

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

Physical activity and comorbidities affect all-cause mortality in a cohort of middle-aged adults with incident asthma

| | |
|-------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2021-049243 |
| Article Type: | Original research |
| Date Submitted by the Author: | 04-Feb-2021 |
| Complete List of Authors: | Tupper, Oliver Djurhuus; Hvidovre Hospital, Department of Respiratory Medicine Andersen, ZJ; University of Copenhagen Department of Public Health, Section of Environmental Health Ulrik, Charlotte; Hvidovre Hospital, Department of Respiratory Medicine |
| Keywords: | Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, Adult thoracic medicine < THORACIC MEDICINE |
| | |

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 **Physical activity and comorbidities affect all-cause mortality in**3 **a cohort of middle-aged adults with incident asthma**4 Oliver Djurhuus Tupper¹, Zorana Jovanovic Andersen², and Charlotte5 Suppli Ulrik^{1,3}6 ¹ Department of Respiratory Medicine, Copenhagen University Hospital Hvidovre,

7 Denmark

8 ² Section of Environmental Health, Department of Public health, University of

9 Copenhagen, Denmark

10 ³ Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark11 **Corresponding Author**

12 Oliver Djurhuus Tupper MD

13 Respiratory Research Unit

14 Department of Respiratory Medicine

15 Hvidovre Hospital

16 Kettegård Alle 30

17 DK-2650 Hvidovre

18 E-mail olivertupper@gmail.com

19

20 Word count abstract: 248

21 Word count main text: 2486

22

23

24

25

26

1
2
3 27
45 28
6
78 29 **Abstract**
910 30 Objectives:
11
12

13 31 We aimed to identify factors associated with all-cause mortality in adults with
14
15 32 incident asthma.

17 33 Setting:
18
19

20 34 Cross-sectional cohort study, in the metropolitan areas of Copenhagen and Aarhus,
21
22 35 Denmark.

24 36 Participants:
25
26

27 37 Adults aged 50–64 years enrolled in the Danish Diet, Cancer, and Health cohort were
28
29 38 followed from baseline (1993–1997) in the National Patients Registry for first-time
30
31 39 admissions for asthma and vital status. We defined incident asthma as at least one first-
32
33 40 time hospital admission with asthma as the primary registered diagnosis occurring
34
35 41 between baseline and end of follow-up (2013), in participants without previously known
36
37 42 asthma. Among the cohort comprising 57 053 individuals, we identified 785 adults (aged
38
39 43 50–64) with incident asthma, of whom 76 died during follow-up.

44 44 Primary and secondary outcome measures:
45
46

47 45 Baseline reported socioeconomic and lifestyle traits, and comorbidities associated with
48
49 46 all-cause mortality.

51 47 Results:
52
53

54 48 Self-reported leisure-time physical activity was associated with a substantial reduction
55
56 49 in risk with an HR of 0.53 (95 % CI 0.33–0.85). Being male, single, and having a diagnosis
57
58 50 of hypertension or diabetes were associated with an increased risk of all-cause mortality
59
60

1
2
3 51 with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–
4
5
6 52 3.95) and of 2.42 (95 % CI 0.96–6.11), respectively.

7
8 53 Conclusions:

9
10 54 This long-term study of adults with hospital contacts for incident asthma revealed
11
12
13 55 that self-reported leisure-time physical activity is associated with an approximately
14
15 56 50% reduction in all-cause mortality. While both hypertension and diabetes were
16
17 57 associated with a higher risk of mortality.

18
19
20 58

21
22 59 **Strengths and limitations of this study:**

- 23
24
25 60 • The present study is one of very few reporting on how physical activity and
26
27 61 comorbidities are associated with all-cause mortality in adults with asthma.
28
29 62 • Seven hundred eighty-five persons with incident asthma were follow-up for
30
31 63 20 years, with no loss to follow-up.
32
33
34 64 • The diagnosis of asthma is based on register information and not an objective
35
36 65 assessment.
37
38
39 66 • There are only very few events among those with previous myocardial
40
41 67 infarction and stroke.

42
43
44 68

45
46 69 **Keywords:** Asthma, middle-aged adults, population cohort, comorbidities, long-term

47
48 70 **Short Title:** Physical activity and asthma mortality

49
50
51 71 **Introduction**

52
53
54 72 With over 300 million persons worldwide suffering from asthma and a multitude of
55
56
57 73 deaths each year, asthma is a disease that continually requires attention.^{1,2} Asthma
58
59 74 remains a disease that carries increased mortality compared with general populations.^{3,4}

1
2
3 75 Asthma specific mortality has, overall, been on a steady decline since the 1950s.⁵⁻⁷
4
5
6 76 However, a study based on the WHO Mortality Database found that mortality trends
7
8 77 have plateaued, with no significant change in mortality between 2006 and 2012.⁸
9
10 78 Furthermore, a British report from 2014 reported that over 67% of deaths related to
11
12 79 asthma were potentially preventable.⁹
13
14
15 80 Asthma specific mortality alone does not provide the whole picture when evaluating the
16
17 81 risks of the disease for individual patients. A study evaluating deaths with asthma as a
18
19 82 contributing factor, in addition to asthma-specific causes, found that asthma as a
20
21 83 contributing factor was associated with more than twice as many deaths compared with
22
23 84 asthma-specific deaths alone.¹⁰ Additionally, studies suggest that patients with asthma
24
25 85 are more prone to acquire other chronic conditions than the background population.¹¹⁻
26
27
28 86 ¹³ As the impact of factors as multimorbidity on all-cause mortality is an area with a
29
30 87 paucity of data, a need for studies in these areas exists.¹⁴ The association between
31
32
33 88 physical activity and long-term mortality has been well established in the general
34
35 89 population and patients with COPD.^{15,16} However, this has not been examined
36
37
38 90 extensively in asthma.¹⁷ The impact of physical activity on asthma specific factors, such
39
40
41 91 as disease control, lung function and exacerbations has been well researched.¹⁷
42
43
44 92 Based on the currently available knowledge, it remains of utmost to further explore
45
46
47 93 factors associated with asthma-related mortality, including not least all-cause mortality.
48
49
50 94 The present study aimed to examine factors associated with long-term all-cause
51
52 95 mortality in adults with incident asthma from a large Danish cohort of adults.
53
54
55 96

97 **Methods**

98 Characteristics of the Diet, Cancer and Health (DCH) cohort have been published
99 previously, with a full description of the cohort.^{18,19} A total of 160,725 individuals
100 (72,729 women) were invited to participate in the DCH Cohort, between 1993 and 1997.
101 All individuals resided in either Copenhagen or Aarhus, which are the two largest cities
102 in Denmark. To be invited participants had to be 50—64 years of age and have no record
103 of cancer at the time of inclusion. A total of 57,053 individuals (52.4% women, n=29,875)
104 were enrolled in the study after accepting the invitation. The Central Danish Ethics
105 Committee approved the main study of the DCH-cohort. The regional Danish Ethics
106 Committee approved this sub-study (H-17025043) and the Danish Data Protection
107 Agency (2014-41-3468). All participants provided written informed consent. Baseline
108 factors were determined based on a comprehensive questionnaire completed by the
109 participants. The questionnaire consisted of questions on general health and diet;
110 demographic factors, including education and occupation; questions on lifestyle,
111 including tobacco exposure; and pre-existing diseases, including asthma, COPD, diabetes,
112 and cardiovascular disease.

113

114 *Study cohort*

115 Participants in the DCH cohort were included in the present analyses as cases if they had
116 the first-ever admission to a hospital, emergency department, or outpatient clinic with
117 a primary diagnosis of asthma, which occurred between cohort baseline (1993-1997)
118 and July 1st, 2013. Participants with a self-reported diagnosis of asthma or COPD at
119 baseline were excluded. Participants in the DCH cohort were linked to the Danish
120 National Patient Registry (DNPR), to extract hospital contacts from 1993-1997 and until

1
2
3 121 July 1st, 2013.²⁰ The link between the DCH and DNPR was done using the unique
4
5 122 identifier all Danish residents have. Every discharge diagnoses from all Danish hospitals
6
7
8 123 since 1978 and from outpatient clinics since 1995 are gathered in the DNPR.²¹ In addition
9
10 124 to hospital contacts, we gathered emergency room visits and visits to respiratory
11
12 125 outpatient clinics. Asthma was classified according to the International Classification of
13
14 126 Diseases (ICD) as ICD-10 codes DJ45–46 and ICD-8 codes 493.00–493.09. Cases were
15
16 127 followed from first-ever asthma admission and until the time of death, or emigration, or
17
18 128 July 1st, 2013, whichever came first.
19
20
21
22

23 129
24
25 130 Physical activity in leisure-time was determined based on a participant filled
26
27 131 questionnaire. An interviewer checked the questionnaire. Participants reported the
28
29 132 number of hours per week they did leisure time and transport-related (ie, to and from
30
31 133 work, shopping) physical activity. Leisure-time physical activity was reported separately
32
33 134 for summer and winter of the previous year and was allocated in the following
34
35 135 categories: cycling, “do-it-yourself” activities (ie, home improvements), gardening,
36
37 136 housework (cleaning, laundry), sports and walking. The two values for summer and
38
39 137 winter were averaged. The questions used have previously been validated in two studies
40
41 138 by Peters et al and Cust et al that found high correlations with movement sensing
42
43 139 measurement and accelerometer measurements, respectively.^{22,23} Participants who are
44
45 140 reported as being physically active in leisure time spent at least half an hour a week on
46
47 141 at one at least one of the six categories.
48
49
50
51
52
53

54 142

55
56
57 143 Statistical Analyses
58
59
60

1
2
3 144 Associations between baseline factors and all-cause mortality were examined using the
4
5 145 Cox proportional hazards model with age as the underlying time scale. We examined the
6
7
8 146 following baseline factors, identified at recruitment between 1993 and 1999: age, sex,
9
10 147 BMI, length of education, employment and civil status, tobacco history, occupational
11
12 148 exposure, leisure-time physical activity, fruit consumption, and co-morbidities. Baseline
13
14 149 factors were assessed in a two-step process: Step one, in a univariate model, with age
15
16 150 as the underlying time scale. Step two was in a multivariate model that included only
17
18 151 variables that were associated with all-cause mortality, defined by backwards
19
20 152 elimination. The proportional hazards assumption was evaluated by testing for a non-
21
22 153 zero slope in a generalised linear regression of the scaled Schoenfeld residuals on
23
24 154 functions of time. Results from the univariate and multivariate model are presented as
25
26 155 hazard ratios (HRs) with 95% confidence intervals (CIs). Stata, version 11.2, was used to
27
28 156 perform statistical analyses.
29
30
31
32
33
34
35
36

157

158 *Patient and Public Involvement*

159 Patients and the public were not involved in the design of the study.

160

161 **Results**

162 We identified 785 adults with an incident diagnosis of asthma, and by that fulfilling the
163 criteria for inclusion in the present analyses. No individuals were lost to follow-up, and
164 therefore complete data were available for all 785 individuals. All characteristics
165 included in the following analyses were obtained at baseline.

1
2
3 166 Between baseline and July 1st, 2013, 76 of the identified adults with incident asthma
4
5 167 died. The majority of cases with incident asthma were women 63% (n=495). Only 45%
6
7 168 (n=351) were never smokers at baseline. Interestingly, a substantial proportion of
8
9 169 ever-smokers were ex-smokers (60%, n=260) and not current smokers (40%, n=174).
10
11 170 The amount of tobacco exposure was much higher among those who died compared
12
13 171 to those with incident asthma still alive at the end of follow-up. On average, persons
14
15 172 that died smoked 3.8 grams of tobacco per day, corresponding to 72% more than
16
17 173 those who were alive at the end of follow-up. Those that died had a daily intake of fruit
18
19 174 that was 16 g (or 8.3 %) less compared with those that were still alive. Further
20
21 175 characteristics are shown in Table 1.
22
23
24
25
26

27 176
28
29 177 Of the baseline characteristics included in the analyses, the following were found to be
30
31 178 associated with all-cause mortality and were therefore included in the final model: (1)
32
33 179 sex, (2) smoking status, (3) physical activity in leisure time, (5) employment status, (6)
34
35 180 marital status, (7) diabetes and (8) hypertension. On the other hand, age and a
36
37 181 previous diagnosis of myocardial infarction or stroke lacked power for precise
38
39 182 estimates for all-cause mortality in univariate analyses and were therefore not
40
41 183 included in the final model.
42
43
44
45

46 184 Male sex was associated with a higher risk for all-cause mortality (HR 1.83, 95% CI
47
48 185 1.14-2.93).
49
50

51 186 Persons who reported being single had a higher mortality risk (HR of 2.16 95% CI 2.06-
52
53 187 4.40) compared with persons who reported being married.
54
55

56 188 Having a diagnosis of hypertension was associated with a substantially increased risk of
57
58 189 all-cause mortality (HR 2.47, 95% CI 1.54–3.95). Self-reported previous myocardial
59
60

1
2
3 190 infarction and a current diagnosis of diabetes had imprecise estimates associated with
4
5 191 all-cause mortality, although, notably, robust associations were detected. For
6
7
8 192 myocardial infarction, we found an HR of 2.87 (95% CI 1.04-7.89) in the univariate
9
10 193 model and diabetes an HR of 2.42 (95% CI 0.96-6.11) in the multivariate model. There
11
12
13 194 was not found an association between previous stroke and all-cause mortality.
14
15 195 The self-reported leisure-time physical activity showed a substantial reduction in all-
16
17 196 cause mortality (HR 0.53, 95% CI 0.33–0.85).
18
19 197 Mean daily fruit intake was not found to be associated with death (table 2).
20
21
22
23
24

25 199 **Discussion**

26
27
28 200 In this Danish cohort of 785 adults with incident asthma followed for 20 years, we found
29
30 201 that physical activity was associated with a lower risk of all-cause mortality. In contrast,
31
32 202 being unmarried or having hypertension were associated with increased all-cause
33
34 203 mortality.
35
36
37

38 204 *Physical Activity*

39
40 205
41
42 206 To the best of our knowledge, this is the first cohort study that has reported the
43
44 207 association between self-reported physical activity and all-cause mortality, specifically
45
46 208 in individuals with asthma. Physical activity has previously been shown to have a
47
48 209 positive effect on multiple aspects of asthma.¹⁷ Particularly relevant are two studies by
49
50 210 Garcia-Aymerich et al²⁴ and Fisher et al²⁵ that found a protective effect of self-reported
51
52 211 physical activity on hospitalisation with asthma exacerbations. While the same effect
53
54 212 could not be found on readmissions for exacerbations in the study by Fisher et al²⁵, it is
55
56 213 an important support of our findings, as exacerbations are associated with morbidity
57
58
59
60

1
2
3 214 and mortality.²⁶ Physical activity also appears to have a positive effect on asthma
4
5 215 control.²⁷ However, BMI appears to be more critical, negating the effects of physical
6
7
8 216 activity in some, but not all, models.¹⁷ It appears though that if persons with asthma do
9
10
11 217 a moderate level of physical activity compared with inactivity and strenuous physical
12
13 218 activity that asthma control is positively affected.²⁸ The positive effects on these other
14
15 219 asthma outcomes could support our finding of physical activities associated with a
16
17
18 220 lower risk of mortality.

19
20 221 The effects of physical activity are prudent to establish as we know that persons with
21
22 222 asthma generally are less physically active than the general population.²⁹ Further, we
23
24
25 223 know from a Cochrane review from 2013 that physical activity is well-tolerated and
26
27
28 224 safe for individuals with asthma.³⁰ The review found that physical activity may improve
29
30 225 cardiopulmonary function in individuals with asthma, without a negative impact on
31
32
33 226 pulmonary function. Furthermore, the Cochrane review is based on shorter-term
34
35 227 studies, long-term findings from the Copenhagen City Heart study suggest that physical
36
37
38 228 activity may diminish long-term lung function decline in individuals with asthma.³¹ The
39
40 229 amount of physical activity required to be defined as physically active in our study is
41
42
43 230 relatively low and, therefore, should be attainable by most. However, future studies
44
45 231 should explore whether there are additional benefits from moderate and high levels of
46
47
48 232 activity. Additionally, is there an upper limit of activity where the risks of adverse
49
50 233 outcomes outweigh the benefits. Based on our findings, there is absolutely reason to
51
52
53 234 motivate persons with asthma to do some form of physical activity in their leisure
54
55 235 time.

56
57 236

58
59 237 *Comorbidities*
60

1
2
3 238 Hypertension had a strong association with death. Overall all included comorbid
4
5 239 conditions at baseline seemed to be associated with a higher risk of death. However,
6
7
8 240 only hypertension had a robust estimate, probably since the remaining comorbidities
9
10 241 (diabetes, stroke and myocardial infarction) had a relatively low prevalence at baseline.
11
12
13 242 There is limited research on how hypertension relates to mortality in person with
14
15 243 asthma.¹⁴ We found one other study by Sumino et al³² from 2014 that report the
16
17 244 association between hypertension and mortality. They found there was a lower OR for
18
19 245 mortality among individuals with hypertension for individuals over the age of 65 years.
20
21
22 246 However, the study by Sumino et al³² had a much shorter follow-up of three years
23
24
25 247 compared to the 20 years of our study. Given that hypertension is a condition that gives
26
27 248 long-term complications, these complications are likely not caught across such a short
28
29 249 period.
30
31
32 250 While the estimated hazard ratio for mortality among those with diabetes was
33
34 251 imprecise, due to lack of power, it is worth mentioning that there appeared to be a
35
36 252 strong association between diabetes and a higher risk of all-cause mortality. While,
37
38 253 again, the amount of other studies is exceedingly limited, there is other literature
39
40 254 supporting this finding. The study by Sumino et al³² found that diabetes was associated
41
42 255 with a higher rate of mortality in persons over the age of 65. Another cohort study by
43
44 256 Koskela et al³³ showed that among 110 patients admitted due to an asthma
45
46 257 exacerbation, there was a higher risk of mortality for those with diabetes. While there
47
48 258 is a clear trend in our data towards higher all-cause mortality risk for individuals with
49
50 259 previous myocardial infarction, once again, the HR estimate was imprecise due to only
51
52 260 four events. Nevertheless, an excess risk of mortality due to cardiovascular disease is an
53
54
55
56
57
58
59
60

1
2
3 261 area that has substantial data supporting it in asthma cohorts, and this certainly
4
5 262 supports our finding.^{34,35}
6
7
8 263 The factors presented in this paper may seem obvious but needs to be verified in asthma
9
10 264 mainly, as many of these factors have not previously been explored in relation to adults
11
12
13 265 with asthma. Not least in large cohorts, as in the present long-term follow-up study of a
14
15 266 large cohort of middle-aged men and women with asthma. The relevance of this is due
16
17 267 to the systemic inflammation present in persons with asthma, which potentially could
18
19
20 268 affect and change which factors are essential to be aware of compared with general
21
22
23 269 populations.^{36,37}
24

25 270

26 271

27 272 *Limitations*

28
29
30 273 The diagnosis of asthma in the included subjects was based on ICD-10 codes connected
31
32 274 to Hospital contacts, which is not as accurate as objectively verified asthma. However,
33
34
35 275 this has previously been established by Jensen et al³⁸ to be a robust method of
36
37
38 276 identifying persons with asthma. The positive predictive value was found to be 65%;
39
40 277 despite this, they discovered that associations found are still relevant. Selecting only
41
42
43 278 persons with either a hospital or outpatient contact means we likely only have those
44
45
46 279 with moderate and severe disease included in the cohort. Meaning the findings in this
47
48
49 280 article cannot be universally applied.

50
51
52 281 The prevalence of asthma in this cohort is low (about 1%), substantially lower than the
53
54 282 current reported prevalence in Denmark of 10%, therefore, the generalizability is
55
56
57 283 limited. The low prevalence is due to only including participants without a previous
58
59 284 diagnosis of asthma and only included individuals referred to secondary care.
60

1
2
3 285 Our definition of physical activity was based on self-reported information, which carries
4
5 286 a certain degree of bias. Additionally, a potential limitation is that the degree of self-
6
7 287 reported physical activity for some was reported multiple years before the first contact
8
9 288 for incident asthma. We can, therefore, not be sure that the level of physical activity still
10
11 289 applies at follow-up. However, previous literature suggests that physical activity tracks
12
13 290 well over time, particularly in adulthood.^{39,40}

14
15 291 We did not have information on the specific cause of death and therefore were unable
16
17 292 to examine factors relating to asthma specific mortality.

18
19 293 As the number of events in this cohort study was not substantial and therefore not
20
21 294 meeting the traditional, events per variable of 10 rule.⁴¹ There is, therefore, a risk of
22
23 295 both type 1 and 2 errors. The results of this study can, therefore, not stand on their own,
24
25 296 yet it provides a valuable source for future studies. This is particularly evident for
26
27 297 diabetes, which shows a clear trend for higher risk of mortality, though it lacks the power
28
29 298 for a precise estimate.

30
31 299

32 300 *Conclusions*

33 301 Our study has shown that for middle-aged individuals with hospital contact for incident
34
35 302 asthma, there appears to be increased mortality for persons with comorbidity, whereas
36
37 303 leisure-time physical activity was found to have a protective effect on mortality risk.

38
39 304

40 305 **Abbreviations:**

41 306 BMI = Body Mass Index

42 307 DCH = Diet Cancer and Health Cohort

43 308 HR = Hazard Ratio

44 309 OR = Odds Ratio

310

311 **Declarations**312 **Ethics approval and consent to participate:** The study was approved by the ethical

313 committee for the Capital Region of Denmark (H-17025043), the regional data safety

314 committee for the capital region of Denmark (P-2019-712), and The Danish Data

315 Protection Agency (2014-41-3468). All participants signed an informed consent form.

316 **Funding:** This research did not receive any specific grant from funding agencies in
317 the public, commercial, or not-for-profit sectors.318 **Competing interests:** ODT, ZJA and CSU have no perceived conflicts of interest in
319 relation to this study.320 **Authors' contributions:** Conception and design—ODT, ZJA and CSU.; preparation of
321 data and statistical analyses - ZJA.; statistical interpretation and drafted the
322 manuscript—ODT; all authors critically reviewed and accepted the final version of the
323 manuscript.324 **Availability of data and material:** The data are available upon reasonable request, but
325 analysis may require approval from the regional data safety committee for the capital
326 region of Denmark (Videnscenter for dataanmeldelser).327 **Acknowledgements:** Thanks to Anne Tjønneland and Kim Overvad for providing us
328 with access to the data from the Diet, Cancer and Health cohort.

329

330 **References**

- 331 1. WHO. Global surveillance, prevention and control of chronic respiratory
-
- 332 diseases: a comprehensive approach.
-
- 333
- <http://www.who.int/gard/publications/GARD Book 2007.pdf?ua=1>
-
- 334 2. Global strategy for asthma management and prevention. Global Initiative for
-
- 335 Asthma (GINA). Published 2020. Accessed June 16, 2020.
- <https://ginasthma.org>

- 336 3. Huovinen E, Kaprio J, Vesterinen E, Koskenvuo M. Mortality of adults with
337 asthma: A prospective cohort study. *Thorax*. 1997;52(1):49-54.
338 doi:10.1136/thx.52.1.49
- 339 4. D'Amato G, Vitale C, Molino A, et al. Asthma-related deaths. *Multidiscip Respir*
340 *Med*. 2016;11(1):1-5. doi:10.1186/s40248-016-0073-0
- 341 5. Speizer FE, Doll R, Heaf P. Observations on Recent Increase in Mortality from
342 Asthma. *Br Med J*. 1968;1(5588):335-339. doi:10.1136/bmj.1.5588.335
- 343 6. Jackson RT, Beaglehole R, Rea HH, Sutherland DC. Mortality from asthma: A new
344 epidemic in New Zealand. *Br Med J*. 1982;285(6344):771-774.
345 doi:10.1136/bmj.285.6344.771
- 346 7. Sly RM. Mortality from asthma, 1979-1984. *J Allergy Clin Immunol*. 1988;82(5
347 PART 1):705-717. doi:10.1016/0091-6749(88)90069-3
- 348 8. Ebmeier S, Thayabaran D, Braithwaite I, Bénamara C, Weatherall M, Beasley R.
349 Trends in international asthma mortality: analysis of data from the WHO
350 Mortality Database from 46 countries (1993–2012). *Lancet*.
351 2017;390(10098):935-945. doi:10.1016/S0140-6736(17)31448-4
- 352 9. Levy ML. The national review of asthma deaths: What did we learn and what
353 needs to change? *Breathe*. 2015;11(1):15-24. doi:10.1183/20734735.008914
- 354 10. McCoy L, Redelings M, Sorvillo F, Simon P. A multiple cause-of-death analysis of
355 asthma mortality in the United States, 1990-2001. *J Asthma*. 2005;42(9):757-
356 763. doi:10.1080/02770900500308189
- 357 11. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of
358 comorbidities in newly diagnosed COPD and asthma in primary care. *Chest*.
359 2005;128(4):2099-2107. doi:10.1378/chest.128.4.2099
- 360 12. Gershon AS, Wang C, Guan J, To T. Burden of comorbidity in individuals with
361 asthma. *Thorax*. 2010;65(7):612-618. doi:10.1136/thx.2009.131078
- 362 13. Adams RJ, Wilson DH, Taylor AW, et al. Coexistent chronic conditions and
363 asthma quality of life: A population-based study. *Chest*. 2006;129(2):285-291.
364 doi:10.1378/chest.129.2.285
- 365 14. Marques de Mello L, Cruz AA. A proposed scheme to cope with comorbidities in
366 asthma. *Pulm Pharmacol Ther*. 2018;52:41-51. doi:10.1016/j.pupt.2018.08.005
- 367 15. Lear SA, Hu W, Rangarajan S, et al. The effect of physical activity on mortality
368 and cardiovascular disease in 130 000 people from 17 high-income, middle-
369 income, and low-income countries: the PURE study. *Lancet*.
370 2017;390(10113):2643-2654. doi:10.1016/s0140-6736(17)31634-3
- 371 16. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of
372 all-cause mortality in patients with COPD: a prospective cohort study. *Chest*.
373 2011;140(2):331-342. doi:10.1378/chest.10-2521
- 374 17. Cordova-Rivera L, Gibson PG, Gardiner PA, McDonald VM. A Systematic Review
375 of Associations of Physical Activity and Sedentary Time with Asthma Outcomes. *J*
376 *Allergy Clin Immunol Pr*. 2018;6(6):1968-1981 e2. doi:10.1016/j.jaip.2018.02.027
- 377 18. Tjønneland A, Olsen A, Boll K, et al. Study design, exposure variables, and
378 socioeconomic determinants of participation in Diet, Cancer and Health: a
379 population-based prospective cohort study of 57,053 men and women in
380 Denmark. *Scand J Public Health*. 2007;35(4):432-441.
381 doi:10.1080/14034940601047986
- 382 19. Bønnelykke K, Raaschou-Nielsen O, Tjønneland A, Ulrik CS, Bisgaard H, Andersen

- 1
2
3 383 ZJ. Postmenopausal hormone therapy and asthma-related hospital admission. *J*
4 384 *Allergy Clin Immunol*. 2015;135(3):813-816.e5. doi:10.1016/j.jaci.2014.11.019
5 385 20. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health*.
6 386 2011;39(7_suppl):22-25. doi:10.1177/1403494810387965
7 387 21. Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT.
8 388 The Danish National Patient Registry: a review of content, data quality, and
9 389 research potential. *Clin Epidemiol*. 2015;7:449. doi:10.2147/CLEP.S91125
10 390 22. Cust AE, Smith BJ, Chau J, et al. Validity and repeatability of the EPIC physical
11 391 activity questionnaire: A validation study using accelerometers as an objective
12 392 measure. *Int J Behav Nutr Phys Act*. 2008;5(1):33. doi:10.1186/1479-5868-5-33
13 393 23. Peters T, Brage S, Westgate K, et al. Validity of a short questionnaire to assess
14 394 physical activity in 10 European countries. *Eur J Epidemiol*. 2012;27(1):15-25.
15 395 doi:10.1007/s10654-011-9625-y
16 396 24. Garcia-Aymerich J, Varraso R, Antó JM, Camargo CA. Prospective study of
17 397 physical activity and risk of asthma exacerbations in older women. *Am J Respir*
18 398 *Crit Care Med*. 2009;179(11):999-1003. doi:10.1164/rccm.200812-1929OC
19 399 25. Fisher JE, Loft S, Ulrik CS, et al. Physical Activity, Air Pollution, and the Risk of
20 400 Asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*.
21 401 2016;194(7):855-865. doi:10.1164/rccm.201510-2036OC
22 402 26. Chipps BE, Zeiger RS, Borish L, et al. Key findings and clinical implications from
23 403 the Epidemiology and Natural History of Asthma: Outcomes and Treatment
24 404 Regimens (TENOR) study. *J Allergy Clin Immunol*. 2012;130(2):332-342.e10.
25 405 doi:10.1016/j.jaci.2012.04.014
26 406 27. Panagiotou M, Koulouris NG, Rovina N. Physical Activity: A Missing Link in
27 407 Asthma Care. *J Clin Med*. 2020;9(3):706. doi:10.3390/jcm9030706
28 408 28. Del Giacco SR, Firinu D, Bjermer L, Carlsen K-H. Exercise and asthma: an
29 409 overview. *Eur Clin Respir J*. 2015;2(1):27984. doi:10.3402/ecrj.v2.27984
30 410 29. van 't Hul AJ, Frouws S, van den Akker E, et al. Decreased physical activity in
31 411 adults with bronchial asthma. *Respir Med*. 2016;114:72-77.
32 412 doi:10.1016/j.rmed.2016.03.016
33 413 30. Kv C, Mg C, Picot J, Mp B, Aj E, Bj S. Physical training for asthma (Review)
34 414 SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Libr*.
35 415 2013;(9):1-73.
36 416 doi:10.1002/14651858.CD001116.pub4.www.cochranelibrary.com
37 417 31. Garcia-Aymerich J, Lange P, Benet M, Schnohr P, Antó JM. Regular physical
38 418 activity modifies smoking-related lung function decline and reduces risk of
39 419 chronic obstructive pulmonary disease: A population-based cohort study. *Am J*
40 420 *Respir Crit Care Med*. 2007;175(5):458-463. doi:10.1164/rccm.200607-896OC
41 421 32. Sumino K, O'Brian K, Bartle B, Au DH, Castro M, Lee TA. Coexisting chronic
42 422 conditions associated with mortality and morbidity in adult patients with
43 423 asthma. *J Asthma*. 2014;51(3):306-314. doi:10.3109/02770903.2013.879881
44 424 33. Koskela HO, Salonen PH, Romppanen J, Niskanen L. A history of diabetes but not
45 425 hyperglycaemia during exacerbation of obstructive lung disease has impact on
46 426 long-term mortality: A prospective, observational cohort study. *BMJ Open*.
47 427 2015;5(1):6794. doi:10.1136/bmjopen-2014-006794
48 428 34. Xu M, Xu J, Yang X. Asthma and risk of cardiovascular disease or all-cause
49 429 mortality: A meta-analysis. *Ann Saudi Med*. 2017;37(2):99-105.

- 1
2
3 430 doi:10.5144/0256-4947.2017.99
4 431 35. Strand LB, Tsai MK, Wen CP, Chang S Sen, Brumpton BM. Is having asthma
5 432 associated with an increased risk of dying from cardiovascular disease? A
6 433 prospective cohort study of 446 346 Taiwanese adults. *BMJ Open*. 2018;8(5).
7 434 doi:10.1136/bmjopen-2017-019992
8 435 36. Denburg JA, Sehmi R, Saito H, Pil-Seob J, Inman MD, O'Byrne PM. Systemic
9 436 aspects of allergic disease: Bone marrow responses. *J Allergy Clin Immunol*.
10 437 2000;106(5):S242-S246. doi:10.1067/mai.2000.110156
11 438 37. Bjermer L. Time for a paradigm shift in asthma treatment: From relieving
12 439 bronchospasm to controlling systemic inflammation. *J Allergy Clin Immunol*.
13 440 2007;120(6):1269-1275. doi:10.1016/j.jaci.2007.09.017
14 441 38. Jensen AO, Nielsen GL, Ehrenstein V. Validity of asthma diagnoses in the Danish
15 442 National Registry of Patients, including an assessment of impact of
16 443 misclassification on risk estimates in an actual dataset. *Clin Epidemiol*.
17 444 2010;2:67-72. <https://www.ncbi.nlm.nih.gov/pubmed/20865105>
18 445 39. Telama R. Tracking of physical activity from childhood to adulthood: A review.
19 446 *Obes Facts*. 2009;2(3):187-195. doi:10.1159/000222244
20 447 40. Mertens E, Clarys P, Mullie P, et al. Stability of physical activity, fitness
21 448 components and diet quality indices. *Eur J Clin Nutr*. 2017;71(4):519-524.
22 449 doi:10.1038/ejcn.2016.172
23 450 41. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in
24 451 logistic and cox regression. *Am J Epidemiol*. 2007;165(6):710-718.
25 452 doi:10.1093/aje/kwk052
26 453
27 454
28 455
29 456
30 457
31 458
32 459
33 460
34 461
35 462
36 463
37 464
38 465
39 466
40 467
41 468
42 469
43 470

471 Tables

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

Table 1 – Baseline characteristics of 785 adults enrolled in the Danish Diet, Cancer and Health Cohort with incident asthma between baseline (1993-1997) and follow-up (July 2013).

473

| | Asthma (N = 785) | Alive (N= 709) | Dead (N = 76) |
|---|-----------------------|-------------------|------------------|
| Age 50-55, n (%) | 50 (6.4) | 44 (6.2) | 6 (7.9) |
| Age 55-60, n (%) | 155 (19.7) | 136 (19.2) | 19 (25.0) |
| Age 60-65, n (%) | 580 (73.9) | 529 (74.6) | 51 (67.1) |
| Men, n (%) | 290 (37) | 136 (19) | 19 (25) |
| Mean body mass index (kg/m ²) | 26.5 (12) | 26.4 (4.2) | 27.1 (4.6) |
| Smoking history, n (%) | Never | 351 (45) | 318 (45) |
| | Previous | 260 (33) | 241 (34) |
| | Current | 174 (22) | 150 (21) |
| Mean smoking duration, years (SD) | 25.9 (12) | 25.3 (12) | 31.1 (12) |
| Mean smoking intensity, g/day (SD) | 5.7 (9.1) | 5.3 (9.0) | 9.1 (10) |
| Exposed to environmental tobacco smoke, n (%) | 449 (57) | 403 (57) | 46 (61) |
| Physically active in leisure time, n (%) | 432 (55) | 404 (57) | 28 (37) |
| Mean fruit intake, g/day (SD) | 192 (145) | 193 (146) | 177 (129) |
| Employed, n (%) | 612 (78) | 559 (79) | 53 (70) |
| Marital status, n (%) | Single | 45 (5.7) | 35 (4.9) |
| | Married | 558 (71) | 507 (72) |
| | Divorced | 136 (17) | 125 (18) |
| | Widowed | 46 (5.9) | 42 (5.9) |
| Years of Education n (%) | < 8 | 223 (28) | 198 (28) |
| | 8 – 10 | 395 (50) | 361 (51) |
| | ≥ 10 | 167 (21) | 150 (21) |
| Comorbidity n (%) | Myocardial infarction | 13 (1.7) | 9 (1.3) |
| | Stroke | 4 (0.5) | 3 (0.4) |
| | Diabetes | 13 (1.7) | 8 (1.1) |
| | Hypertension | 155 (20) | 126 (18) |
| | Hypercholesterolemia | 46 (5.9) | 45 (6.3) |

SD = standard deviation

474

475

476

477

478

479
480 **Table 2 - Determinants at baseline of survival in 785 adults with incident asthma during follow-up**
481 **(2013) among participants in the Danish Diet, Cancer and Health Cohort.**

| | | Univariate model HR (95% CI) | Multivariate model HR (95% CI) |
|-------------------------------------|--|------------------------------------|--------------------------------------|
| Age | 50-55 | 1.00 | - |
| | 55-60 | 0.84 (0.33-2.14) | |
| | 60-65 | 0.76 (0.28-2.08) | |
| Sex | Female | 1.00 | 1.00 |
| | Male | 1.76 (1.12-2.75) | 1.83 (1.14-2.93) |
| Body Mass index | Underweight/Normal (<25 kg/m ²) | 1.00 | - |
| | Overweight (25-30 kg/m ²) | 1.56 (0.93-2.63) | - |
| | Obese (≥ 30 kg/m ²) | 1.52 (0.79-2.91) | - |
| Smoking | Never | 1.00 | 1.00 |
| | Previous | 0.67 (0.38-1.18) | 0.59 (0.33-1.05) |
| | Current | 1.64 (0.96-2.78) | 1.39 (0.81-2.38) |
| Activity in Leisure Time | Inactive | 1.00 | 1.00 |
| | Active | 0.47 (0.29-0.74) | 0.53 (0.33-0.85) |
| Mean fruit intake | g/day | 0.91 (0.76-1.07) | - |
| Employment | Yes | 1.00 | 1.00 |
| | No | 1.17 (0.70-1.96) | 1.04 (0.87-1.25) |
| Marital Status | Single | 2.77 (1.40-5.48) | 2.16 (2.06-4.40) |
| | Married | 1.00 | 1.00 |
| | Divorced | 0.79 (0.41-1.51) | 0.76 (0.40-1.47) |
| | Widowed | 0.83 (0.30-2.30) | 1.15 (0.40-3.27) |
| Myocardial infarction | - | 1.00 | - |
| | + | 2.87 (1.04-7.89) | - |
| Stroke | - | 1.00 | - |
| | + | 1.58 (0.22- 11.43) | - |
| Diabetes | - | 1.00 | 1.00 |
| | + | 3.58 (1.44-8.90) | 2.42 (0.96-6.11) |
| Hypertension | - | 1.00 | 1.00 |
| | + | 2.57 (1.61-4.09) | 2.47 (1.54-3.95) |

482 HR = Hazard Ratio. CI = Confidence interval.

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

| | Item No | Recommendation |
|------------------------------|---------|---|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract – page 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found - page 2 |
| Introduction | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported -page 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses -page 4 |
| Methods | | |
| Study design | 4 | Present key elements of study design early in the paper -page 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection -page 4-5 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up -page 4-5 (b) For matched studies, give matching criteria and number of exposed and unexposed - N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable -page 4-6 |
| 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 -page 4-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at -page 4-5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page- 5-6 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding -page 6 (b) Describe any methods used to examine subgroups and interactions -N/A (c) Explain how missing data were addressed -N/A (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses -N/A |

| 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 Page -4 and 8 (b) Give reasons for non-participation at each stage -due to space limitations non-participation for the DCH cohort is available in the referenced previous articles. (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders -table 1 (b) Indicate number of participants with missing data for each variable of interest -N/A (c) Summarise follow-up time (eg, average and total amount) -page 8 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time |
| 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 -table 2 (b) Report category boundaries when continuous variables were categorized -tabel 2 (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -N/A |
| Discussion | | |
| Key results | 18 | Summarise key results with reference to study objectives -page 8 |
| 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 Page 11-12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence -page 8-11 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results -page 11 |
| Other information | | |
| 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 -page 12 |

*Give information separately for exposed and unexposed groups.

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

For peer review only

BMJ Open

Physical activity and comorbidities as risk factors for all-cause mortality in a cohort of middle-aged adults with incident asthma?

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2021-049243.R1 |
| Article Type: | Original research |
| Date Submitted by the Author: | 23-Jun-2021 |
| Complete List of Authors: | Tupper, Oliver Djurhuus; Hvidovre Hospital, Department of Respiratory Medicine Andersen, ZJ; University of Copenhagen Department of Public Health, Section of Environmental Health Ulrik, Charlotte; Hvidovre Hospital, Department of Respiratory Medicine |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Respiratory medicine |
| Keywords: | Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, Adult thoracic medicine < THORACIC MEDICINE |
| | |

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 **Physical activity and comorbidities as risk factors for all-cause**
4
5
6 **mortality in a cohort of middle-aged adults with incident**
7
8 **asthma?**
9
10

11
12
13 Oliver Djurhuus Tupper¹, Zorana Jovanovic Andersen², and Charlotte

14
15
16 Suppli Ulrik^{1,3}
17

18
19 ¹ Department of Respiratory Medicine, Copenhagen University Hospital Hvidovre,
20
21 Denmark
22

23
24 ² Section of Environmental Health, Department of Public health, University of
25
26 Copenhagen, Denmark
27

28
29 ³ Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
30

31 **Corresponding Author**

32 Oliver Djurhuus Tupper MD
33
34 Respiratory Research Unit
35
36 Department of Respiratory Medicine
37
38 Hvidovre Hospital
39
40 Kettegård Alle 30
41
42 DK-2650 Hvidovre
43
44 E-mail olivertupper@gmail.com
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Word count abstract: 250
Word count main text: 2598

Abstract

Objectives:

We aimed to identify factors associated with all-cause mortality in adults with incident asthma.

Design and setting:

Cross-sectional cohort study, in the metropolitan areas of Copenhagen and Aarhus, Denmark.

Participants:

Adults aged 50–64 years enrolled in the Danish Diet, Cancer, and Health cohort were followed from baseline (1993–1997) in the National Patients Registry for first-time admissions for asthma and vital status. We defined incident asthma as at least one first-time hospital admission with asthma as the primary registered diagnosis between baseline and end of follow-up (2013) in participants without previously known asthma. Among the cohort comprising 57 053 individuals, we identified 785 adults (aged 50–64) with incident asthma, of whom 76 died during follow-up.

Primary and secondary outcome measures:

Baseline reported socioeconomic and lifestyle traits, and comorbidities associated with all-cause mortality.

Results:

Self-reported leisure-time physical activity was associated with a substantial reduction in risk with an HR of 0.53 (95 % CI 0.33–0.85). Being male, single, and having a diagnosis of hypertension or diabetes were associated with an increased risk of all-cause mortality

1
2
3 with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–
4
5 3.95) and of 2.42 (95 % CI 0.96–6.11), respectively.
6
7

8 Conclusions: 9

10 This long-term study of adults with hospital contacts for incident asthma revealed
11 that self-reported leisure-time physical activity is associated with an approximately
12
13 50% reduction in all-cause mortality. In contrast, both hypertension and diabetes
14
15 were associated with a higher risk of mortality.
16
17
18
19
20
21

22 **Strengths and limitations of this study:** 23

- 24 • The present study is one of very few reporting on how physical activity and
25 comorbidities are associated with all-cause mortality in adults with asthma.
26
27
- 28 • Seven hundred eighty-five persons with incident asthma were followed-up
29 for 20 years, with no loss to follow-up.
30
31
- 32 • The diagnosis of asthma is based on register information and not an objective
33 assessment.
34
35
- 36 • There are only very few events among those with previous myocardial
37 infarction and stroke.
38
39
40
41
42
43
44
45

46 **Keywords:** Asthma, middle-aged adults, population cohort, comorbidities, long-term
47

48 **Short Title:** Physical activity and asthma mortality
49
50

51 **Introduction** 52

53
54 With over 300 million persons worldwide suffering from asthma and many deaths each
55 year, asthma is a disease that continually requires attention.[1,2] Asthma remains a
56
57 disease that carries increased mortality compared with general populations.[3,4]
58
59
60

1
2
3 Asthma-specific mortality has, overall, been on a steady decline since the 1950s.[5–7]
4
5
6 However, a study based on the WHO Mortality Database found that mortality trends
7
8 have plateaued, with no significant change in mortality between 2006 and 2012.[8]
9
10
11 Furthermore, a British report from 2014 reported that over 67% of deaths related to
12
13 asthma were potentially preventable.[9]

14
15 Asthma-specific mortality alone does not provide the whole picture when evaluating the
16
17 risks of the disease for individual patients. A study assessing deaths with asthma as a
18
19 contributing factor, in addition to asthma-specific causes, found that asthma as a
20
21 contributing factor was associated with more than twice as many deaths compared with
22
23 asthma-specific deaths alone.[10] Studies suggest that patients with asthma are more
24
25 prone to acquire other chronic conditions than the background population.[11–13] As
26
27 the impact of factors as multimorbidity on all-cause mortality is an area with a paucity
28
29 of data, a need for studies in these areas exists.[14] The association between physical
30
31 activity and long-term mortality has been well established in the general population and
32
33 patients with COPD.[15,16] However, this has not been examined extensively in
34
35 asthma.[17] The impact of physical activity on asthma-specific factors, such as disease
36
37 control, lung function, and exacerbations has been well researched.[17]

38
39
40 Based on the currently available knowledge, it remains of utmost to further explore
41
42 factors associated with asthma-related mortality, including not least all-cause mortality.
43
44
45 The present study aimed to examine factors associated with long-term all-cause
46
47 mortality in adults with incident asthma from a large Danish cohort of adults.
48
49
50
51
52
53
54
55
56
57
58
59
60

Methods

Characteristics of the Diet, Cancer, and Health (DCH) cohort have been published previously, with a full description of the cohort.[18,19] A total of 160,725 individuals (72,729 women) were invited to participate in the DCH Cohort between 1993 and 1997. All individuals resided in either Copenhagen or Aarhus, which are the two largest cities in Denmark. To be invited, participants had to be 50–64 years of age and have no record of cancer at the time of inclusion. A total of 57,053 individuals (52.4% women, n=29,875) were enrolled in the study after accepting the invitation. The Central Danish Ethics Committee approved the main study of the DCH-cohort. The regional Danish Ethics Committee approved this sub-study (H-17025043) and the Danish Data Protection Agency (2014-41-3468). All participants provided written informed consent. Baseline factors were determined based on a comprehensive questionnaire completed by the participants. The questionnaire consisted of questions on general health and diet; demographic factors, including education and occupation; questions on lifestyle, including tobacco exposure; and pre-existing diseases, including asthma, COPD, diabetes, and cardiovascular disease.

Study cohort

Participants in the DCH cohort were defined as having incident asthma and included in the present analyses as cases if they had the first-ever admission to a hospital, emergency department, or outpatient clinic with a primary diagnosis of asthma, which occurred between cohort baseline (1993-1997) and July 1st, 2013. Asthma was classified according to the International Classification of Diseases (ICD) as ICD-10 codes DJ45–46 and ICD-8 codes 493.00–493.09. Participants with a self-reported diagnosis of asthma

1
2
3 or COPD at baseline were excluded. Participants in the DCH cohort were linked to the
4
5 Danish National Patient Registry (DNPR) to extract hospital contacts from 1993-1997
6
7 until July 1st, 2013.[20] The link between the DCH and DNPR was done using the unique
8
9 identifier all Danish residents have. Every discharge diagnosis from all Danish hospitals
10
11 since 1978 and from outpatient clinics since 1995 are gathered in the DNPR.[21] In
12
13 addition to hospital contacts, we gathered emergency room visits and visits to
14
15 respiratory outpatient clinics. Cases were followed from first-ever asthma admission
16
17 until the time of death, emigration, or July 1st, 2013, whichever came first.
18
19
20
21
22
23
24

25 Physical activity in leisure time was determined based on a participant completed
26
27 questionnaire. An interviewer checked the questionnaire. Participants reported the
28
29 number of hours per week they did leisure time and transport-related (i.e., to and from
30
31 work, shopping) physical activity. Leisure-time physical activity was reported separately
32
33 for summer and winter of the previous year. It was allocated in the following categories:
34
35 cycling, "do-it-yourself" activities (i.e., home improvements), gardening, housework
36
37 (cleaning, laundry), sports, and walking. The two values for summer and winter were
38
39 averaged. The questions used have previously been validated in two studies by Peters
40
41 et al and Cust et al that found high correlations with movement sensing measurement
42
43 and accelerometer measurements, respectively.[22,23] Participants reported as being
44
45 physically active in leisure time, spent at least half an hour a week on at least one of the
46
47 six categories.
48
49
50
51
52
53
54
55
56

57 Statistical Analyses

58
59
60

1
2
3 Associations between baseline factors and all-cause mortality were examined using the
4
5 Cox proportional hazards model with age as the underlying time scale. We examined the
6
7 following baseline factors identified at recruitment between 1993 and 1999: age, sex,
8
9 BMI, length of education, employment and civil status, tobacco history, occupational
10
11 exposure, leisure-time physical activity, fruit consumption, and comorbidities. Baseline
12
13 factors were assessed in a two-step process: Step one, in a univariate model, with age
14
15 as the underlying time scale. Step two was in a multivariate model that included only
16
17 variables associated with all-cause mortality, defined by backward elimination. The
18
19 proportional hazards assumption was evaluated by testing for a non-zero slope in a
20
21 generalised linear regression of the scaled Schoenfeld residuals on functions of time.
22
23 The univariate and multivariate model results are presented as hazard ratios (HRs) with
24
25 95% confidence intervals (CIs). Stata, version 11.2, was used to perform statistical
26
27 analyses.
28
29
30
31
32
33
34
35
36
37
38

Patient and Public Involvement

39 Patients and the public were not involved in the design of the study.
40
41
42
43
44

Results

45
46
47 We identified 785 adults with an incident diagnosis of asthma and fulfilled the criteria
48
49 for inclusion in the present analyses. No individuals were lost to follow-up, and
50
51 therefore complete data were available for all 785 individuals. All characteristics
52
53 included in the following analyses were obtained at baseline.
54
55
56
57
58
59
60

1
2
3 Between baseline and July 1st, 2013, 76 of the identified adults with incident asthma
4 died. The majority of cases with incident asthma were women 63% (n=495). Only 45%
5
6 (n=351) were never smokers at baseline. Interestingly, a substantial proportion of
7
8 ever-smokers were ex-smokers (60%, n=260) and not current smokers (40%, n=174).
9
10
11 The amount of tobacco exposure was much higher among those who died than those
12
13 with incident asthma still alive at the end of follow-up. On average, persons who died
14
15 smoked 3.8 grams of tobacco per day, corresponding to 72% more than those alive at
16
17 the end of follow-up. Those who died had a daily intake of fruit that was 16 g (or 8.3 %)
18
19 less than those still alive. Further characteristics are shown in Table 1.
20
21
22
23
24
25
26
27

28 Of the baseline characteristics included in the analyses, the following were found to be
29
30 associated with all-cause mortality and were therefore included in the final model: (1)
31
32 sex, (2) smoking status, (3) physical activity in leisure time, (5) employment status, (6)
33
34 marital status, (7) diabetes and (8) hypertension. On the other hand, age and a
35
36 previous diagnosis of myocardial infarction or stroke lacked power for precise
37
38 estimates for all-cause mortality in univariate analyses and were therefore not
39
40 included in the final model.
41
42
43
44

45 Male sex was associated with a higher risk for all-cause mortality (HR 1.83, 95% CI
46
47 1.14-2.93).
48

49 Persons who reported being single had a higher mortality risk (HR of 2.16 95% CI 2.06-
50
51 4.40) compared with persons who reported being married.
52

53 A diagnosis of hypertension was associated with a substantially increased risk of all-
54
55 cause mortality (HR 2.47, 95% CI 1.54–3.95). Self-reported previous myocardial
56
57 infarction and a current diagnosis of diabetes had imprecise estimates associated with
58
59
60

1
2
3 all-cause mortality, although, notably, robust associations were detected. We found an
4
5 HR of 2.87 (95% CI 1.04-7.89) in the univariate model for myocardial infarction. An HR
6
7 of 2.42 (95% CI 0.96-6.11) for diabetes was found in the multivariate model. There was
8
9 not found an association between previous stroke and all-cause mortality.
10
11

12
13 The self-reported leisure-time physical activity showed a substantial reduction in all-
14
15 cause mortality (HR 0.53, 95% CI 0.33–0.85).
16

17
18 Mean daily fruit intake was not found to be associated with death (table 2).
19
20

21 22 **Discussion**

23
24
25 In this Danish cohort of 785 adults with incident asthma followed for 20 years, we found
26
27 that physical activity was associated with a lower risk of all-cause mortality. In contrast,
28
29 being unmarried or having hypertension were associated with increased all-cause
30
31 mortality.
32
33

34 35 *Physical Activity*

36
37
38 To the best of our knowledge, this is the first cohort study that has reported the
39
40 association between self-reported physical activity and all-cause mortality, specifically
41
42 in individuals with asthma. Physical activity has previously been shown to have a
43
44 positive effect on multiple aspects of asthma.[17] Particularly relevant are two studies
45
46 by Garcia-Aymerich et al[24] and Fisher et al[25] that found a protective effect of self-
47
48 reported physical activity on hospitalisation with asthma exacerbations. While the
49
50 same effect could not be found on readmissions for exacerbations in the study by
51
52 Fisher et al[25], their findings are essential support of our findings, as exacerbations
53
54 are associated with morbidity and mortality.[26] Physical activity also appears to have
55
56
57
58
59
60

1
2
3 a positive effect on asthma control.[27] However, BMI appears to be more critical,
4
5 negating the effects of physical activity in some, but not all, models.[17] It appears that
6
7 if persons with asthma do a moderate level of physical activity compared with
8
9 inactivity and strenuous physical activity, asthma control is positively affected.[28] The
10
11 positive effects on these other asthma outcomes could support our finding that
12
13 physical activity is associated with lower mortality risk.
14
15

16
17 The effects of physical activity are prudent to establish as we know that persons with
18
19 asthma generally are less physically active than the general population.[29] Further,
20
21 we know from a Cochrane review from 2013 that physical activity is well-tolerated and
22
23 safe for individuals with asthma.[30] The review found that physical activity may
24
25 improve cardiopulmonary function in individuals with asthma without a negative
26
27 impact on pulmonary function. Furthermore, the Cochrane review is based on shorter-
28
29 term studies. Long-term findings from the Copenhagen City Heart study suggest that
30
31 physical activity may diminish long-term lung function decline in individuals with
32
33 asthma.[31] The amount of physical activity required to be defined as physically active
34
35 in our study is relatively low and, therefore, should be attainable by most. However,
36
37 future studies should explore whether there are additional benefits from moderate
38
39 and high levels of activity. Additionally, would a high or very high level of activity mean
40
41 the risks of adverse outcomes outweigh the benefits? A study by Russell et al.[32]
42
43 found that the benefits of physical activity on asthma symptoms were only present at
44
45 light levels of activity and not at intense activity levels. Based on our findings, there is
46
47 absolutely reason to motivate persons with asthma to do some form of physical
48
49 activity in their leisure time.
50
51
52
53
54
55
56
57
58
59
60

Comorbidities

Hypertension had a strong association with death. Overall all included comorbid conditions at baseline appeared to be associated with a higher risk of death. However, only hypertension had a robust estimate, probably since the remaining comorbidities (diabetes, stroke and myocardial infarction) had a relatively low prevalence at baseline.

There is limited research on how hypertension relates to mortality in a person with asthma.[14] We found one other study by Sumino et al[33] from 2014 that report the association between hypertension and mortality. They found a lower OR for mortality among individuals with hypertension for individuals over the age of 65 years. However, the study by Sumino et al[33] had a much shorter follow-up of three years compared with the 20 years of our study. Given that hypertension is a condition that gives long-term complications, these complications are likely not caught across such a short period.

While the estimated hazard ratio for mortality among those with diabetes was imprecise due to lack of power, it is worth mentioning that there appeared to be a strong association between diabetes and a higher risk of all-cause mortality. While the amount of other studies is exceedingly limited, there is other literature supporting this finding.

The study by Sumino et al[33] found that diabetes was associated with a higher mortality rate in persons over the age of 65. Another cohort study by Koskela et al[34] showed that among 110 patients admitted due to an asthma exacerbation, there was a higher risk of mortality for those with diabetes. While there is a clear trend in our data towards higher all-cause mortality risk for individuals with previous myocardial infarction, the HR estimate was imprecise once again due to only four events. Nevertheless, an excess risk of mortality due to cardiovascular disease is an area that has substantial data supporting it in asthma cohorts, and this certainly supports our finding.[35,36]

1
2
3 The factors presented in this paper may seem obvious but needs to be verified in asthma
4
5 mainly, as many of these factors have not previously been explored in relation to adults
6
7 with asthma. Not least in large cohorts, as in the present long-term follow-up study of a
8
9 large cohort of middle-aged men and women with asthma. The relevance of this is due
10
11 to the systemic inflammation present in persons with asthma, which potentially could
12
13 affect and change which factors are essential to be aware of compared with general
14
15 populations.[37,38]
16
17
18
19
20
21
22
23
24

25 *Limitations*

26
27 The diagnosis of asthma in the included subjects was based on ICD-10 codes connected
28
29 to hospital contacts, which is not as accurate as objectively verified asthma. However,
30
31 this has previously been established by Jensen et al[39] to be a robust method of
32
33 identifying persons with asthma. The positive predictive value was found to be 65%;
34
35 despite this, they discovered that associations found are still relevant. Selecting only
36
37 persons with either a hospital or outpatient contact means we may limit
38
39 generalisability, with the majority of persons included may have moderate or severe
40
41 disease. Nonetheless, a study from 2014 found that upwards of 25% of asthma
42
43 patients with mild to moderate disease experience poor asthma control and hospital
44
45 admissions.[40]
46
47
48
49
50

51
52 The prevalence of asthma in this cohort is low (about 1%), substantially lower than the
53
54 current reported prevalence in Denmark of 10%; therefore, the generalizability is
55
56 limited. The low prevalence is due to only including participants without a previous
57
58 diagnosis of asthma and only included individuals referred to secondary care.
59
60

1
2
3 Our definition of physical activity was based on self-reported information, which carries
4 a certain degree of bias. Additionally, a potential limitation is that the degree of self-
5 reported physical activity for some was reported multiple years before the first contact
6 for incident asthma. We can, therefore, not be sure that the level of physical activity still
7 applies at follow-up. However, previous literature suggests that physical activity tracks
8 well over time, particularly in adulthood.[41,42]
9

10 We did not have information on the specific cause of death and could not examine
11 factors relating to asthma-specific mortality. Furthermore, we did not have data on
12 asthma severity, medication, pulmonary function and previous exacerbation, which
13 influences mortality risk.
14

15 As the number of events in this cohort study was not substantial, there is a risk of both
16 under and overestimating the importance of the identified risk factors. Therefore, the
17 results of this study cannot stand on their own, yet it provides a valuable source for
18 future studies. This is particularly evident for diabetes, which shows a clear trend for a
19 higher risk of mortality, though it lacks the power for a precise estimate.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 *Conclusions*

43
44 Our study has shown that for middle-aged individuals with hospital contact for incident
45 asthma, there appears to be increased mortality for persons with comorbidity. In
46 contrast, leisure-time physical activity was found to have a protective effect on mortality
47 risk.
48
49
50
51
52
53
54
55
56

57 **Abbreviations:**

58 BMI = Body Mass Index
59
60

1
2
3 DCH = Diet Cancer and Health Cohort

4
5 HR = Hazard Ratio

6
7 OR = Odds Ratio

8
9
10
11 **Declarations**

12
13 **Ethics approval and consent to participate:** The study was approved by the ethical
14 committee for the Capital Region of Denmark (H-17025043), the regional data safety
15 committee for the capital region of Denmark (P-2019-712), and The Danish Data
16 Protection Agency (2014-41-3468). All participants signed an informed consent form.

17
18
19
20
21
22
23 **Funding:** This research did not receive any specific grant from funding agencies in
24 the public, commercial, or not-for-profit sectors.

25
26
27
28 **Competing interests:** ODT, ZJA and CSU have no perceived conflicts of interest in
29 relation to this study.

30
31
32
33 **Authors' contributions:** Conception and design—ODT, ZJA and CSU.; preparation of
34 data and statistical analyses - ZJA.; statistical interpretation and drafted the
35 manuscript—ODT; all authors critically reviewed and accepted the final version of the
36 manuscript.

37
38
39
40
41
42
43 **Availability of data and material:** The data are available upon reasonable request, but
44 analysis may require approval from the regional data safety committee for the capital
45 region of Denmark (Videnscenter for dataanmeldelser).

46
47
48
49
50 **Acknowledgements:** Thanks to Anne Tjønneland and Kim Overvad for providing us
51 with access to the data from the Diet, Cancer and Health cohort.

References

- 1 WHO. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. <http://www.who.int/gard/publications/GARD Book 2007.pdf?ua=1>
- 2 Global strategy for asthma management and prevention. Glob. Initiat. Asthma. 2020. <https://ginasthma.org> (accessed 16 Jun 2020).
- 3 Huovinen E, Kaprio J, Vesterinen E, *et al.* Mortality of adults with asthma: A prospective cohort study. *Thorax* 1997;**52**:49–54. doi:10.1136/thx.52.1.49
- 4 D’Amato G, Vitale C, Molino A, *et al.* Asthma-related deaths. *Multidiscip Respir Med* 2016;**11**:1–5. doi:10.1186/s40248-016-0073-0
- 5 Speizer FE, Doll R, Heaf P. Observations on Recent Increase in Mortality from Asthma. *Br Med J* 1968;**1**:335–9. doi:10.1136/bmj.1.5588.335
- 6 Jackson RT, Beaglehole R, Rea HH, *et al.* Mortality from asthma: A new epidemic in New Zealand. *Br Med J* 1982;**285**:771–4. doi:10.1136/bmj.285.6344.771
- 7 Sly RM. Mortality from asthma, 1979–1984. *J Allergy Clin Immunol* 1988;**82**:705–17. doi:10.1016/0091-6749(88)90069-3
- 8 Ebmeier S, Thayabaran D, Braithwaite I, *et al.* Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993–2012). *Lancet* 2017;**390**:935–45. doi:10.1016/S0140-6736(17)31448-4
- 9 Levy ML. The national review of asthma deaths: What did we learn and what needs to change? *Breathe* 2015;**11**:15–24. doi:10.1183/20734735.008914
- 10 McCoy L, Redelings M, Sorvillo F, *et al.* A multiple cause-of-death analysis of asthma mortality in the United States, 1990–2001. *J Asthma* 2005;**42**:757–63. doi:10.1080/02770900500308189
- 11 Soriano JB, Visick GT, Muellerova H, *et al.* Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;**128**:2099–107. doi:10.1378/chest.128.4.2099
- 12 Gershon AS, Wang C, Guan J, *et al.* Burden of comorbidity in individuals with asthma. *Thorax* 2010;**65**:612–8. doi:10.1136/thx.2009.131078
- 13 Adams RJ, Wilson DH, Taylor AW, *et al.* Coexistent chronic conditions and asthma quality of life: A population-based study. *Chest* 2006;**129**:285–91. doi:10.1378/chest.129.2.285
- 14 Marques de Mello L, Cruz AA. A proposed scheme to cope with comorbidities in asthma. *Pulm Pharmacol Ther* 2018;**52**:41–51. doi:10.1016/j.pupt.2018.08.005
- 15 Lear SA, Hu W, Rangarajan S, *et al.* The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet* 2017;**390**:2643–54. doi:10.1016/s0140-6736(17)31634-3
- 16 Waschki B, Kirsten A, Holz O, *et al.* Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011;**140**:331–42. doi:10.1378/chest.10-2521
- 17 Cordova-Rivera L, Gibson PG, Gardiner PA, *et al.* A Systematic Review of Associations of Physical Activity and Sedentary Time with Asthma Outcomes. *J Allergy Clin Immunol Pr* 2018;**6**:1968–1981 e2. doi:10.1016/j.jaip.2018.02.027
- 18 Tjønneland A, Olsen A, Boll K, *et al.* Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in

- Denmark. *Scand J Public Health* 2007;**35**:432–41. doi:10.1080/14034940601047986
- 19 Bønnelykke K, Raaschou-Nielsen O, Tjønneland A, *et al.* Postmenopausal hormone therapy and asthma-related hospital admission. *J Allergy Clin Immunol* 2015;**135**:813–816.e5. doi:10.1016/j.jaci.2014.11.019
- 20 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**:22–5. doi:10.1177/1403494810387965
- 21 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449. doi:10.2147/CLEP.S91125
- 22 Cust AE, Smith BJ, Chau J, *et al.* Validity and repeatability of the EPIC physical activity questionnaire: A validation study using accelerometers as an objective measure. *Int J Behav Nutr Phys Act* 2008;**5**:33. doi:10.1186/1479-5868-5-33
- 23 Peters T, Brage S, Westgate K, *et al.* Validity of a short questionnaire to assess physical activity in 10 European countries. *Eur J Epidemiol* 2012;**27**:15–25. doi:10.1007/s10654-011-9625-y
- 24 Garcia-Aymerich J, Varraso R, Antó JM, *et al.* Prospective study of physical activity and risk of asthma exacerbations in older women. *Am J Respir Crit Care Med* 2009;**179**:999–1003. doi:10.1164/rccm.200812-1929OC
- 25 Fisher JE, Loft S, Ulrik CS, *et al.* Physical Activity, Air Pollution, and the Risk of Asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016;**194**:855–65. doi:10.1164/rccm.201510-2036OC
- 26 Chippes BE, Zeiger RS, Borish L, *et al.* Key findings and clinical implications from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2012;**130**:332–342.e10. doi:10.1016/j.jaci.2012.04.014
- 27 Panagiotou M, Koulouris NG, Rovina N. Physical Activity: A Missing Link in Asthma Care. *J Clin Med* 2020;**9**:706. doi:10.3390/jcm9030706
- 28 Del Giacco SR, Firinu D, Bjermer L, *et al.* Exercise and asthma: an overview. *Eur Clin Respir J* 2015;**2**:27984. doi:10.3402/ecrj.v2.27984
- 29 van 't Hul AJ, Frouws S, van den Akker E, *et al.* Decreased physical activity in adults with bronchial asthma. *Respir Med* 2016;**114**:72–7. doi:10.1016/j.rmed.2016.03.016
- 30 Kv C, Mg C, Picot J, *et al.* Physical training for asthma (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Libr* 2013;:1–73. doi:10.1002/14651858.CD001116.pub4.www.cochranelibrary.com
- 31 Garcia-Aymerich J, Lange P, Benet M, *et al.* Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: A population-based cohort study. *Am J Respir Crit Care Med* 2007;**175**:458–63. doi:10.1164/rccm.200607-896OC
- 32 Russell MA, Janson C, Real FG, *et al.* Physical activity and asthma: A longitudinal and multi-country study. *J Asthma* 2017;**54**:938–45. doi:10.1080/02770903.2017.1281293
- 33 Sumino K, O'Brian K, Bartle B, *et al.* Coexisting chronic conditions associated with mortality and morbidity in adult patients with asthma. *J Asthma* 2014;**51**:306–14. doi:10.3109/02770903.2013.879881
- 34 Koskela HO, Salonen PH, Romppanen J, *et al.* A history of diabetes but not

- 1
2
3 hyperglycaemia during exacerbation of obstructive lung disease has impact on
4 long-term mortality: A prospective, observational cohort study. *BMJ Open*
5 2015;**5**:6794. doi:10.1136/bmjopen-2014-006794
6
7 35 Xu M, Xu J, Yang X. Asthma and risk of cardiovascular disease or all-cause
8 mortality: A meta-analysis. *Ann Saudi Med* 2017;**37**:99–105. doi:10.5144/0256-
9 4947.2017.99
10
11 36 Strand LB, Tsai MK, Wen CP, *et al*. Is having asthma associated with an increased
12 risk of dying from cardiovascular disease? A prospective cohort study of 446 346
13 Taiwanese adults. *BMJ Open* 2018;**8**. doi:10.1136/bmjopen-2017-019992
14
15 37 Denburg JA, Sehmi R, Saito H, *et al*. Systemic aspects of allergic disease: Bone
16 marrow responses. *J Allergy Clin Immunol* 2000;**106**:S242–6.
17 doi:10.1067/mai.2000.110156
18
19 38 Bjermer L. Time for a paradigm shift in asthma treatment: From relieving
20 bronchospasm to controlling systemic inflammation. *J Allergy Clin Immunol*
21 2007;**120**:1269–75. doi:10.1016/j.jaci.2007.09.017
22
23 39 Jensen AO, Nielsen GL, Ehrenstein V. Validity of asthma diagnoses in the Danish
24 National Registry of Patients, including an assessment of impact of
25 misclassification on risk estimates in an actual dataset. *Clin Epidemiol*
26 2010;**2**:67–72. <https://www.ncbi.nlm.nih.gov/pubmed/20865105>
27
28 40 von Bülow A, Kriegbaum M, Backer V, *et al*. The Prevalence of Severe Asthma
29 and Low Asthma Control Among Danish Adults. *J Allergy Clin Immunol Pract*
30 2014;**2**:759-767.e2. doi:10.1016/j.jaip.2014.05.005
31
32 41 Telama R. Tracking of physical activity from childhood to adulthood: A review.
33 *Obes. Facts.* 2009;**2**:187–95. doi:10.1159/000222244
34
35 42 Mertens E, Clarys P, Mullie P, *et al*. Stability of physical activity, fitness
36 components and diet quality indices. *Eur J Clin Nutr* 2017;**71**:519–24.
37 doi:10.1038/ejcn.2016.172
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tables

Table 1 – Baseline characteristics of 785 adults enrolled in the Danish Diet, Cancer and Health Cohort with incident asthma between baseline (1993-1997) and follow-up (July 2013).

| | Asthma (N = 785) | Alive (N= 709) | Dead (N = 76) |
|---|-----------------------|-------------------|------------------|
| Age 50-55, n (%) | 50 (6.4) | 44 (6.2) | 6 (7.9) |
| Age 55-60, n (%) | 155 (19.7) | 136 (19.2) | 19 (25.0) |
| Age 60-65, n (%) | 580 (73.9) | 529 (74.6) | 51 (67.1) |
| Men, n (%) | 290 (37) | 136 (19) | 19 (25) |
| Mean body mass index (kg/m ²) | 26.5 (12) | 26.4 (4.2) | 27.1 (4.6) |
| Smoking history, n (%) | Never | 351 (45) | 318 (45) |
| | Previous | 260 (33) | 241 (34) |
| | Current | 174 (22) | 150 (21) |
| Mean smoking duration, years (SD) | 25.9 (12) | 25.3 (12) | 31.1 (12) |
| Mean smoking intensity, g/day (SD) | 5.7 (9.1) | 5.3 (9.0) | 9.1 (10) |
| Exposed to environmental tobacco smoke, n (%) | 449 (57) | 403 (57) | 46 (61) |
| Physically active in leisure time, n (%) | 432 (55) | 404 (57) | 28 (37) |
| Mean fruit intake, g/day (SD) | 192 (145) | 193 (146) | 177 (129) |
| Employed, n (%) | 612 (78) | 559 (79) | 53 (70) |
| Marital status, n (%) | Single | 45 (5.7) | 35 (4.9) |
| | Married | 558 (71) | 507 (72) |
| | Divorced | 136 (17) | 125 (18) |
| | Widowed | 46 (5.9) | 42 (5.9) |
| Years of Education n (%) | < 8 | 223 (28) | 198 (28) |
| | 8 – 10 | 395 (50) | 361 (51) |
| | ≥ 10 | 167 (21) | 150 (21) |
| Comorbidity n (%) | Myocardial infarction | 13 (1.7) | 9 (1.3) |
| | Stroke | 4 (0.5) | 3 (0.4) |
| | Diabetes | 13 (1.7) | 8 (1.1) |
| | Hypertension | 155 (20) | 126 (18) |
| | Hypercholesterolemia | 46 (5.9) | 45 (6.3) |

SD = standard deviation

Table 2 - Determinants at baseline of survival in 785 adults with incident asthma during follow-up (2013) among participants in the Danish Diet, Cancer and Health Cohort.

| | | Univariate model HR (95% CI) | Multivariate model HR (95% CI) |
|-----------------------------|--|------------------------------------|--------------------------------------|
| Age | 50-55 | 1.00 | - |
| | 55-60 | 0.84 (0.33-2.14) | |
| | 60-65 | 0.76 (0.28-2.08) | |
| Sex | Female | 1.00 | 1.00 |
| | Male | 1.76 (1.12-2.75) | 1.83 (1.14-2.93) |
| Body Mass index | Underweight/Normal (<25 kg/m ²) | 1.00 | - |
| | Overweight (25-30 kg/m ²) | 1.56 (0.93-2.63) | - |
| | Obese (≥ 30 kg/m ²) | 1.52 (0.79-2.91) | - |
| Smoking | Never | 1.00 | 1.00 |
| | Previous | 0.67 (0.38-1.18) | 0.59 (0.33-1.05) |
| | Current | 1.64 (0.96-2.78) | 1.39 (0.81-2.38) |
| Activity in Leisure Time | Inactive | 1.00 | 1.00 |
| | Active | 0.47 (0.29-0.74) | 0.53 (0.33-0.85) |
| Mean fruit intake | g/day | 0.91 (0.76-1.07) | - |
| Employment | Yes | 1.00 | 1.00 |
| | No | 1.17 (0.70-1.96) | 1.04 (0.87-1.25) |
| Marital Status | Single | 2.77 (1.40-5.48) | 2.16 (2.06-4.40) |
| | Married | 1.00 | 1.00 |
| | Divorced | 0.79 (0.41-1.51) | 0.76 (0.40-1.47) |
| | Widowed | 0.83 (0.30-2.30) | 1.15 (0.40-3.27) |
| Myocardial infarction | - | 1.00 | - |
| | + | 2.87 (1.04-7.89) | - |
| Stroke | - | 1.00 | - |
| | + | 1.58 (0.22-11.43) | - |
| Diabetes | - | 1.00 | 1.00 |
| | + | 3.58 (1.44-8.90) | 2.42 (0.96-6.11) |
| Hypertension | - | 1.00 | 1.00 |
| | + | 2.57 (1.61-4.09) | 2.47 (1.54-3.95) |

HR = Hazard Ratio. CI = Confidence interval.

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

| | Item No | Recommendation |
|------------------------------|---------|---|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract – page 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found - page 2 |
| Introduction | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported -page 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses -page 4 |
| Methods | | |
| Study design | 4 | Present key elements of study design early in the paper -page 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection -page 4-5 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up -page 4-5 (b) For matched studies, give matching criteria and number of exposed and unexposed - N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable -page 4-6 |
| 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 -page 4-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at -page 4-5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page- 5-6 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding -page 6 (b) Describe any methods used to examine subgroups and interactions -N/A (c) Explain how missing data were addressed -N/A (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses -N/A |

| 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 Page -4 and 8 (b) Give reasons for non-participation at each stage -due to space limitations non-participation for the DCH cohort is available in the referenced previous articles. (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders -table 1 (b) Indicate number of participants with missing data for each variable of interest -N/A (c) Summarise follow-up time (eg, average and total amount) -page 8 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time |
| 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 -table 2 (b) Report category boundaries when continuous variables were categorized -table 2 (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -N/A |
| Discussion | | |
| Key results | 18 | Summarise key results with reference to study objectives -page 8 |
| 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 Page 11-12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence -page 8-11 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results -page 11 |
| Other information | | |
| 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 -page 12 |

*Give information separately for exposed and unexposed groups.

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

For peer review only

BMJ Open

Demographic, lifestyle, and comorbid risk factors for all-cause mortality in a Danish cohort of middle-aged adults with incident asthma

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2021-049243.R2 |
| Article Type: | Original research |
| Date Submitted by the Author: | 24-Jul-2021 |
| Complete List of Authors: | Tupper, Oliver Djurhuus; Hvidovre Hospital, Department of Respiratory Medicine Andersen, ZJ; University of Copenhagen Department of Public Health, Section of Environmental Health Ulrik, Charlotte; Hvidovre Hospital, Department of Respiratory Medicine |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Respiratory medicine |
| Keywords: | Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, Adult thoracic medicine < THORACIC MEDICINE |
| | |

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 **Demographic, lifestyle, and comorbid risk factors for all-cause**
4
5
6 **mortality in a Danish cohort of middle-aged adults with**
7
8
9 **incident asthma**

10
11
12
13 Oliver Djurhuus Tupper¹, Zorana Jovanovic Andersen², and Charlotte

14
15
16 Suppli Ulrik^{1,3}

17
18
19 ¹ Department of Respiratory Medicine, Copenhagen University Hospital Hvidovre,
20
21 Denmark

22
23
24 ² Section of Environmental Health, Department of Public health, University of
25
26 Copenhagen, Denmark

27
28
29 ³ Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

30
31 **Corresponding Author**

32
33 Oliver Djurhuus Tupper MD, PhD

34
35 Respiratory Research Unit

36
37 Department of Respiratory Medicine

38
39 Hvidovre Hospital

40
41 Kettegård Alle 30

42
43 DK-2650 Hvidovre

44
45 E-mail olivertupper@gmail.com

46
47
48 Word count abstract: 248

49
50 Word count main text: 2600

Abstract

Objectives:

We aimed to identify factors associated with all-cause mortality in adults with incident asthma.

Design and setting:

Cross-sectional cohort study, in the metropolitan areas of Copenhagen and Aarhus, Denmark.

Participants:

Adults aged 50–64 years enrolled in the Danish Diet, Cancer, and Health cohort were followed from baseline (1993–1997) in the National Patients Registry for first-time admissions for asthma and vital status. We defined incident asthma as at least one first-time hospital admission with asthma as the primary registered diagnosis between baseline and end of follow-up (2013) in participants without previously known asthma. Among the cohort comprising 57 053 individuals, we identified 785 adults (aged 50–64) with incident asthma, of whom 76 died during follow-up.

Primary and secondary outcome measures:

Baseline reported socioeconomic and lifestyle traits, and comorbidities associated with all-cause mortality.

Results:

Self-reported leisure-time physical activity was associated with a substantial reduction in risk with an HR of 0.53 (95 % CI 0.33–0.85). Being male, single, and having a diagnosis of hypertension or diabetes were associated with an increased risk of all-cause mortality

1
2
3 with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–
4
5 3.95) and of 2.42 (95 % CI 0.96–6.11), respectively.

6 7 8 Conclusions:

9
10 This long-term study of adults with hospital contacts for incident asthma revealed
11
12 that self-reported leisure-time physical activity is associated with an approximately
13
14 50% reduction in all-cause mortality. In contrast, both hypertension and diabetes
15
16 were associated with a higher risk of mortality.
17
18

19 20 21 22 **Strengths and limitations of this study:**

- 23
24 • The present study is one of very few reporting on how physical activity and
25
26 comorbidities are associated with all-cause mortality in adults with asthma.
27
- 28
29 • Seven hundred eighty-five persons with incident asthma were followed-up
30
31 for 20 years, with no loss to follow-up.
32
- 33
34 • The diagnosis of asthma is based on register information and not an objective
35
36 assessment.
37
- 38
39 • There are only very few events among those with previous myocardial
40
41 infarction and stroke.
42
43
44
45

46 **Keywords:** Asthma, middle-aged adults, population cohort, comorbidities, long-term

47
48 **Short Title:** Physical activity and asthma mortality

49 50 51 **Introduction**

52
53 With over 300 million persons worldwide suffering from asthma and many deaths each
54
55 year, asthma is a disease that continually requires attention.[1,2] Asthma remains a
56
57 disease that carries increased mortality compared with general populations.[3,4]
58
59
60

1
2
3 Asthma-specific mortality has, overall, been on a steady decline since the 1950s.[5–7]
4
5
6 However, a study based on the WHO Mortality Database found that mortality trends
7
8 have plateaued, with no significant change in mortality between 2006 and 2012.[8]
9
10
11 Furthermore, a British report from 2014 reported that over 67% of deaths related to
12
13 asthma were potentially preventable.[9]

14
15 Asthma-specific mortality alone does not provide the whole picture when evaluating the
16
17 risks of the disease for individual patients. A study assessing deaths with asthma as a
18
19 contributing factor, in addition to asthma-specific causes, found that asthma as a
20
21 contributing factor was associated with more than twice as many deaths compared with
22
23 asthma-specific deaths alone.[10] Studies suggest that patients with asthma are more
24
25 prone to acquire other chronic conditions than the background population.[11–13] As
26
27 the impact of factors as multimorbidity on all-cause mortality is an area with a paucity
28
29 of data, a need for studies in these areas exists.[14] The association between physical
30
31 activity and long-term mortality has been well established in the general population and
32
33 patients with COPD.[15,16] However, this has not been examined extensively in
34
35 asthma.[17] The impact of physical activity on asthma-specific factors, such as disease
36
37 control, lung function, and exacerbations has been well researched.[17]

38
39 Based on the currently available knowledge, it remains of utmost to further explore
40
41 factors associated with asthma-related mortality, including not least all-cause mortality.
42
43 The present study aimed to examine demographic, lifestyle and comorbid factors
44
45 associated with long-term all-cause mortality in adults with incident asthma from a large
46
47 Danish cohort.
48
49
50
51
52
53
54
55
56
57
58
59
60

Methods

Characteristics of the Diet, Cancer, and Health (DCH) cohort have been published previously, with a full description of the cohort.[18,19] A total of 160,725 individuals (72,729 women) were invited to participate in the DCH Cohort between 1993 and 1997. All individuals resided in either Copenhagen or Aarhus, which are the two largest cities in Denmark. To be invited, participants had to be 50–64 years of age and have no record of cancer at the time of inclusion. A total of 57,053 individuals (52.4% women, n=29,875) were enrolled in the study after accepting the invitation. The Central Danish Ethics Committee approved the main study of the DCH-cohort. The regional Danish Ethics Committee approved this sub-study (H-17025043) and the Danish Data Protection Agency (2014-41-3468). All participants provided written informed consent. Baseline factors were determined based on a comprehensive questionnaire completed by the participants. The questionnaire consisted of questions on general health and diet; demographic factors, including education and occupation; questions on lifestyle, including tobacco exposure; and pre-existing diseases, including asthma, COPD, diabetes, and cardiovascular disease.

Study cohort

Participants in the DCH cohort were defined as having incident asthma and included in the present analyses as cases if they had the first-ever admission to a hospital, emergency department, or outpatient clinic with a primary diagnosis of asthma, which occurred between cohort baseline (1993-1997) and July 1st, 2013. Asthma was classified according to the International Classification of Diseases (ICD) as ICD-10 codes DJ45–46 and ICD-8 codes 493.00–493.09. Participants with a self-reported diagnosis of asthma

1
2
3 or COPD at baseline were excluded. Participants in the DCH cohort were linked to the
4
5 Danish National Patient Registry (DNPR) to extract hospital contacts from 1993-1997
6
7 until July 1st, 2013.[20] The link between the DCH and DNPR was done using the unique
8
9 identifier all Danish residents have. Every discharge diagnosis from all Danish hospitals
10
11 since 1978 and from outpatient clinics since 1995 are gathered in the DNPR.[21] In
12
13 addition to hospital contacts, we gathered emergency room visits and visits to
14
15 respiratory outpatient clinics. Cases were followed from first-ever asthma admission
16
17 until the time of death, emigration, or July 1st, 2013, whichever came first.
18
19
20
21
22
23
24

25 Physical activity in leisure time was determined based on a participant completed
26
27 questionnaire. An interviewer checked the questionnaire. Participants reported the
28
29 number of hours per week they did leisure time and transport-related (i.e., to and from
30
31 work, shopping) physical activity. Leisure-time physical activity was reported separately
32
33 for summer and winter of the previous year. It was allocated in the following categories:
34
35 cycling, "do-it-yourself" activities (i.e., home improvements), gardening, housework
36
37 (cleaning, laundry), sports, and walking. The two values for summer and winter were
38
39 averaged. The questions used have previously been validated in two studies by Peters
40
41 et al and Cust et al that found high correlations with movement sensing measurement
42
43 and accelerometer measurements, respectively.[22,23] Participants reported as being
44
45 physically active in leisure time, spent at least half an hour a week on at least one of the
46
47
48
49
50
51
52 six categories.
53
54
55
56

57 Statistical Analyses

58
59
60

1
2
3 Associations between baseline factors and all-cause mortality were examined using the
4
5 Cox proportional hazards model with age as the underlying time scale. We examined the
6
7 following baseline factors identified at recruitment between 1993 and 1999: age, sex,
8
9 BMI, length of education, employment and civil status, tobacco history, occupational
10
11 exposure, leisure-time physical activity, fruit consumption, and comorbidities. Baseline
12
13 factors were assessed in a two-step process: Step one, in a univariate model, with age
14
15 as the underlying time scale. Step two was in a multivariate model that included only
16
17 variables associated with all-cause mortality, defined by backward elimination. The
18
19 proportional hazards assumption was evaluated by testing for a non-zero slope in a
20
21 generalised linear regression of the scaled Schoenfeld residuals on functions of time.
22
23 The univariate and multivariate model results are presented as hazard ratios (HRs) with
24
25 95% confidence intervals (CIs). Stata, version 11.2, was used to perform statistical
26
27 analyses.
28
29
30
31
32
33
34
35
36
37
38

Patient and Public Involvement

39 Patients and the public were not involved in the design of the study.
40
41
42
43
44

Results

45
46
47 We identified 785 adults with an incident diagnosis of asthma and fulfilled the criteria
48
49 for inclusion in the present analyses. No individuals were lost to follow-up, and
50
51 therefore complete data were available for all 785 individuals. All characteristics
52
53 included in the following analyses were obtained at baseline.
54
55
56
57
58
59
60

1
2
3 Between baseline and July 1st, 2013, 76 of the identified adults with incident asthma
4
5 died. The majority of cases with incident asthma were women 63% (n=495). Only 45%
6
7 (n=351) were never smokers at baseline. Interestingly, a substantial proportion of
8
9 ever-smokers were ex-smokers (60%, n=260) and not current smokers (40%, n=174).
10
11 The amount of tobacco exposure was much higher among those who died than those
12
13 with incident asthma still alive at the end of follow-up. On average, persons who died
14
15 smoked 3.8 grams of tobacco per day, corresponding to 72% more than those alive at
16
17 the end of follow-up. Those who died had a daily intake of fruit that was 16 g (or 8.3 %)
18
19 less than those still alive. Further characteristics are shown in Table 1.
20
21
22
23
24
25
26
27

28 Of the baseline characteristics included in the analyses, the following were found to be
29
30 associated with all-cause mortality and were therefore included in the final model: (1)
31
32 sex, (2) smoking status, (3) physical activity in leisure time, (5) employment status, (6)
33
34 marital status, (7) diabetes and (8) hypertension. On the other hand, age and a
35
36 previous diagnosis of myocardial infarction or stroke lacked power for precise
37
38 estimates for all-cause mortality in univariate analyses and were therefore not
39
40 included in the final model.
41
42
43
44

45 Male sex was associated with a higher risk for all-cause mortality (HR 1.83, 95% CI
46
47 1.14-2.93).
48

49 Persons who reported being single had a higher mortality risk (HR of 2.16 95% CI 2.06-
50
51 4.40) compared with persons who reported being married.
52

53 A diagnosis of hypertension was associated with a substantially increased risk of all-
54
55 cause mortality (HR 2.47, 95% CI 1.54–3.95). Self-reported previous myocardial
56
57 infarction and a current diagnosis of diabetes had imprecise estimates associated with
58
59
60

1
2
3 all-cause mortality, although, notably, robust associations were detected. We found an
4
5 HR of 2.87 (95% CI 1.04-7.89) in the univariate model for myocardial infarction. An HR
6
7 of 2.42 (95% CI 0.96-6.11) for diabetes was found in the multivariate model. There was
8
9 not found an association between previous stroke and all-cause mortality.
10
11

12
13 The self-reported leisure-time physical activity showed a substantial reduction in all-
14
15 cause mortality (HR 0.53, 95% CI 0.33–0.85).
16

17
18 Mean daily fruit intake was not found to be associated with death (table 2).
19
20

21 22 **Discussion**

23
24
25 In this Danish cohort of 785 adults with incident asthma followed for 20 years, we found
26
27 that physical activity was associated with a lower risk of all-cause mortality. In contrast,
28
29 being unmarried or having hypertension were associated with increased all-cause
30
31 mortality.
32
33

34 35 *Physical Activity*

36
37
38 To the best of our knowledge, this is the first cohort study that has reported the
39
40 association between self-reported physical activity and all-cause mortality, specifically
41
42 in individuals with asthma. Physical activity has previously been shown to have a
43
44 positive effect on multiple aspects of asthma.[17] Particularly relevant are two studies
45
46 by Garcia-Aymerich et al[24] and Fisher et al[25] that found a protective effect of self-
47
48 reported physical activity on hospitalisation with asthma exacerbations. While the
49
50 same effect could not be found on readmissions for exacerbations in the study by
51
52 Fisher et al[25], their findings are essential support of our findings, as exacerbations
53
54 are associated with morbidity and mortality.[26] Physical activity also appears to have
55
56
57
58
59
60

1
2
3 a positive effect on asthma control.[27] However, BMI appears to be more critical,
4
5 negating the effects of physical activity in some, but not all, models.[17] It appears that
6
7 if persons with asthma do a moderate level of physical activity compared with
8
9 inactivity and strenuous physical activity, asthma control is positively affected.[28] The
10
11 positive effects on these other asthma outcomes could support our finding that
12
13 physical activity is associated with lower mortality risk.
14
15

16
17 The effects of physical activity are prudent to establish as we know that persons with
18
19 asthma generally are less physically active than the general population.[29] Further,
20
21 we know from a Cochrane review from 2013 that physical activity is well-tolerated and
22
23 safe for individuals with asthma.[30] The review found that physical activity may
24
25 improve cardiopulmonary function in individuals with asthma without a negative
26
27 impact on pulmonary function. Furthermore, the Cochrane review is based on shorter-
28
29 term studies. Long-term findings from the Copenhagen City Heart study suggest that
30
31 physical activity may diminish long-term lung function decline in individuals with
32
33 asthma.[31] The amount of physical activity required to be defined as physically active
34
35 in our study is relatively low and, therefore, should be attainable by most. However,
36
37 future studies should explore whether there are additional benefits from moderate
38
39 and high levels of activity. Additionally, would a high or very high level of activity mean
40
41 the risks of adverse outcomes outweigh the benefits? A study by Russell et al.[32]
42
43 found that the benefits of physical activity on asthma symptoms were only present at
44
45 light levels of activity and not at intense activity levels. Based on our findings, there is
46
47 absolutely reason to motivate persons with asthma to do some form of physical
48
49 activity in their leisure time.
50
51
52
53
54
55
56
57
58
59
60

Comorbidities

Hypertension had a strong association with death. Overall all included comorbid conditions at baseline appeared to be associated with a higher risk of death. However, only hypertension had a robust estimate, probably since the remaining comorbidities (diabetes, stroke and myocardial infarction) had a relatively low prevalence at baseline.

There is limited research on how hypertension relates to mortality in a person with asthma.[14] We found one other study by Sumino et al[33] from 2014 that report the association between hypertension and mortality. They found a lower OR for mortality among individuals with hypertension for individuals over the age of 65 years. However, the study by Sumino et al[33] had a much shorter follow-up of three years compared with the 20 years of our study. Given that hypertension is a condition that gives long-term complications, these complications are likely not caught across such a short period.

While the estimated hazard ratio for mortality among those with diabetes was imprecise due to lack of power, it is worth mentioning that there appeared to be a strong association between diabetes and a higher risk of all-cause mortality. While the amount of other studies is exceedingly limited, there is other literature supporting this finding.

The study by Sumino et al[33] found that diabetes was associated with a higher mortality rate in persons over the age of 65. Another cohort study by Koskela et al[34] showed that among 110 patients admitted due to an asthma exacerbation, there was a higher risk of mortality for those with diabetes. While there is a clear trend in our data towards higher all-cause mortality risk for individuals with previous myocardial infarction, the HR estimate was imprecise once again due to only four events. Nevertheless, an excess risk of mortality due to cardiovascular disease is an area that has substantial data supporting it in asthma cohorts, and this certainly supports our finding.[35,36]

1
2
3 The factors presented in this paper may seem obvious but needs to be verified in asthma
4
5 mainly, as many of these factors have not previously been explored in relation to adults
6
7 with asthma. Not least in large cohorts, as in the present long-term follow-up study of a
8
9 large cohort of middle-aged men and women with asthma. The relevance of this is due
10
11 to the systemic inflammation present in persons with asthma, which potentially could
12
13 affect and change which factors are essential to be aware of compared with general
14
15 populations.[37,38]
16
17
18
19
20
21
22
23
24

25 *Limitations*

26
27 The diagnosis of asthma in the included subjects was based on ICD-10 codes connected
28
29 to hospital contacts, which is not as accurate as objectively verified asthma. However,
30
31 this has previously been established by Jensen et al[39] to be a robust method of
32
33 identifying persons with asthma. The positive predictive value was found to be 65%;
34
35 despite this, they discovered that associations found are still relevant. Selecting only
36
37 persons with either a hospital or outpatient contact means we may limit
38
39 generalisability, with the majority of persons included may have moderate or severe
40
41 disease. Nonetheless, a study from 2014 found that upwards of 25% of asthma
42
43 patients with mild to moderate disease experience poor asthma control and hospital
44
45 admissions.[40]
46
47
48
49
50

51
52 The prevalence of asthma in this cohort is low (about 1%), substantially lower than the
53
54 current reported prevalence in Denmark of 10%; therefore, the generalizability is
55
56 limited. The low prevalence is due to only including participants without a previous
57
58 diagnosis of asthma and only included individuals referred to secondary care.
59
60

1
2
3 Our definition of physical activity was based on self-reported information, which carries
4 a certain degree of bias. Additionally, a potential limitation is that the degree of self-
5 reported physical activity for some was reported multiple years before the first contact
6 for incident asthma. We can, therefore, not be sure that the level of physical activity still
7 applies at follow-up. However, previous literature suggests that physical activity tracks
8 well over time, particularly in adulthood.[41,42]
9

10 We did not have information on the specific cause of death and could not examine
11 factors relating to asthma-specific mortality. Furthermore, we did not have data on
12 asthma severity, medication, pulmonary function and previous exacerbation, which
13 influences mortality risk.
14

15 As the number of events in this cohort study was not substantial, there is a risk of both
16 under and overestimating the importance of the identified risk factors. Therefore, the
17 results of this study cannot stand on their own, yet it provides a valuable source for
18 future studies. This is particularly evident for diabetes, which shows a clear trend for a
19 higher risk of mortality, though it lacks the power for a precise estimate.
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41

42 *Conclusions*

43
44 Our study has shown that for middle-aged individuals with hospital contact for incident
45 asthma, there appears to be increased mortality for persons with comorbidity. In
46 contrast, leisure-time physical activity was found to have a protective effect on mortality
47 risk.
48
49
50
51
52
53
54
55
56

57 **Abbreviations:**

58 BMI = Body Mass Index
59
60

1
2
3 DCH = Diet Cancer and Health Cohort

4
5 HR = Hazard Ratio

6
7 OR = Odds Ratio

8
9
10
11 **Declarations**

12
13 **Ethics approval and consent to participate:** The study was approved by the ethical
14
15 committee for the Capital Region of Denmark (H-17025043), the regional data safety
16
17 committee for the capital region of Denmark (P-2019-712), and The Danish Data
18
19 Protection Agency (2014-41-3468). All participants signed an informed consent form.

20
21
22
23 **Funding:** This research did not receive any specific grant from funding agencies in
24
25 the public, commercial, or not-for-profit sectors.

26
27
28 **Competing interests:** ODT, ZJA and CSU have no perceived conflicts of interest in
29
30 relation to this study.

31
32
33 **Authors' contributions:** Conception and design—ODT, ZJA and CSU.; preparation of
34
35 data and statistical analyses - ZJA.; statistical interpretation and drafted the
36
37 manuscript—ODT; all authors critically reviewed and accepted the final version of the
38
39 manuscript.

40
41
42 **Availability of data and material:** The data are available upon reasonable request, but
43
44 analysis may require approval from the regional data safety committee for the capital
45
46 region of Denmark (Videnscenter for dataanmeldelser).

47
48
49 **Acknowledgements:** Thanks to Anne Tjønneland and Kim Overvad for providing us
50
51 with access to the data from the Diet, Cancer and Health cohort.

References

- 1 WHO. Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach. <http://www.who.int/gard/publications/GARD Book 2007.pdf?ua=1>
- 2 Global strategy for asthma management and prevention. Glob. Initiat. Asthma. 2020. <https://ginasthma.org> (accessed 16 Jun 2020).
- 3 Huovinen E, Kaprio J, Vesterinen E, *et al.* Mortality of adults with asthma: A prospective cohort study. *Thorax* 1997;**52**:49–54. doi:10.1136/thx.52.1.49
- 4 D'Amato G, Vitale C, Molino A, *et al.* Asthma-related deaths. *Multidiscip Respir Med* 2016;**11**:1–5. doi:10.1186/s40248-016-0073-0
- 5 Speizer FE, Doll R, Heaf P. Observations on Recent Increase in Mortality from Asthma. *Br Med J* 1968;**1**:335–9. doi:10.1136/bmj.1.5588.335
- 6 Jackson RT, Beaglehole R, Rea HH, *et al.* Mortality from asthma: A new epidemic in New Zealand. *Br Med J* 1982;**285**:771–4. doi:10.1136/bmj.285.6344.771
- 7 Sly RM. Mortality from asthma, 1979–1984. *J Allergy Clin Immunol* 1988;**82**:705–17. doi:10.1016/0091-6749(88)90069-3
- 8 Ebmeier S, Thayabaran D, Braithwaite I, *et al.* Trends in international asthma mortality: analysis of data from the WHO Mortality Database from 46 countries (1993–2012). *Lancet* 2017;**390**:935–45. doi:10.1016/S0140-6736(17)31448-4
- 9 Levy ML. The national review of asthma deaths: What did we learn and what needs to change? *Breathe* 2015;**11**:15–24. doi:10.1183/20734735.008914
- 10 McCoy L, Redelings M, Sorvillo F, *et al.* A multiple cause-of-death analysis of asthma mortality in the United States, 1990–2001. *J Asthma* 2005;**42**:757–63. doi:10.1080/02770900500308189
- 11 Soriano JB, Visick GT, Muellerova H, *et al.* Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. *Chest* 2005;**128**:2099–107. doi:10.1378/chest.128.4.2099
- 12 Gershon AS, Wang C, Guan J, *et al.* Burden of comorbidity in individuals with asthma. *Thorax* 2010;**65**:612–8. doi:10.1136/thx.2009.131078
- 13 Adams RJ, Wilson DH, Taylor AW, *et al.* Coexistent chronic conditions and asthma quality of life: A population-based study. *Chest* 2006;**129**:285–91. doi:10.1378/chest.129.2.285
- 14 Marques de Mello L, Cruz AA. A proposed scheme to cope with comorbidities in asthma. *Pulm Pharmacol Ther* 2018;**52**:41–51. doi:10.1016/j.pupt.2018.08.005
- 15 Lear SA, Hu W, Rangarajan S, *et al.* The effect of physical activity on mortality and cardiovascular disease in 130 000 people from 17 high-income, middle-income, and low-income countries: the PURE study. *Lancet* 2017;**390**:2643–54. doi:10.1016/s0140-6736(17)31634-3
- 16 Waschki B, Kirsten A, Holz O, *et al.* Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *Chest* 2011;**140**:331–42. doi:10.1378/chest.10-2521
- 17 Cordova-Rivera L, Gibson PG, Gardiner PA, *et al.* A Systematic Review of Associations of Physical Activity and Sedentary Time with Asthma Outcomes. *J Allergy Clin Immunol Pr* 2018;**6**:1968–1981 e2. doi:10.1016/j.jaip.2018.02.027
- 18 Tjønneland A, Olsen A, Boll K, *et al.* Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in

- Denmark. *Scand J Public Health* 2007;**35**:432–41. doi:10.1080/14034940601047986
- 19 Bønnelykke K, Raaschou-Nielsen O, Tjønneland A, *et al.* Postmenopausal hormone therapy and asthma-related hospital admission. *J Allergy Clin Immunol* 2015;**135**:813–816.e5. doi:10.1016/j.jaci.2014.11.019
- 20 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**:22–5. doi:10.1177/1403494810387965
- 21 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449. doi:10.2147/CLEP.S91125
- 22 Cust AE, Smith BJ, Chau J, *et al.* Validity and repeatability of the EPIC physical activity questionnaire: A validation study using accelerometers as an objective measure. *Int J Behav Nutr Phys Act* 2008;**5**:33. doi:10.1186/1479-5868-5-33
- 23 Peters T, Brage S, Westgate K, *et al.* Validity of a short questionnaire to assess physical activity in 10 European countries. *Eur J Epidemiol* 2012;**27**:15–25. doi:10.1007/s10654-011-9625-y
- 24 Garcia-Aymerich J, Varraso R, Antó JM, *et al.* Prospective study of physical activity and risk of asthma exacerbations in older women. *Am J Respir Crit Care Med* 2009;**179**:999–1003. doi:10.1164/rccm.200812-1929OC
- 25 Fisher JE, Loft S, Ulrik CS, *et al.* Physical Activity, Air Pollution, and the Risk of Asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016;**194**:855–65. doi:10.1164/rccm.201510-2036OC
- 26 Chippes BE, Zeiger RS, Borish L, *et al.* Key findings and clinical implications from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2012;**130**:332–342.e10. doi:10.1016/j.jaci.2012.04.014
- 27 Panagiotou M, Koulouris NG, Rovina N. Physical Activity: A Missing Link in Asthma Care. *J Clin Med* 2020;**9**:706. doi:10.3390/jcm9030706
- 28 Del Giacco SR, Firinu D, Bjermer L, *et al.* Exercise and asthma: an overview. *Eur Clin Respir J* 2015;**2**:27984. doi:10.3402/ecrj.v2.27984
- 29 van 't Hul AJ, Frouws S, van den Akker E, *et al.* Decreased physical activity in adults with bronchial asthma. *Respir Med* 2016;**114**:72–7. doi:10.1016/j.rmed.2016.03.016
- 30 Kv C, Mg C, Picot J, *et al.* Physical training for asthma (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Libr* 2013;:1–73. doi:10.1002/14651858.CD001116.pub4.www.cochranelibrary.com
- 31 Garcia-Aymerich J, Lange P, Benet M, *et al.* Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: A population-based cohort study. *Am J Respir Crit Care Med* 2007;**175**:458–63. doi:10.1164/rccm.200607-896OC
- 32 Russell MA, Janson C, Real FG, *et al.* Physical activity and asthma: A longitudinal and multi-country study. *J Asthma* 2017;**54**:938–45. doi:10.1080/02770903.2017.1281293
- 33 Sumino K, O'Brian K, Bartle B, *et al.* Coexisting chronic conditions associated with mortality and morbidity in adult patients with asthma. *J Asthma* 2014;**51**:306–14. doi:10.3109/02770903.2013.879881
- 34 Koskela HO, Salonen PH, Romppanen J, *et al.* A history of diabetes but not

- 1
2
3 hyperglycaemia during exacerbation of obstructive lung disease has impact on
4 long-term mortality: A prospective, observational cohort study. *BMJ Open*
5 2015;**5**:6794. doi:10.1136/bmjopen-2014-006794
6
7 35 Xu M, Xu J, Yang X. Asthma and risk of cardiovascular disease or all-cause
8 mortality: A meta-analysis. *Ann Saudi Med* 2017;**37**:99–105. doi:10.5144/0256-
9 4947.2017.99
10
11 36 Strand LB, Tsai MK, Wen CP, *et al*. Is having asthma associated with an increased
12 risk of dying from cardiovascular disease? A prospective cohort study of 446 346
13 Taiwanese adults. *BMJ Open* 2018;**8**. doi:10.1136/bmjopen-2017-019992
14
15 37 Denburg JA, Sehmi R, Saito H, *et al*. Systemic aspects of allergic disease: Bone
16 marrow responses. *J Allergy Clin Immunol* 2000;**106**:S242–6.
17 doi:10.1067/mai.2000.110156
18
19 38 Bjermer L. Time for a paradigm shift in asthma treatment: From relieving
20 bronchospasm to controlling systemic inflammation. *J Allergy Clin Immunol*
21 2007;**120**:1269–75. doi:10.1016/j.jaci.2007.09.017
22
23 39 Jensen AO, Nielsen GL, Ehrenstein V. Validity of asthma diagnoses in the Danish
24 National Registry of Patients, including an assessment of impact of
25 misclassification on risk estimates in an actual dataset. *Clin Epidemiol*
26 2010;**2**:67–72. <https://www.ncbi.nlm.nih.gov/pubmed/20865105>
27
28 40 von Bülow A, Kriegbaum M, Backer V, *et al*. The Prevalence of Severe Asthma
29 and Low Asthma Control Among Danish Adults. *J Allergy Clin Immunol Pract*
30 2014;**2**:759-767.e2. doi:10.1016/j.jaip.2014.05.005
31
32 41 Telama R. Tracking of physical activity from childhood to adulthood: A review.
33 *Obes. Facts.* 2009;**2**:187–95. doi:10.1159/000222244
34
35 42 Mertens E, Clarys P, Mullie P, *et al*. Stability of physical activity, fitness
36 components and diet quality indices. *Eur J Clin Nutr* 2017;**71**:519–24.
37 doi:10.1038/ejcn.2016.172
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Tables

Table 1 – Baseline characteristics of 785 adults enrolled in the Danish Diet, Cancer and Health Cohort with incident asthma between baseline (1993-1997) and follow-up (July

| | 2013 | Asthma (N = 785) | Alive (N= 709) | Dead (N = 76) |
|---|-----------------------|---------------------|-------------------|------------------|
| Age 50-55, n (%) | | 50 (6.4) | 44 (6.2) | 6 (7.9) |
| Age 55-60, n (%) | | 155 (19.7) | 136 (19.2) | 19 (25.0) |
| Age 60-65, n (%) | | 580 (73.9) | 529 (74.6) | 51 (67.1) |
| Men, n (%) | | 290 (37) | 136 (19) | 19 (25) |
| Mean body mass index (kg/m ²) | | 26.5 (12) | 26.4 (4.2) | 27.1 (4.6) |
| Smoking history, n (%) | Never | 351 (45) | 318 (45) | 33 (43) |
| | Previous | 260 (33) | 241 (34) | 33 (25) |
| | Current | 174 (22) | 150 (21) | 19 (32) |
| Mean smoking duration, years (SD) | | 25.9 (12) | 25.3 (12) | 31.1 (12) |
| Mean smoking intensity, g/day (SD) | | 5.7 (9.1) | 5.3 (9.0) | 9.1 (10) |
| Exposed to environmental tobacco smoke, n (%) | | 449 (57) | 403 (57) | 46 (61) |
| Physically active in leisure time, n (%) | | 432 (55) | 404 (57) | 28 (37) |
| Mean fruit intake, g/day (SD) | | 192 (145) | 193 (146) | 177 (129) |
| Employed, n (%) | | 612 (78) | 559 (79) | 53 (70) |
| Marital status, n (%) | Single | 45 (5.7) | 35 (4.9) | 10 (13) |
| | Married | 558 (71) | 507 (72) | 51 (67) |
| | Divorced | 136 (17) | 125 (18) | 11 (16) |
| | Widowed | 46 (5.9) | 42 (5.9) | 4 (5.3) |
| Years of Education n (%) | < 8 | 223 (28) | 198 (28) | 25 (33) |
| | 8 – 10 | 395 (50) | 361 (51) | 34 (45) |
| | ≥ 10 | 167 (21) | 150 (21) | 23 (30) |
| Comorbidity n (%) | Myocardial infarction | 13 (1.7) | 9 (1.3) | 4 (5.3) |
| | Stroke | 4 (0.5) | 3 (0.4) | 1 (1.3) |
| | Diabetes | 13 (1.7) | 8 (1.1) | 5 (6.6) |
| | Hypertension | 155 (20) | 126 (18) | 29 (38) |
| | Hypercholesterolemia | 46 (5.9) | 45 (6.3) | 1 (1.3) |

SD = standard deviation

Table 2 - Determinants at baseline of survival in 785 adults with incident asthma during follow-up (2013) among participants in the Danish Diet, Cancer and Health Cohort.

| | | Univariate model HR (95% CI) | Multivariate model HR (95% CI) |
|---------------------------------|---|------------------------------------|--------------------------------------|
| Age | 50-55 | 1.00 | - |
| | 55-60 | 0.84 (0.33-2.14) | |
| | 60-65 | 0.76 (0.28-2.08) | |
| Sex | Female | 1.00 | 1.00 |
| | Male | 1.76 (1.12-2.75) | 1.83 (1.14-2.93) |
| Body Mass index | Underweight/Normal (<25 kg/m ²) | 1.00 | - |
| | Overweight (25-30 kg/m ²) | 1.56 (0.93-2.63) | - |
| | Obese (≥ 30 kg/m ²) | 1.52 (0.79-2.91) | - |
| Smoking | Never | 1.00 | 1.00 |
| | Previous | 0.67 (0.38-1.18) | 0.59 (0.33-1.05) |
| | Current | 1.64 (0.96-2.78) | 1.39 (0.81-2.38) |
| Activity in Leisure Time | Inactive | 1.00 | 1.00 |
| | Active | 0.47 (0.29-0.74) | 0.53 (0.33-0.85) |
| Mean fruit intake | g/day | 0.91 (0.76-1.07) | - |
| Employment | Yes | 1.00 | 1.00 |
| | No | 1.17 (0.70-1.96) | 1.04 (0.87-1.25) |
| Marital Status | Single | 2.77 (1.40-5.48) | 2.16 (2.06-4.40) |
| | Married | 1.00 | 1.00 |
| | Divorced | 0.79 (0.41-1.51) | 0.76 (0.40-1.47) |
| | Widowed | 0.83 (0.30-2.30) | 1.15 (0.40-3.27) |
| Myocardial infarction | - | 1.00 | - |
| | + | 2.87 (1.04-7.89) | - |
| Stroke | - | 1.00 | - |
| | + | 1.58 (0.22-11.43) | - |
| Diabetes | - | 1.00 | 1.00 |
| | + | 3.58 (1.44-8.90) | 2.42 (0.96-6.11) |
| Hypertension | - | 1.00 | 1.00 |
| | + | 2.57 (1.61-4.09) | 2.47 (1.54-3.95) |

HR = Hazard Ratio. CI = Confidence interval.

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

| | Item No | Recommendation |
|------------------------------|---------|---|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract – page 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found - page 2 |
| Introduction | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported -page 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses -page 4 |
| Methods | | |
| Study design | 4 | Present key elements of study design early in the paper -page 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection -page 4-5 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up -page 4-5 (b) For matched studies, give matching criteria and number of exposed and unexposed - N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable -page 4-6 |
| 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 -page 4-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at -page 4-5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page- 5-6 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding -page 6 (b) Describe any methods used to examine subgroups and interactions -N/A (c) Explain how missing data were addressed -N/A (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses -N/A |

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**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 Page -4 and 8 (b) Give reasons for non-participation at each stage -due to space limitations non-participation for the DCH cohort is available in the referenced previous articles. (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders -table 1 (b) Indicate number of participants with missing data for each variable of interest -N/A (c) Summarise follow-up time (eg, average and total amount) -page 8 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time |
| 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 -table 2 (b) Report category boundaries when continuous variables were categorized -table 2 (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -N/A |
| Discussion | | |
| Key results | 18 | Summarise key results with reference to study objectives -page 8 |
| 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 Page 11-12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence -page 8-11 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results -page 11 |
| Other information | | |
| 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 -page 12 |

*Give information separately for exposed and unexposed groups.

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

For peer review only

BMJ Open

Demographic, lifestyle, and comorbid risk factors for all-cause mortality in a Danish cohort of middle-aged adults with incident asthma

| | |
|---------------------------------|--|
| Journal: | <i>BMJ Open</i> |
| Manuscript ID | bmjopen-2021-049243.R3 |
| Article Type: | Original research |
| Date Submitted by the Author: | 01-Sep-2021 |
| Complete List of Authors: | Tupper, Oliver Djurhuus; Hvidovre Hospital, Department of Respiratory Medicine Andersen, ZJ; University of Copenhagen Department of Public Health, Section of Environmental Health Ulrik, Charlotte; Hvidovre Hospital, Department of Respiratory Medicine |
| Primary Subject Heading: | Epidemiology |
| Secondary Subject Heading: | Respiratory medicine |
| Keywords: | Asthma < THORACIC MEDICINE, Epidemiology < THORACIC MEDICINE, Adult thoracic medicine < THORACIC MEDICINE |
| | |

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 **Demographic, lifestyle, and comorbid risk factors for all-cause**
4
5
6 **mortality in a Danish cohort of middle-aged adults with**
7
8
9 **incident asthma**

10
11
12
13 Oliver Djurhuus Tupper¹, Zorana Jovanovic Andersen², and Charlotte

14
15
16 Suppli Ulrik^{1,3}

17
18
19 ¹ Department of Respiratory Medicine, Copenhagen University Hospital Hvidovre,
20
21 Denmark

22
23
24 ² Section of Environmental Health, Department of Public health, University of
25
26 Copenhagen, Denmark

27
28
29 ³ Institute of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

30
31 **Corresponding Author**

32
33 Oliver Djurhuus Tupper MD, PhD

34
35 Respiratory Research Unit

36
37 Department of Respiratory Medicine

38
39 Hvidovre Hospital

40
41 Kettegård Alle 30

42
43 DK-2650 Hvidovre

44
45 E-mail olivertupper@gmail.com

46
47
48 Word count abstract: 248

49
50 Word count main text: 2600

Abstract

Objectives:

We aimed to identify factors associated with all-cause mortality in adults with incident asthma.

Design and setting:

Cross-sectional cohort study, in the metropolitan areas of Copenhagen and Aarhus, Denmark.

Participants:

Adults aged 50–64 years enrolled in the Danish Diet, Cancer, and Health cohort were followed from baseline (1993–1997) in the National Patients Registry for first-time admissions for asthma and vital status. We defined incident asthma as at least one first-time hospital admission with asthma as the primary registered diagnosis between baseline and end of follow-up (2013) in participants without previously known asthma. Among the cohort comprising 57 053 individuals, we identified 785 adults (aged 50–64) with incident asthma, of whom 76 died during follow-up.

Primary and secondary outcome measures:

Baseline reported socioeconomic and lifestyle traits, and comorbidities associated with all-cause mortality.

Results:

Self-reported leisure-time physical activity was associated with a substantial reduction in risk with an HR of 0.53 (95 % CI 0.33–0.85). Being male, single, and having a diagnosis of hypertension or diabetes were associated with an increased risk of all-cause mortality

1
2
3 with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–
4
5 3.95) and of 2.42 (95 % CI 0.96–6.11), respectively.
6
7

8 Conclusions:

9
10 This long-term study of adults with hospital contacts for incident asthma revealed
11
12 that self-reported leisure-time physical activity is associated with an approximately
13
14 50% reduction in all-cause mortality. In contrast, both hypertension and diabetes
15
16 were associated with a higher risk of mortality.
17
18

19 **Strengths and limitations of this study:**

- 20
21
22
23
24
25 • The present study is one of very few reporting on how physical activity and
26
27 comorbidities are associated with all-cause mortality in adults with asthma.
28
29 • Seven hundred eighty-five persons with incident asthma were followed up
30
31 for 20 years, with no loss to follow-up.
32
33 • The diagnosis of asthma is based on registry information and not a verified
34
35 objective assessment.
36
37 • There are only very few events among those with previous myocardial
38
39 infarction and stroke.
40
41
42
43
44
45

46 **Keywords:** Asthma, middle-aged adults, population cohort, comorbidities, long-term
47

48 **Short Title:** Physical activity and asthma mortality
49

50 **Introduction**

51
52 With over 300 million persons worldwide suffering from asthma and many deaths each
53
54 year, asthma is a disease that continually requires attention.[1,2] Asthma remains a
55
56 disease that carries increased mortality compared with general populations.[3,4]
57
58
59
60

1
2
3 Asthma-specific mortality has, overall, been on a steady decline since the 1950s.[5–7]
4
5
6 However, a study based on the WHO Mortality Database found that mortality trends
7
8 have plateaued, with no significant change in mortality between 2006 and 2012.[8]
9
10
11 Furthermore, a British report from 2014 reported that over 67% of deaths related to
12
13 asthma were potentially preventable.[9]

14
15 Asthma-specific mortality alone does not provide the whole picture when evaluating the
16
17 risks of the disease for individual patients. A study assessing deaths with asthma as a
18
19 contributing factor, in addition to asthma-specific causes, found that asthma as a
20
21 contributing factor was associated with more than twice as many deaths compared with
22
23 asthma-specific deaths alone.[10] Studies suggest that patients with asthma are more
24
25 prone to acquire other chronic conditions than the background population.[11–13] As
26
27 the impact of factors such as multimorbidity on all-cause mortality is an area with a
28
29 paucity of data, there is a need for further studies within this area.[14] The association
30
31 between physical activity and long-term mortality has been well established in the
32
33 general population and among patients with COPD.[15,16] However, this has not been
34
35 examined extensively in asthma.[17] The impact of physical activity on asthma-specific
36
37 factors, such as disease control, lung function, and exacerbations, has been well
38
39 researched.[17]

40
41
42 Based on the currently available knowledge, it remains of utmost importance to further
43
44 explore factors associated with asthma-related mortality, including not least all-cause
45
46 mortality.

47
48
49 The present study aimed to examine demographic, lifestyle and comorbid factors
50
51 associated with long-term all-cause mortality in adults with incident asthma from a large
52
53 Danish cohort.
54
55
56
57
58
59
60

Methods

Characteristics of the Diet, Cancer, and Health (DCH) cohort have been published previously, with a full description of the cohort.[18,19] A total of 160 725 individuals (72 729 women) were invited to participate in the DCH Cohort between 1993 and 1997. All individuals resided in either Copenhagen or Aarhus, which are the two largest cities in Denmark. To be invited, participants had to be 50–64 years of age and have no record of cancer at the time of inclusion. A total of 57 053 individuals (52.4% women, n=29 875) were enrolled in the study after accepting the invitation. The Central Danish Ethics Committee approved the main study of the DCH-cohort. The regional Danish Ethics Committee approved this sub-study (H-17025043) and the Danish Data Protection Agency (2014-41-3468). All participants provided written informed consent. Baseline factors were determined based on a comprehensive questionnaire completed by the participants. The questionnaire consisted of questions on general health and diet; demographic factors, including education and occupation; questions on lifestyle, including tobacco exposure; and pre-existing diseases, including asthma, COPD, diabetes, and cardiovascular disease.

Study cohort

Participants in the DCH cohort were defined as having incident asthma and included in the present analyses as cases if they had the first-ever admission to a hospital, emergency department, or outpatient clinic with a primary diagnosis of asthma, which occurred between cohort baseline (1993–1997) and July 1st, 2013. Asthma was

1
2
3 classified according to the International Classification of Diseases (ICD) as ICD-10 codes
4
5 DJ45–46 and ICD-8 codes 493.00–493.09. Participants with a self-reported diagnosis of
6
7 asthma or COPD at baseline were excluded. Participants in the DCH cohort were linked
8
9 to the Danish National Patient Registry (DNPR) to extract hospital contacts from 1993—
10
11 1997 until July 1st, 2013.[20] The link between the DCH and DNPR was done using the
12
13 unique identifier all Danish residents have. Every discharge diagnosis from all Danish
14
15 hospitals since 1978 and outpatient clinics since 1995 is gathered in the DNPR.[21] In
16
17 addition to hospital contacts, we obtained emergency room visits and visits to
18
19 respiratory outpatient clinics. Cases were followed from first-ever asthma admission
20
21 until the time of death, emigration, or July 1st, 2013, whichever came first.
22
23
24
25
26
27
28
29

30 Physical activity in leisure time was determined based on a participant completed
31
32 questionnaire. An interviewer checked the questionnaire. Participants reported the
33
34 number of hours per week they did leisure time and transport-related (i.e., to and from
35
36 work, shopping) physical activity. Leisure-time physical activity was reported separately
37
38 for summer and winter of the previous year. It was allocated in the following categories:
39
40 cycling, “do-it-yourself” activities (i.e., home improvements), gardening, housework
41
42 (cleaning, laundry), sports, and walking. The two values for summer and winter were
43
44 averaged. The questions used have previously been validated in two studies by Peters
45
46 et al and Cust et al that found high correlations with movement sensing measurement
47
48 and accelerometer measurements, respectively.[22,23] Participants reported as being
49
50 physically active in leisure time, spent at least half an hour a week on at least one of the
51
52 six categories.
53
54
55
56
57
58
59
60

Statistical Analyses

Associations between baseline factors and all-cause mortality were examined using the Cox proportional hazards model with age as the underlying time scale. We examined the following baseline factors identified at recruitment between 1993 and 1999: age, sex, BMI, length of education, employment and civil status, tobacco history, occupational exposure, leisure-time physical activity, fruit consumption, and comorbidities. Baseline factors were assessed in a two-step process: Step one, in a univariate model, with age as the underlying time scale. Step two was in a multivariate model that included only variables associated with all-cause mortality, defined by backward elimination. The proportional hazards assumption was evaluated by testing for a non-zero slope in a generalised linear regression of the scaled Schoenfeld residuals on functions of time. The univariate and multivariate model results are presented as hazard ratios (HRs) with 95% confidence intervals (CIs). Stata, version 11.2, was used to perform statistical analyses.

Patient and Public Involvement

Patients and the public were not involved in the design of the study.

Results

We identified 785 adults with an incident diagnosis of asthma and by that fulfilling the criteria for inclusion in the present analyses. No individuals were lost to follow-up, and therefore complete data were available for all 785 individuals. All characteristics included in the following analyses were obtained at baseline.

1
2
3 Between baseline and July 1st, 2013, 76 of the identified adults with incident asthma
4
5 died. The majority of cases with incident asthma were women 63% (n=495). Only 45%
6
7 (n=351) were never smokers at baseline. Interestingly, a substantial proportion of
8
9 ever-smokers were ex-smokers (60%, n=260) and not current smokers (40%, n=174).
10
11 The amount of tobacco exposure was much higher among those who died than those
12
13 with incident asthma still alive at the end of follow-up. Persons who died had an
14
15 average daily tobacco usage of 3.8 grams of tobacco, corresponding to 72% more than
16
17 those alive at the end of follow-up. Those who died had a daily intake of fruit that was
18
19 16 g (or 8.3 %) less than those still alive. Further characteristics are shown in Table 1.
20
21
22
23
24
25
26
27

28 Of the baseline characteristics included in the analyses, the following were found to be
29
30 associated with all-cause mortality and were therefore included in the final model: (1)
31
32 sex, (2) smoking status, (3) physical activity in leisure time, (5) employment status, (6)
33
34 marital status, (7) diabetes and (8) hypertension. On the other hand, age and a
35
36 previous diagnosis of myocardial infarction or stroke lacked power for precise
37
38 estimates for all-cause mortality in univariate analyses and were therefore not
39
40 included in the final model.
41
42
43
44

45 Male sex was associated with a higher risk for all-cause mortality (HR 1.83, 95% CI
46
47 1.14-2.93). Participants who reported being single had a higher mortality risk (HR of
48
49 2.16 95% CI 2.06-4.40) compared with those who reported being married. A diagnosis
50
51 of hypertension was associated with a substantially increased risk of all-cause
52
53 mortality (HR 2.47, 95% CI 1.54–3.95). Self-reported previous myocardial infarction
54
55 and a current diagnosis of diabetes had imprecise estimates associated with all-cause
56
57 mortality, although, notably, robust associations were detected. We found an HR of
58
59
60

1
2
3 2.87 (95% CI 1.04-7.89) in the univariate model for myocardial infarction. An HR of 2.42
4
5 (95% CI 0.96-6.11) for diabetes was found in the multivariate model. We did not found
6
7 an association between previous stroke and all-cause mortality.
8
9

10 The self-reported leisure-time physical activity showed a substantial reduction in all-
11
12 cause mortality (HR 0.53, 95% CI 0.33–0.85). Mean daily fruit intake was not found to
13
14 be associated with death (table 2).
15
16

17 18 19 20 **Discussion**

21
22
23 In this Danish cohort of 785 adults with incident asthma followed for 20 years, we found
24
25 that physical activity was associated with a lower risk of all-cause mortality. In contrast,
26
27 being single or having hypertension were associated with increased all-cause mortality.
28
29

30 31 32 *Physical Activity*

33
34 To the best of our knowledge, this is the first cohort study that has reported the
35
36 association between self-reported physical activity and all-cause mortality, specifically
37
38 in individuals with asthma. Physical activity has previously been shown to have a
39
40 positive effect on multiple aspects of asthma.[17] Particularly relevant are two studies
41
42 by Garcia-Aymerich et al[24] and Fisher et al[25] that found a protective effect of self-
43
44 reported physical activity on hospitalisation with asthma exacerbations. While the
45
46 same effect could not be found on readmissions for exacerbations in the study by
47
48 Fisher et al[25], their findings are essential to support our findings, as exacerbations
49
50 are associated with overall morbidity and mortality.[26] Physical activity also appears
51
52 to have a positive effect on asthma control.[27] However, BMI appears to be more
53
54 critical, negating the effects of physical activity in some, but not all, models.[17] It
55
56
57
58
59
60

1
2
3 appears that if persons with asthma have a moderate level of physical activity
4
5 compared with inactivity and strenuous physical activity, asthma control is positively
6
7 affected.[28] The positive effects on these other asthma outcomes could support our
8
9 finding that physical activity is associated with lower mortality risk.
10
11

12
13 The effects of physical activity are prudent to establish as we know that patients with
14
15 asthma generally are less physically active than the general population.[29] Further,
16
17 we know from a Cochrane review from 2013 that physical activity is well-tolerated and
18
19 safe for individuals with asthma.[30] The review found that physical activity may
20
21 improve cardiopulmonary function in individuals with asthma without negatively
22
23 impacting pulmonary function. Furthermore, the Cochrane review is based on shorter-
24
25 term studies. Long-term findings from the Copenhagen City Heart study suggest that
26
27 physical activity may diminish long-term lung function decline in individuals with
28
29 asthma.[31] The amount of physical activity required to be defined as physically active
30
31 in our study is relatively low and, therefore, should be attainable by most. However,
32
33 future studies should explore whether there are additional benefits from moderate
34
35 and high levels of activity. Additionally, would a high or very high level of activity mean
36
37 the risks of adverse outcomes outweigh the benefits? A study by Russell et al.[32]
38
39 found that the benefits of physical activity on asthma symptoms were only present at
40
41 light levels of activity and not at intense activity levels. Based on our findings, there is
42
43 absolutely reason to motivate persons with asthma to do physical activity in their
44
45 leisure time.
46
47
48
49
50
51
52
53
54
55
56

57 *Sex*
58
59
60

1
2
3 We found that men had a higher hazard ratio for early death than women. Our
4
5 finding of higher all-cause mortality among men with asthma is well in line with
6
7 what is found by previous studies by Lemmetyinen et al[33] and Connolly et al.[34]
8
9
10 However, because of the way the analyses are carried out, it is likely more a
11
12 reflection of a general higher mortality among men than specifically asthma-
13
14 related.
15
16

17 18 19 *Marital status*

20
21
22 Being single (never married) compared to married showed an independently
23
24 higher risk of death, while being divorced or widowed showed no change. This
25
26 effect has been shown repeatedly in previous studies.[35,36] The reasons behind
27
28 this effect is still much discussed, partly studies suggest that there is a selection of
29
30 less robust individuals to remain single or become divorced. Additionally, there
31
32 also seems to be a protective effect in being married.[37] A study by Dantzer et al
33
34 [38], found that there was no difference between single and married individuals
35
36 with asthma. However, they had not stratified single, as we have done, into three
37
38 different groups. Therefore, persons who were widowed or divorced were
39
40 included in the single group. As we found, being widowed or divorced is not
41
42 associated with all-cause mortality, which may explain the discrepancies in
43
44 findings.
45
46
47
48
49
50
51

52 53 *Comorbidities*

54
55 Hypertension had a strong association with death. Overall, all included comorbid
56
57 conditions at baseline appeared to be associated with a higher risk of death. However,
58
59
60

1
2
3 only hypertension had a robust estimate, probably since the remaining comorbidities
4
5 (diabetes, stroke and myocardial infarction) had a relatively low prevalence at baseline.
6
7

8 There is limited research on how hypertension relates to mortality in a person with
9
10 asthma.[14] We found one other study by Sumino et al[39] from 2014 that report the
11
12 association between hypertension and mortality. They found a lower OR for mortality
13
14 among individuals with hypertension over the age of 65. However, the study by Sumino
15
16 et al[39] had a much shorter follow-up of three years compared with the 20 years of our
17
18 study. Given that hypertension is a condition that gives long-term complications, these
19
20 complications are likely not caught across such a short period.
21
22

23
24 While the estimated hazard ratio for mortality among those with diabetes was imprecise
25
26 due to lack of power, it is worth mentioning that there appeared to be a strong
27
28 association between diabetes and a higher risk of all-cause mortality. While the amount
29
30 of other studies is exceedingly limited, there is other literature supporting this finding.
31
32 Sumino et al[39] found that diabetes was associated with a higher mortality rate in
33
34 persons over 65. Another cohort study by Koskela et al[40] showed that among 110
35
36 patients admitted due to an asthma exacerbation, there was a higher risk of mortality
37
38 for those with diabetes. While there is a clear trend in our data towards higher all-cause
39
40 mortality risk for individuals with previous myocardial infarction, the HR estimate was
41
42 imprecise once again due to only four events. Nevertheless, an excess risk of mortality
43
44 due to cardiovascular disease is an area that has substantial data supporting it in asthma
45
46 cohorts, and this certainly supports our finding.[41,42]
47
48
49
50
51
52
53

54 The factors presented in this paper may seem obvious but needs to be verified in asthma
55
56 mainly, as many of these factors have not previously been explored in relation to adults
57
58 with asthma. Not least in large cohorts, as in the present long-term follow-up study of a
59
60

1
2
3 large cohort of middle-aged men and women with asthma. The relevance of this is due
4
5 to the systemic inflammation present in persons with asthma, which potentially could
6
7 affect and change which factors are essential to be aware of compared with general
8
9 populations.[43,44]
10
11
12
13

14 15 *Limitations*

16
17 The diagnosis of asthma in the included subjects was based on ICD-10 codes connected
18
19 to hospital contacts, which is not as accurate as objectively verified asthma. However,
20
21 this has previously been established by Jensen et al[45] to be a robust method of
22
23 identifying persons with asthma. The positive predictive value was found to be 65%;
24
25 despite this, they discovered that associations found are still relevant. Selecting only
26
27 persons with either a hospital or outpatient contact means we may limit
28
29 generalisability, with the majority of persons included may have moderate or severe
30
31 disease. Nonetheless, a study from 2014 found that upwards of 25% of asthma
32
33 patients with mild to moderate disease experience poor asthma control and hospital
34
35 admissions.[46]
36
37
38
39
40
41

42 The prevalence of asthma in this cohort is low (about 1%), substantially lower than the
43
44 current reported prevalence in Denmark of 10%; therefore, the generalisability is
45
46 limited. The low prevalence is due to only including participants without a previous
47
48 diagnosis of asthma and only included individuals referred to secondary care.
49
50

51 Our definition of physical activity was based on self-reported information, which carries
52
53 a certain degree of bias. Additionally, a potential limitation is that the degree of self-
54
55 reported physical activity for some was reported multiple years before the first contact
56
57 for incident asthma. We can, therefore, not be sure that the level of physical activity still
58
59
60

1
2
3 applies at follow-up. However, previous literature suggests that physical activity tracks
4
5 well over time, particularly in adulthood.[47,48]
6
7

8 We did not have information on the specific cause of death and could not examine
9
10 factors relating to asthma-specific mortality. Furthermore, we did not have data on
11
12 asthma severity, medication, pulmonary function and previous exacerbation, which
13
14 influences mortality risk.
15
16

17 As the number of events in this cohort study was not substantial, there is a risk of under
18
19 and overestimating the importance of the identified risk factors. Therefore, the results
20
21 of this study cannot stand on their own, yet it provides a valuable source for future
22
23 studies. This is particularly evident for diabetes, which shows a clear trend for a higher
24
25 risk of mortality, though it lacks the power for a precise estimate.
26
27
28
29
30
31

32 *Conclusions*

33
34 Our study has shown that for middle-aged individuals with hospital contact for incident
35
36 asthma, persons with comorbidity or are single are at an increased risk of early all-cause
37
38 mortality. In contrast, leisure-time physical activity was found to have a protective effect
39
40 on mortality risk. Our findings, therefore, suggest that it is important to encourage our
41
42 asthma patients to do physical activity. Future studies should examine how varying
43
44 levels of physical activity affect mortality in persons with asthma, is there a diminishing
45
46 or negative effect at very high levels of activity?
47
48
49
50
51
52
53

54 **Abbreviations:**

55
56 BMI = Body Mass Index

57
58 DCH = Diet Cancer and Health Cohort

59
60 HR = Hazard Ratio

1
2
3 OR = Odds Ratio
4
5
6

7 **Declarations**

10 **Ethics approval and consent to participate:** The study was approved by the ethical
11 committee for the Capital Region of Denmark (H-17025043), the regional data safety
12 committee for the capital region of Denmark (P-2019-712), and The Danish Data
13 Protection Agency (2014-41-3468). All participants signed an informed consent form.
14
15

16
17 **Funding:** This research did not receive any specific grant from funding agencies in
18 the public, commercial, or not-for-profit sectors.
19

20
21 **Competing interests:** ODT, ZJA, and CSU have no perceived conflicts of interest in
22 relation to this study.
23

24
25 **Authors' contributions:** Conception and design—ODT, ZJA and CSU.; preparation of
26 data and statistical analyses - ZJA.; statistical interpretation and drafted the
27 manuscript—ODT; all authors critically reviewed and accepted the final version of the
28 manuscript.
29

30
31 **Availability of data and material:** The data are available upon reasonable request, but
32 analysis may require approval from the regional data safety committee for the capital
33 region of Denmark (Videnscenter for dataanmeldelser).
34
35

36
37 **Acknowledgements:** Thanks to Anne Tjønneland and Kim Overvad for providing us
38 with access to the data from the Diet, Cancer and Health cohort.
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

56 **References**

- 57 1 WHO. Global surveillance, prevention and control of chronic respiratory
58 diseases: a comprehensive approach.
59 <http://www.who.int/gard/publications/GARD Book 2007.pdf?ua=1>
60

- 1
2
3 2 Global strategy for asthma management and prevention. Glob. Initiasthma. 2020.<https://ginasthma.org> (accessed 16 Jun 2020).
- 4
5
6 3 Huovinen E, Kaprio J, Vesterinen E, *et al.* Mortality of adults with asthma: A
7 prospective cohort study. *Thorax* 1997;**52**:49–54. doi:10.1136/thx.52.1.49
- 8
9 4 D’Amato G, Vitale C, Molino A, *et al.* Asthma-related deaths. *Multidiscip Respir
10 Med* 2016;**11**:1–5. doi:10.1186/s40248-016-0073-0
- 11
12 5 Speizer FE, Doll R, Heaf P. Observations on Recent Increase in Mortality from
13 Asthma. *Br Med J* 1968;**1**:335–9. doi:10.1136/bmj.1.5588.335
- 14
15 6 Jackson RT, Beaglehole R, Rea HH, *et al.* Mortality from asthma: A new epidemic
16 in New Zealand. *Br Med J* 1982;**285**:771–4. doi:10.1136/bmj.285.6344.771
- 17
18 7 Sly RM. Mortality from asthma, 1979-1984. *J Allergy Clin Immunol* 1988;**82**:705–
19 17. doi:10.1016/0091-6749(88)90069-3
- 20
21 8 Ebmeier S, Thayabaran D, Braithwaite I, *et al.* Trends in international asthma
22 mortality: analysis of data from the WHO Mortality Database from 46 countries
23 (1993–2012). *Lancet* 2017;**390**:935–45. doi:10.1016/S0140-6736(17)31448-4
- 24
25 9 Levy ML. The national review of asthma deaths: What did we learn and what
26 needs to change? *Breathe* 2015;**11**:15–24. doi:10.1183/20734735.008914
- 27
28 10 McCoy L, Redelings M, Sorvillo F, *et al.* A multiple cause-of-death analysis of
29 asthma mortality in the United States, 1990-2001. *J Asthma* 2005;**42**:757–63.
30 doi:10.1080/02770900500308189
- 31
32 11 Soriano JB, Visick GT, Muellerova H, *et al.* Patterns of comorbidities in newly
33 diagnosed COPD and asthma in primary care. *Chest* 2005;**128**:2099–107.
34 doi:10.1378/chest.128.4.2099
- 35
36 12 Gershon AS, Wang C, Guan J, *et al.* Burden of comorbidity in individuals with
37 asthma. *Thorax* 2010;**65**:612–8. doi:10.1136/thx.2009.131078
- 38
39 13 Adams RJ, Wilson DH, Taylor AW, *et al.* Coexistent chronic conditions and
40 asthma quality of life: A population-based study. *Chest* 2006;**129**:285–91.
41 doi:10.1378/chest.129.2.285
- 42
43 14 Marques de Mello L, Cruz AA. A proposed scheme to cope with comorbidities in
44 asthma. *Pulm Pharmacol Ther* 2018;**52**:41–51. doi:10.1016/j.pupt.2018.08.005
- 45
46 15 Lear SA, Hu W, Rangarajan S, *et al.* The effect of physical activity on mortality
47 and cardiovascular disease in 130 000 people from 17 high-income, middle-
48 income, and low-income countries: the PURE study. *Lancet* 2017;**390**:2643–54.
49 doi:10.1016/s0140-6736(17)31634-3
- 50
51 16 Waschki B, Kirsten A, Holz O, *et al.* Physical activity is the strongest predictor of
52 all-cause mortality in patients with COPD: a prospective cohort study. *Chest*
53 2011;**140**:331–42. doi:10.1378/chest.10-2521
- 54
55 17 Cordova-Rivera L, Gibson PG, Gardiner PA, *et al.* A Systematic Review of
56 Associations of Physical Activity and Sedentary Time with Asthma Outcomes. *J
57 Allergy Clin Immunol Pr* 2018;**6**:1968-1981 e2. doi:10.1016/j.jaip.2018.02.027
- 58
59 18 Tjønneland A, Olsen A, Boll K, *et al.* Study design, exposure variables, and
60 socioeconomic determinants of participation in Diet, Cancer and Health: a
population-based prospective cohort study of 57,053 men and women in
Denmark. *Scand J Public Health* 2007;**35**:432–41.
doi:10.1080/14034940601047986
- 19 Bønnelykke K, Raaschou-Nielsen O, Tjønneland A, *et al.* Postmenopausal
hormone therapy and asthma-related hospital admission. *J Allergy Clin Immunol*

- 2015;**135**:813-816.e5. doi:10.1016/j.jaci.2014.11.019
- 20 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**:22–5. doi:10.1177/1403494810387965
- 21 Schmidt M, Schmidt SAJ, Sandegaard JL, *et al.* The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449. doi:10.2147/CLEP.S91125
- 22 Cust AE, Smith BJ, Chau J, *et al.* Validity and repeatability of the EPIC physical activity questionnaire: A validation study using accelerometers as an objective measure. *Int J Behav Nutr Phys Act* 2008;**5**:33. doi:10.1186/1479-5868-5-33
- 23 Peters T, Brage S, Westgate K, *et al.* Validity of a short questionnaire to assess physical activity in 10 European countries. *Eur J Epidemiol* 2012;**27**:15–25. doi:10.1007/s10654-011-9625-y
- 24 Garcia-Aymerich J, Varraso R, Antó JM, *et al.* Prospective study of physical activity and risk of asthma exacerbations in older women. *Am J Respir Crit Care Med* 2009;**179**:999–1003. doi:10.1164/rccm.200812-1929OC
- 25 Fisher JE, Loft S, Ulrik CS, *et al.* Physical Activity, Air Pollution, and the Risk of Asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2016;**194**:855–65. doi:10.1164/rccm.201510-2036OC
- 26 Chippes BE, Zeiger RS, Borish L, *et al.* Key findings and clinical implications from the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2012;**130**:332-342.e10. doi:10.1016/j.jaci.2012.04.014
- 27 Panagiotou M, Koulouris NG, Rovina N. Physical Activity: A Missing Link in Asthma Care. *J Clin Med* 2020;**9**:706. doi:10.3390/jcm9030706
- 28 Del Giacco SR, Firinu D, Bjermer L, *et al.* Exercise and asthma: an overview. *Eur Clin Respir J* 2015;**2**:27984. doi:10.3402/ecrj.v2.27984
- 29 van 't Hul AJ, Frouws S, van den Akker E, *et al.* Decreased physical activity in adults with bronchial asthma. *Respir Med* 2016;**114**:72–7. doi:10.1016/j.rmed.2016.03.016
- 30 Kv C, Mg C, Picot J, *et al.* Physical training for asthma (Review) SUMMARY OF FINDINGS FOR THE MAIN COMPARISON. *Cochrane Libr* 2013;:1–73. doi:10.1002/14651858.CD001116.pub4.www.cochranelibrary.com
- 31 Garcia-Aymerich J, Lange P, Benet M, *et al.* Regular physical activity modifies smoking-related lung function decline and reduces risk of chronic obstructive pulmonary disease: A population-based cohort study. *Am J Respir Crit Care Med* 2007;**175**:458–63. doi:10.1164/rccm.200607-896OC
- 32 Russell MA, Janson C, Real FG, *et al.* Physical activity and asthma: A longitudinal and multi-country study. *J Asthma* 2017;**54**:938–45. doi:10.1080/02770903.2017.1281293
- 33 Lemmetyinen RE, Karjalainen J V., But A, *et al.* Higher mortality of adults with asthma: A 15-year follow-up of a population-based cohort. *Allergy Eur J Allergy Clin Immunol* 2018;**73**:1479–88. doi:10.1111/all.13431
- 34 Connolly CK, Alcock SM, Prescott RJ. Mortality in asthmatics over 15 yrs: A dynamic cohort study from 1983-1998. *Eur Respir J* 2002;**19**:593–8. doi:10.1183/09031936.02.00203002
- 35 Farr. The Influence of Marriage Upon the Rate of Mortality. *Lancet* 1879;**113**. doi:10.1016/s0140-6736(02)46313-1

- 1
2
3 36 Hu YR, Goldman N. Mortality differentials by marital status: an international
4 comparison. *Demography* 1990;**27**:233–
5 50. <https://www.ncbi.nlm.nih.gov/pubmed/2332088>
6
7 37 Robards J, Evandrou M, Falkingham J, *et al.* Marital status, health and mortality.
8 *Maturitas* 2012;**73**:295–9. doi:10.1016/j.maturitas.2012.08.007
9
10 38 Dantzer C, Tessier JF, Nejjari C, *et al.* Mortality of elderly subjects with self-
11 reported asthma in a French cohort, 1991-1996. *Eur J Epidemiol* 2001;**17**:57–63.
12 doi:10.1023/A:1010996718008
13
14 39 Sumino K, O'Brian K, Bartle B, *et al.* Coexisting chronic conditions associated
15 with mortality and morbidity in adult patients with asthma. *J Asthma*
16 2014;**51**:306–14. doi:10.3109/02770903.2013.879881
17
18 40 Koskela HO, Salonen PH, Romppanen J, *et al.* A history of diabetes but not
19 hyperglycaemia during exacerbation of obstructive lung disease has impact on
20 long-term mortality: A prospective, observational cohort study. *BMJ Open*
21 2015;**5**:6794. doi:10.1136/bmjopen-2014-006794
22
23 41 Xu M, Xu J, Yang X. Asthma and risk of cardiovascular disease or all-cause
24 mortality: A meta-analysis. *Ann Saudi Med* 2017;**37**:99–105. doi:10.5144/0256-
25 4947.2017.99
26
27 42 Strand LB, Tsai MK, Wen CP, *et al.* Is having asthma associated with an increased
28 risk of dying from cardiovascular disease? A prospective cohort study of 446 346
29 Taiwanese adults. *BMJ Open* 2018;**8**. doi:10.1136/bmjopen-2017-019992
30
31 43 Denburg JA, Sehmi R, Saito H, *et al.* Systemic aspects of allergic disease: Bone
32 marrow responses. *J Allergy Clin Immunol* 2000;**106**:S242–6.
33 doi:10.1067/mai.2000.110156
34
35 44 Bjermer L. Time for a paradigm shift in asthma treatment: From relieving
36 bronchospasm to controlling systemic inflammation. *J Allergy Clin Immunol*
37 2007;**120**:1269–75. doi:10.1016/j.jaci.2007.09.017
38
39 45 Jensen AO, Nielsen GL, Ehrenstein V. Validity of asthma diagnoses in the Danish
40 National Registry of Patients, including an assessment of impact of
41 misclassification on risk estimates in an actual dataset. *Clin Epidemiol*
42 2010;**2**:67–72. <https://www.ncbi.nlm.nih.gov/pubmed/20865105>
43
44 46 von Bülow A, Kriegbaum M, Backer V, *et al.* The Prevalence of Severe Asthma
45 and Low Asthma Control Among Danish Adults. *J Allergy Clin Immunol Pract*
46 2014;**2**:759-767.e2. doi:10.1016/j.jaip.2014.05.005
47
48 47 Telama R. Tracking of physical activity from childhood to adulthood: A review.
49 *Obes. Facts.* 2009;**2**:187–95. doi:10.1159/000222244
50
51 48 Mertens E, Clarys P, Mullie P, *et al.* Stability of physical activity, fitness
52 components and diet quality indices. *Eur J Clin Nutr* 2017;**71**:519–24.
53 doi:10.1038/ejcn.2016.172
54
55
56
57
58
59
60

Tables

Table 1 – Baseline characteristics of 785 adults enrolled in the Danish Diet, Cancer and Health Cohort with incident asthma between baseline (1993-1997) and follow-up (July 2013).

| | Asthma (N = 785) | Alive (N= 709) | Dead (N = 76) |
|---|---------------------|-------------------|------------------|
| Age 50-55, n (%) | 50 (6.4) | 44 (6.2) | 6 (7.9) |
| Age 55-60, n (%) | 155 (19.7) | 136 (19.2) | 19 (25.0) |
| Age 60-65, n (%) | 580 (73.9) | 529 (74.6) | 51 (67.1) |
| Men, n (%) | 290 (37) | 136 (19) | 19 (25) |
| Mean body mass index (kg/m ²) | 26.5 (12) | 26.4 (4.2) | 27.1 (4.6) |
| Smoking history, n (%) | Never | 351 (45) | 318 (45) |
| | Previous | 260 (33) | 241 (34) |
| | Current | 174 (22) | 150 (21) |
| Mean smoking duration, years (SD) | 25.9 (12) | 25.3 (12) | 31.1 (12) |
| Mean smoking intensity, g/day (SD) | 5.7 (9.1) | 5.3 (9.0) | 9.1 (10) |
| Exposed to environmental tobacco smoke, n (%) | 449 (57) | 403 (57) | 46 (61) |
| Physically active in leisure time, n (%) | 432 (55) | 404 (57) | 28 (37) |
| Mean fruit intake, g/day (SD) | 192 (145) | 193 (146) | 177 (129) |
| Employed, n (%) | 612 (78) | 559 (79) | 53 (70) |
| Marital status, n (%) | Single | 45 (5.7) | 35 (4.9) |
| | Married | 558 (71) | 507 (72) |
| | Divorced | 136 (17) | 125 (18) |
| | Widowed | 46 (5.9) | 42 (5.9) |
| Years of Education | < 8 | 223 (28) | 198 (28) |
| | | 25 (33) | |

| | | | | |
|-------------------|-----------------------|----------|----------|---------|
| n (%) | 8 – 10 | 395 (50) | 361 (51) | 34 (45) |
| | ≥ 10 | 167 (21) | 150 (21) | 23 (30) |
| Comorbidity n (%) | Myocardial infarction | 13 (1.7) | 9 (1.3) | 4 (5.3) |
| | Stroke | 4 (0.5) | 3 (0.4) | 1 (1.3) |
| | Diabetes | 13 (1.7) | 8 (1.1) | 5 (6.6) |
| | Hypertension | 155 (20) | 126 (18) | 29 (38) |
| | Hypercholesterolemia | 46 (5.9) | 45 (6.3) | 1 (1.3) |

SD = standard deviation

For peer review only

Table 2 - Determinants at baseline of survival in 785 adults with incident asthma during follow-up (2013) among participants in the Danish Diet, Cancer and Health Cohort.

| | | Univariate model HR (95% CI) | Multivariate model HR (95% CI) |
|-----------------------------|--|------------------------------------|--------------------------------------|
| Age | 50-55 | 1.00 | - |
| | 55-60 | 0.84 (0.33-2.14) | |
| | 60-65 | 0.76 (0.28-2.08) | |
| Sex | Female | 1.00 | 1.00 |
| | Male | 1.76 (1.12-2.75) | 1.83 (1.14-2.93) |
| Body Mass index | Underweight/Normal (<25 kg/m ²) | 1.00 | - |
| | Overweight (25-30 kg/m ²) | 1.56 (0.93-2.63) | - |
| | Obese (≥ 30 kg/m ²) | 1.52 (0.79-2.91) | - |
| Smoking | Never | 1.00 | 1.00 |
| | Previous | 0.67 (0.38-1.18) | 0.59 (0.33-1.05) |
| | Current | 1.64 (0.96-2.78) | 1.39 (0.81-2.38) |
| Activity in Leisure Time | Inactive | 1.00 | 1.00 |
| | Active | 0.47 (0.29-0.74) | 0.53 (0.33-0.85) |
| Mean fruit intake | g/day | 0.91 (0.76-1.07) | - |
| Employment | Yes | 1.00 | 1.00 |
| | No | 1.17 (0.70-1.96) | 1.04 (0.87-1.25) |
| Marital Status | Single | 2.77 (1.40-5.48) | 2.16 (2.06-4.40) |
| | Married | 1.00 | 1.00 |
| | Divorced | 0.79 (0.41-1.51) | 0.76 (0.40-1.47) |
| | Widowed | 0.83 (0.30-2.30) | 1.15 (0.40-3.27) |
| Myocardial infarction | - | 1.00 | - |
| | + | 2.87 (1.04-7.89) | - |
| Stroke | - | 1.00 | - |
| | + | 1.58 (0.22-11.43) | - |
| Diabetes | - | 1.00 | 1.00 |
| | + | 3.58 (1.44-8.90) | 2.42 (0.96-6.11) |
| Hypertension | - | 1.00 | 1.00 |
| | + | 2.57 (1.61-4.09) | 2.47 (1.54-3.95) |

HR = Hazard Ratio. CI = Confidence interval.

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

| | Item No | Recommendation |
|------------------------------|---------|---|
| Title and abstract | 1 | (a) Indicate the study's design with a commonly used term in the title or the abstract – page 1 (b) Provide in the abstract an informative and balanced summary of what was done and what was found - page 2 |
| Introduction | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported -page 3-4 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses -page 4 |
| Methods | | |
| Study design | 4 | Present key elements of study design early in the paper -page 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection -page 4-5 |
| Participants | 6 | (a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up -page 4-5 (b) For matched studies, give matching criteria and number of exposed and unexposed - N/A |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable -page 4-6 |
| 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 -page 4-6 |
| Bias | 9 | Describe any efforts to address potential sources of bias |
| Study size | 10 | Explain how the study size was arrived at -page 4-5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page- 5-6 |
| Statistical methods | 12 | (a) Describe all statistical methods, including those used to control for confounding -page 6 (b) Describe any methods used to examine subgroups and interactions -N/A (c) Explain how missing data were addressed -N/A (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses -N/A |

| 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 Page -4 and 8 <hr/> (b) Give reasons for non-participation at each stage -due to space limitations non-participation for the DCH cohort is available in the referenced previous articles. <hr/> (c) Consider use of a flow diagram |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders -table 1 <hr/> (b) Indicate number of participants with missing data for each variable of interest -N/A <hr/> (c) Summarise follow-up time (eg, average and total amount) -page 8 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time |
| 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 -table 2 <hr/> (b) Report category boundaries when continuous variables were categorized -table 2 <hr/> (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses -N/A |
| Discussion | | |
| Key results | 18 | Summarise key results with reference to study objectives -page 8 |
| 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 Page 11-12 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence -page 8-11 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results -page 11 |
| Other information | | |
| 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 -page 12 |

*Give information separately for exposed and unexposed groups.

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

For peer review only