	21	Discuss the generalisability (external validity) of the study results	17-18
20				
21	Other information			
22	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18
23				
24				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.