

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

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## ABSTRACT

**Objective** 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 up 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 to 0.85). Being male, single and having a diagnosis of hypertension or diabetes were associated with an increased risk of all-cause mortality with an HR of 1.83 (95% CI 1.14 to 2.38), 2.16 (95% CI 2.06 to 4.40), 2.47 (95% CI 1.54 to 3.95) and of 2.42 (95% CI 0.96 to 6.11), respectively.

**Conclusions** This long-term study of adults with hospital contacts for incident asthma revealed that self-reported leisure-time physical activity is associated with an approximately 50% reduction in all-cause mortality. In contrast, both hypertension and diabetes were associated with a higher risk of mortality.

## INTRODUCTION

With over 300 million persons worldwide suffering from asthma and many deaths each year, asthma is a disease that continually requires attention.<sup>1 2</sup> Asthma remains a disease that carries increased mortality compared with general populations.<sup>3 4</sup>

Asthma-specific mortality has, overall, been on a steady decline since the 1950s.<sup>5–7</sup> However, a study based on the WHO Mortality Database found that mortality trends have

## Strengths and limitations of this study

- The present study is one of very few reporting on how physical activity and comorbidities are associated with all-cause mortality in adults with asthma.
- Seven hundred eighty-five persons with incident asthma were followed up for 20 years, with no loss to follow-up.
- The diagnosis of asthma is based on registry information and not a verified objective assessment.
- There are only very few events among those with previous myocardial infarction and stroke.

plateaued, with no significant change in mortality between 2006 and 2012.<sup>8</sup> Furthermore, a British report from 2014 reported that over 67% of deaths related to asthma were potentially preventable.<sup>9</sup>

Asthma-specific mortality alone does not provide the whole picture when evaluating the risks of the disease for individual patients. A study assessing deaths with asthma as a contributing factor, in addition to asthma-specific causes, found that asthma as a contributing factor was associated with more than twice as many deaths compared with asthma-specific deaths alone.<sup>10</sup> Studies suggest that patients with asthma are more prone to acquire other chronic conditions than the background population.<sup>11–13</sup> As the impact of factors such as multimorbidity on all-cause mortality is an area with a paucity of data, there is a need for further studies within this area.<sup>14</sup> The association between physical activity and long-term mortality has been well established in the general population and among patients with chronic obstructive pulmonary disease (COPD).<sup>15 16</sup> However, this has not been examined extensively in asthma.<sup>17</sup> The impact of physical activity on asthma-specific factors, such as disease control, lung function and exacerbations, has been well researched.<sup>17</sup>

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

The present study aimed to examine demographic, lifestyle and comorbid factors associated with long-term all-cause mortality in adults with incident asthma from a large Danish cohort.

## METHODS

Characteristics of the Diet, Cancer, and Health (DCH) cohort have been published previously, with a full description of the cohort.<sup>18 19</sup> 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. 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, OPD, 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 first, 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 or COPD at baseline were excluded. Participants in the DCH cohort were linked to the Danish National Patient Registry (DNPR) to extract hospital contacts from 1993–1997 to 1 July 2013.<sup>20</sup> The link between the DCH and DNPR was done using the unique identifier all Danish residents have. Every discharge diagnosis from all Danish hospitals since 1978 and outpatient clinics since 1995 is gathered in the DNPR.<sup>21</sup> In addition to hospital contacts, we obtained emergency room visits and visits to respiratory outpatient clinics. Cases were followed up from first-ever asthma admission until the time of death, emigration, or 1 July 2013, whichever came first.

Physical activity in leisure time was determined based on a participant's completed questionnaire. An interviewer checked the questionnaire. Participants reported the number of hours per week they did leisure time and transport-related (ie, to and from work, shopping)

physical activity. Leisure-time physical activity was reported separately for summer and winter of the previous year. It was allocated in the following categories: cycling, 'do-it-yourself' activities (ie, home improvements), gardening, housework (cleaning, laundry), sports and walking. The two values for summer and winter were averaged. The questions used have previously been validated in two studies by Peters *et al*<sup>22</sup> and Cust *et al*<sup>23</sup> that found high correlations with movement sensing measurement and accelerometer measurements, respectively. Participants reported as being physically active in leisure time spent at least half an hour a week on at least one of the six categories.

### 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, body mass index (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 1 was 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 HRs with 95% CIs. Stata V.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.

Between baseline and 1 July 2013, 76 of the identified adults with incident asthma died. The majority of cases with incident asthma were women (63%, n=495). Only 45% (n=351) were never smokers at baseline. Interestingly, a substantial proportion of ever-smokers were ex-smokers (60%, n=260) and not current smokers (40%, n=174). The amount of tobacco exposure was much higher among those who died than those with incident asthma still alive at the end of follow-up. Persons who died had an average daily tobacco usage of 3.8 g of tobacco, corresponding to 72% more than those alive at the end

**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 <sup>2</sup> )	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)
Hypercholesterolaemia	46 (5.9)	45 (6.3)	1 (1.3)

SD, Standard Deviation.

of follow-up. Those who died had a daily intake of fruit that was 16 g (or 8.3%) less than those still alive. Further characteristics are shown in [table 1](#).

Of the baseline characteristics included in the analyses, the following were found to be associated with all-cause mortality and were therefore included in the final model: (1) sex, (2) smoking status, (3) physical activity in leisure time, (5) employment status, (6) marital status, (7) diabetes and (8) hypertension. On the other hand, age and a previous diagnosis of myocardial infarction or stroke lacked power for precise estimates for all-cause mortality in univariate analyses and were therefore not included in the final model.

Male sex was associated with a higher risk of all-cause mortality (HR 1.83, 95% CI 1.14 to 2.93). Participants who

reported being single had a higher mortality risk (HR of 2.16 95% CI 2.06 to 4.40) compared with those who reported being married. A diagnosis of hypertension was associated with a substantially increased risk of all-cause mortality (HR 2.47, 95% CI 1.54 to 3.95). Self-reported previous myocardial infarction and a current diagnosis of diabetes had imprecise estimates associated with all-cause mortality, although, notably, robust associations were detected. We found an HR of 2.87 (95% CI 1.04 to 7.89) in the univariate model for myocardial infarction. An HR of 2.42 (95% CI 0.96 to 6.11) for diabetes was found in the multivariate model. We did not find an association between previous stroke and all-cause mortality.

The self-reported leisure-time physical activity showed a substantial reduction in all-cause mortality (HR 0.53,

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

CI, Confidence Interval; HR, Hazard Ratio.

95% CI 0.33 to 0.85). Mean daily fruit intake was not found to be associated with death (table 2).

## DISCUSSION

In this Danish cohort of 785 adults with incident asthma followed up for 20 years, we found that physical activity was associated with a lower risk of all-cause mortality. In contrast, being single or having hypertension was associated with increased all-cause mortality.

### Physical activity

To the best of our knowledge, this is the first cohort study that has reported the association between self-reported physical activity and all-cause mortality, specifically in individuals with asthma. Physical activity has previously been shown to have a positive effect on multiple aspects of asthma.<sup>17</sup> Particularly relevant are two studies by Garcia-Aymerich *et al*<sup>24</sup> and Fisher *et al*<sup>25</sup> that found a protective effect of self-reported physical activity on hospitalisation with asthma exacerbations. While the same effect could not be found on readmissions for exacerbations in the study by Fisher *et al*,<sup>25</sup> their findings are essential to support our findings, as exacerbations are associated with overall morbidity and mortality.<sup>26</sup> Physical activity also appears to have a positive effect on asthma control.<sup>27</sup> However, BMI appears to be more critical, negating the effects of physical activity in some, but not all, models.<sup>17</sup> It appears that if persons with asthma have a moderate level of physical activity compared with inactivity and strenuous physical activity, asthma control is positively affected.<sup>28</sup> The positive effects on these other asthma outcomes could support our finding that physical activity is associated with lower mortality risk.

The effects of physical activity are prudent to establish as we know that patients with asthma generally are less physically active than the general population.<sup>29</sup> Further, we know from a Cochrane review from 2013 that physical activity is well tolerated and safe for individuals with asthma.<sup>30</sup> The review found that physical activity may improve cardiopulmonary function in individuals with asthma without negatively impacting pulmonary function. Furthermore, the Cochrane review is based on shorter-term studies. Long-term findings from the Copenhagen City Heart study suggest that physical activity may diminish long-term lung function decline in individuals with asthma.<sup>31</sup> The amount of physical activity required to be defined as physically active in our study is relatively low and, therefore, should be attainable by most. However, future studies should explore whether there are additional benefits from moderate and high levels of activity. Additionally, would a high or very high level of activity mean the risks of adverse outcomes outweigh the benefits? A study by Russell *et al*<sup>32</sup> found that the benefits of physical activity on asthma symptoms were only present at light levels of activity and not at intense activity levels. Based on our findings, there is absolutely reason

to motivate persons with asthma to do physical activity in their leisure time.

### Sex

We found that men had a higher HR for early death than women. Our finding of higher all-cause mortality among men with asthma is well in line with what is found by previous studies by Lemmetyinen *et al*<sup>33</sup> and Connolly *et al*.<sup>34</sup> However, because of the way the analyses are carried out, it is likely more a reflection of a general higher mortality among men than specifically asthma-related.

### Marital status

Being single (never married) compared with married showed an independently higher risk of death, while being divorced or widowed showed no change. This effect has been shown repeatedly in previous studies.<sup>35 36</sup> The reasons behind this effect is still much discussed; partly studies suggest that there is a selection of less robust individuals to remain single or become divorced. Additionally, there also seems to be a protective effect in being married.<sup>37</sup> A study by Dantzer *et al*<sup>38</sup> found that there was no difference between single and married individuals with asthma. However, they had not stratified single, as we have done, into three different groups. Therefore, persons who were widowed or divorced were included in the single group. As we found, being widowed or divorced is not associated with all-cause mortality, which may explain the discrepancies in findings.

### 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.<sup>14</sup> We found one other study by Sumino *et al*<sup>39</sup> from 2014 that reported the association between hypertension and mortality. They found a lower OR for mortality among individuals with hypertension over the age of 65. However, the study by Sumino *et al*<sup>39</sup> had a much shorter follow-up of 3 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 HR 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. Sumino *et al*<sup>39</sup> found that diabetes was associated with a higher mortality rate in persons over 65. Another cohort study by Koskela *et al*<sup>40</sup> 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.<sup>41 42</sup>

The factors presented in this paper may seem obvious but needs to be verified in asthma, mainly as many of these factors have not previously been explored concerning adults with asthma; not least in large cohorts, as in the present long-term follow-up study of a large cohort of middle-aged men and women with asthma. The relevance of this is due to the systemic inflammation present in persons with asthma, which potentially could affect and change which factors are essential to be aware of compared with general populations.<sup>43 44</sup>

### Limitations

The diagnosis of asthma in the included subjects was based on International Classification of Diseases, 10th Revision (ICD-10) codes connected to hospital contacts, which is not as accurate as objectively verified asthma. However, this has previously been established by Jensen *et al*<sup>45</sup> to be a robust method of identifying persons with asthma. The positive predictive value was found to be 65%; despite this, they discovered that associations found are still relevant. Selecting only persons with either a hospital or outpatient contact means we may limit generalisability, with the majority of persons included having moderate or severe disease. Nonetheless, a study from 2014 found that upwards of 25% of asthma patients with mild to moderate disease experience poor asthma control and hospital admissions.<sup>46</sup>

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

Our definition of physical activity was based on self-reported information, which carries a certain degree of bias. Additionally, a potential limitation is that the degree of self-reported physical activity for some was reported multiple years before the first contact for incident asthma. We can, therefore, not be sure that the level of physical activity still applies at follow-up. However, previous literature suggests that physical activity tracks well over time, particularly in adulthood.<sup>47 48</sup>

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

As the number of events in this cohort study was not substantial, there is a risk of underestimating and overestimating the importance of the identified risk factors.

Therefore, the results of this study cannot stand on their own, yet provide a valuable source for future studies. This is particularly evident for diabetes, which shows a clear trend for a higher risk of mortality, though it lacks the power for a precise estimate.

### CONCLUSIONS

Our study has shown that for middle-aged individuals with hospital contact for incident asthma, persons with comorbidity or are single are at an increased risk of early all-cause mortality. In contrast, leisure-time physical activity was found to have a protective effect on mortality risk. Our findings, therefore, suggest that it is important to encourage our asthma patients to do physical activity. Future studies should examine how varying levels of physical activity affect mortality in persons with asthma. Is there a diminishing or negative effect at very high levels of activity?

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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

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**Data availability statement** Data are available upon reasonable request. Data analysis may require approval from the regional data safety committee for the capital region of Denmark (Videnscenter for dataanmeldelser).

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