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

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Abstract

Objectives:

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

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 occurring 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

with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–3.95) and of 2.42 (95 % CI 0.96-6.11), 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. While both hypertension and diabetes were associated with a higher risk of mortality.

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 follow-up for 20 years, with no loss to follow-up.
- The diagnosis of asthma is based on register information and not an objective assessment.
- There are only very few events among those with previous myocardial infarction and stroke.

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

Short Title: Physical activity and asthma mortality

Introduction

With over 300 million persons worldwide suffering from asthma and a multitude of deaths each year, asthma is a disease that continually requires attention.[1,2] Asthma remains a disease that carries increased mortality compared with general populations.[3,4]

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

Asthma specific mortality alone does not provide the whole picture when evaluating the risks of the disease for individual patients. A study evaluating 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.[10] Additionally, studies suggest that patients with asthma are more prone to acquire other chronic conditions than the background population.[11–13] As the impact of factors as multimorbidity on all-cause mortality is an area with a paucity of data, a need for studies in these areas exists.[14] The association between physical activity and long-term mortality has been well established in the general population and patients with COPD.[15,16] However, this has not been examined extensively in asthma.[17] The impact of physical activity on asthma specific factors, such as disease control, lung function and exacerbations has been well researched.[17]

Based on the currently available knowledge, it remains of utmost to further explore factors associated with asthma-related mortality, including not least all-cause mortality. The present study aimed to examine factors associated with long-term all-cause mortality in adults with incident asthma from a large Danish cohort ~~of adults~~.

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 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. 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 and until

July 1st, 2013.[20] The link between the DCH and DNPR was done using the unique identifier all Danish residents have. Every discharge diagnoses from all Danish hospitals since 1978 and from outpatient clinics since 1995 are gathered in the DNPR.[21] In addition to hospital contacts, we gathered emergency room visits and visits to respiratory outpatient clinics. 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. Cases were followed from first-ever asthma admission and until the time of death, or emigration, or July 1st, 2013, whichever came first.

Physical activity in leisure-time was determined based on a participant filled 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 and 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 and Cust et al that found high correlations with movement sensing measurement and accelerometer measurements, respectively.[22,23] Participants who are reported as being physically active in leisure time spent at least half an hour a week on at one 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, BMI, length of education, employment and civil status, tobacco history, occupational exposure, leisure-time physical activity, fruit consumption, and co-morbidities. 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 that were associated with all-cause mortality, defined by backwards 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. Results from the univariate and multivariate model 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.

Between baseline and July 1st, 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 compared to those with incident asthma still alive at the end of follow-up. On average, persons that died smoked 3.8 grams of tobacco per day, corresponding to 72% more than those who were alive at the end of follow-up. Those that died had a daily intake of fruit that was 16 g (or 8.3 %) less compared with those that were 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 for all-cause mortality (HR 1.83, 95% CI 1.14-2.93).

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

Having a diagnosis of hypertension was associated with a substantially increased risk of all-cause mortality (HR 2.47, 95% CI 1.54–3.95). 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. For myocardial infarction, we found an HR of 2.87 (95% CI 1.04-7.89) in the univariate model and diabetes an HR of 2.42 (95% CI 0.96-6.11) in the multivariate model. There was not found 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, 95% CI 0.33–0.85).

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 for 20 years, we found that physical activity was associated with a lower risk of all-cause mortality. In contrast, being unmarried or having hypertension were 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.[17] Particularly relevant are two studies by Garcia-Aymerich et al[24] and Fisher et al[25] 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[25], it is an important support of our findings, as exacerbations are associated with morbidity

and mortality.[26] Physical activity also appears to have a positive effect on asthma control.[27] However, BMI appears to be more critical, negating the effects of physical activity in some, but not all, models.[17] It appears though that if persons with asthma do a moderate level of physical activity compared with inactivity and strenuous physical activity that asthma control is positively affected.[28] The positive effects on these other asthma outcomes could support our finding of physical activities associated with a lower risk of mortality.

The effects of physical activity are prudent to establish as we know that persons with asthma generally are less physically active than the general population.[29] Further, we know from a Cochrane review from 2013 that physical activity is well-tolerated and safe for individuals with asthma.[30] The review found that physical activity may improve cardiopulmonary function in individuals with asthma, without a negative impact on 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.[31] 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, is there an upper limit of activity were the risks of adverse outcomes outweigh the benefits. Based on our findings, there is absolutely reason to motivate persons with asthma to do some form of physical activity in their leisure time.

Comorbidities

Hypertension had a strong association with death. Overall all included comorbid conditions at baseline seemed 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 person with asthma.[14] We found one other study by Sumino et al[32] from 2014 that report the association between hypertension and mortality. They found there was a lower OR for mortality among individuals with hypertension for individuals over the age of 65 years. However, the study by Sumino et al[32] had a much shorter follow-up of three years compared to 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, again, the amount of other studies is exceedingly limited, there is other literature supporting this finding. The study by Sumino et al[32] found that diabetes was associated with a higher rate of mortality in persons over the age of 65. Another cohort study by Koskela et al[33] 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, once again, the HR estimate was imprecise 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.[34,35]

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 in relation to 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.[36,37]

Limitations

The diagnosis of asthma in the included subjects was based on 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[38] 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 likely only have those with moderate and severe disease included in the cohort. Meaning the findings in this article cannot be universally applied.

The prevalence of asthma in this cohort is low (about 1%), substantially lower than the current reported prevalence in Denmark of 10%, therefore, the generalizability is limited. The low prevalence is due to only including participants without a previous diagnosis of asthma and only included 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.[39,40]

We did not have information on the specific cause of death and therefore were unable to examine factors relating to asthma specific mortality.

As the number of events in this cohort study was not substantial and therefore not meeting the traditional, events per variable of 10 rule.[41] There is, therefore, a risk of both type 1 and 2 errors. The results of this study can, therefore, not stand on their own, yet it provides a valuable source for future studies. This is particularly evident for diabetes, which shows a clear trend for 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, there appears to be increased mortality for persons with comorbidity, whereas leisure-time physical activity was found to have a protective effect on mortality risk.

Abbreviations:

BMI = Body Mass Index

DCH = Diet Cancer and Health Cohort

HR = Hazard Ratio

OR = Odds Ratio

Declarations

Ethics approval and consent to participate: 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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Competing interests: ODT, ZJA and CSU have no perceived conflicts of interest in relation to this study.

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

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

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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).

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		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)

474 SD = standard deviation

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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/m2)	1.00	-
	Overweight (25-30 kg/m2)	1.56 (0.93-2.63)	-
	Obese (≥ 30 kg/m2)	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 -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.

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

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

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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

with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–3.95) and of 2.42 (95 % CI 0.96-6.11), 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.

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 register information and not an objective assessment.
- There are only very few events among those with previous myocardial infarction and stroke.

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

Short Title: Physical activity and asthma mortality

Introduction

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

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

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.[10] Studies suggest that patients with asthma are more prone to acquire other chronic conditions than the background population.[11–13] As the impact of factors as multimorbidity on all-cause mortality is an area with a paucity of data, a need for studies in these areas exists.[14] The association between physical activity and long-term mortality has been well established in the general population and patients with COPD.[15,16] However, this has not been examined extensively in asthma.[17] The impact of physical activity on asthma-specific factors, such as disease control, lung function, and exacerbations has been well researched.[17]

Based on the currently available knowledge, it remains of utmost to further explore factors associated with asthma-related mortality, including not least all-cause mortality. The present study aimed to examine factors associated with long-term all-cause mortality in adults with incident asthma from a large Danish cohort ~~of adults~~.

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

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 until July 1st, 2013.[20] 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 from outpatient clinics since 1995 are gathered in the DNPR.[21] In addition to hospital contacts, we gathered emergency room visits and visits to respiratory outpatient clinics. Cases were followed from first-ever asthma admission until the time of death, emigration, or July 1st, 2013, whichever came first.

Physical activity in leisure time was determined based on a participant completed questionnaire. An interviewer checked the questionnaire. Participants reported the number of hours per week they did leisure time and transport-related (i.e., 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 (i.e., 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 and Cust et al that found high correlations with movement sensing measurement and accelerometer measurements, respectively.[22,23] 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, 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 fulfilled 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 July 1st, 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. On average, persons who died smoked 3.8 grams of tobacco per day, corresponding to 72% more than those alive at the end 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 for all-cause mortality (HR 1.83, 95% CI 1.14-2.93).

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

A diagnosis of hypertension was associated with a substantially increased risk of all-cause mortality (HR 2.47, 95% CI 1.54–3.95). 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 1.04-7.89) in the univariate model for myocardial infarction. An HR of 2.42 (95% CI 0.96-6.11) for diabetes was found in the multivariate model. There was not found 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, 95% CI 0.33–0.85).

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 for 20 years, we found that physical activity was associated with a lower risk of all-cause mortality. In contrast, being unmarried or having hypertension were 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.[17] Particularly relevant are two studies by Garcia-Aymerich et al[24] and Fisher et al[25] 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[25], their findings are essential support of our findings, as exacerbations are associated with morbidity and mortality.[26] Physical activity also appears to have

a positive effect on asthma control.[27] However, BMI appears to be more critical, negating the effects of physical activity in some, but not all, models.[17] It appears that if persons with asthma do a moderate level of physical activity compared with inactivity and strenuous physical activity, asthma control is positively affected.[28] 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 persons with asthma generally are less physically active than the general population.[29] Further, we know from a Cochrane review from 2013 that physical activity is well-tolerated and safe for individuals with asthma.[30] The review found that physical activity may improve cardiopulmonary function in individuals with asthma without a negative impact on 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.[31] 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.[32] 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 some form of physical activity in their leisure time.

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]

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 in relation to 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.[37,38]

Limitations

The diagnosis of asthma in the included subjects was based on 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[39] 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 may have 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.[40]

The prevalence of asthma in this cohort is low (about 1%), substantially lower than the current reported prevalence in Denmark of 10%; therefore, the generalizability is limited. The low prevalence is due to only including participants without a previous diagnosis of asthma and only included 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.[41,42]

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 influences mortality risk.

As the number of events in this cohort study was not substantial, there is a risk of both under and overestimating the importance of the identified risk factors. Therefore, the results of this study cannot stand on their own, yet it provides 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, there appears to be increased mortality for persons with comorbidity. In contrast, leisure-time physical activity was found to have a protective effect on mortality risk.

Abbreviations:

BMI = Body Mass Index

DCH = Diet Cancer and Health Cohort

HR = Hazard Ratio

OR = Odds Ratio

Declarations

Ethics approval and consent to participate: 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.

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

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

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

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

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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/m2)	1.00	-
	Overweight (25-30 kg/m2)	1.56 (0.93-2.63)	-
	Obese (≥ 30 kg/m2)	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 -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.

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

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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

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

with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–3.95) and of 2.42 (95 % CI 0.96-6.11), 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.

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 register information and not an objective assessment.
- There are only very few events among those with previous myocardial infarction and stroke.

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

Short Title: Physical activity and asthma mortality

Introduction

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

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

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.[10] Studies suggest that patients with asthma are more prone to acquire other chronic conditions than the background population.[11–13] As the impact of factors as multimorbidity on all-cause mortality is an area with a paucity of data, a need for studies in these areas exists.[14] The association between physical activity and long-term mortality has been well established in the general population and patients with COPD.[15,16] However, this has not been examined extensively in asthma.[17] The impact of physical activity on asthma-specific factors, such as disease control, lung function, and exacerbations has been well researched.[17]

Based on the currently available knowledge, it remains of utmost 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.[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

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 until July 1st, 2013.[20] 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 from outpatient clinics since 1995 are gathered in the DNPR.[21] In addition to hospital contacts, we gathered emergency room visits and visits to respiratory outpatient clinics. Cases were followed from first-ever asthma admission until the time of death, emigration, or July 1st, 2013, whichever came first.

Physical activity in leisure time was determined based on a participant completed questionnaire. An interviewer checked the questionnaire. Participants reported the number of hours per week they did leisure time and transport-related (i.e., 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 (i.e., 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 and Cust et al that found high correlations with movement sensing measurement and accelerometer measurements, respectively.[22,23] 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, 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 fulfilled 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 July 1st, 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. On average, persons who died smoked 3.8 grams of tobacco per day, corresponding to 72% more than those alive at the end 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 for all-cause mortality (HR 1.83, 95% CI 1.14-2.93).

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

A diagnosis of hypertension was associated with a substantially increased risk of all-cause mortality (HR 2.47, 95% CI 1.54–3.95). 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 1.04-7.89) in the univariate model for myocardial infarction. An HR of 2.42 (95% CI 0.96-6.11) for diabetes was found in the multivariate model. There was not found 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, 95% CI 0.33–0.85).

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 for 20 years, we found that physical activity was associated with a lower risk of all-cause mortality. In contrast, being unmarried or having hypertension were 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.[17] Particularly relevant are two studies by Garcia-Aymerich et al[24] and Fisher et al[25] 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[25], their findings are essential support of our findings, as exacerbations are associated with morbidity and mortality.[26] Physical activity also appears to have

a positive effect on asthma control.[27] However, BMI appears to be more critical, negating the effects of physical activity in some, but not all, models.[17] It appears that if persons with asthma do a moderate level of physical activity compared with inactivity and strenuous physical activity, asthma control is positively affected.[28] 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 persons with asthma generally are less physically active than the general population.[29] Further, we know from a Cochrane review from 2013 that physical activity is well-tolerated and safe for individuals with asthma.[30] The review found that physical activity may improve cardiopulmonary function in individuals with asthma without a negative impact on 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.[31] 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.[32] 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 some form of physical activity in their leisure time.

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]

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 in relation to 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.[37,38]

Limitations

The diagnosis of asthma in the included subjects was based on 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[39] 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 may have 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.[40]

The prevalence of asthma in this cohort is low (about 1%), substantially lower than the current reported prevalence in Denmark of 10%; therefore, the generalizability is limited. The low prevalence is due to only including participants without a previous diagnosis of asthma and only included 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.[41,42]

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 influences mortality risk.

As the number of events in this cohort study was not substantial, there is a risk of both under and overestimating the importance of the identified risk factors. Therefore, the results of this study cannot stand on their own, yet it provides 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, there appears to be increased mortality for persons with comorbidity. In contrast, leisure-time physical activity was found to have a protective effect on mortality risk.

Abbreviations:

BMI = Body Mass Index

DCH = Diet Cancer and Health Cohort

HR = Hazard Ratio

OR = Odds Ratio

Declarations

Ethics approval and consent to participate: 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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Authors' contributions: Conception and design—ODT, ZJA and CSU.; preparation of data and statistical analyses - ZJA.; statistical interpretation and drafted the manuscript—ODT; all authors critically reviewed and accepted the final version of the manuscript.

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

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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/m2)	1.00	-
	Overweight (25-30 kg/m2)	1.56 (0.93-2.63)	-
	Obese (≥ 30 kg/m2)	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 -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.

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

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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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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

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

with an HR of 1.83 (95 % CI 1.14–2.38), 2.16 (95 % CI 2.06–4.40), 2.47 (95 % CI 1.54–3.95) and of 2.42 (95 % CI 0.96-6.11), 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.

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.

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

Short Title: Physical activity and asthma mortality

Introduction

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

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

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.[10] Studies suggest that patients with asthma are more prone to acquire other chronic conditions than the background population.[11–13] 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.[14] The association between physical activity and long-term mortality has been well established in the general population and among patients with COPD.[15,16] However, this has not been examined extensively in asthma.[17] The impact of physical activity on asthma-specific factors, such as disease control, lung function, and exacerbations, has been well researched.[17]

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.[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 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 until July 1st, 2013.[20] 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.[21] In addition to hospital contacts, we obtained emergency room visits and visits to respiratory outpatient clinics. Cases were followed from first-ever asthma admission until the time of death, emigration, or July 1st, 2013, whichever came first.

Physical activity in leisure time was determined based on a participant completed questionnaire. An interviewer checked the questionnaire. Participants reported the number of hours per week they did leisure time and transport-related (i.e., 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 (i.e., 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 and Cust et al that found high correlations with movement sensing measurement and accelerometer measurements, respectively.[22,23] 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, 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.

Between baseline and July 1st, 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 grams of tobacco, corresponding to 72% more than those alive at the end 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 for all-cause mortality (HR 1.83, 95% CI 1.14-2.93). Participants who reported being single had a higher mortality risk (HR of 2.16 95% CI 2.06-4.40) 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 1.54–3.95). 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 1.04-7.89) in the univariate model for myocardial infarction. An HR of 2.42 (95% CI 0.96-6.11) for diabetes was found in the multivariate model. We did not found 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, 95% CI 0.33–0.85). 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 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 were 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.[17] Particularly relevant are two studies by Garcia-Aymerich et al[24] and Fisher et al[25] 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[25], their findings are essential to support our findings, as exacerbations are associated with overall morbidity and mortality.[26] Physical activity also appears to have a positive effect on asthma control.[27] However, BMI appears to be more critical, negating the effects of physical activity in some, but not all, models.[17] 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.[28] 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.[29] Further, we know from a Cochrane review from 2013 that physical activity is well-tolerated and safe for individuals with asthma.[30] 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.[31] 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.[32] 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 hazard ratio 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[33] and Connolly et al.[34] 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 to 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.[35,36] 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.[37] A study by Dantzer et al [38], 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.[14] We found one other study by Sumino et al[39] from 2014 that report 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[39] 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. Sumino et al[39] found that diabetes was associated with a higher mortality rate in persons over 65. Another cohort study by Koskela et al[40] 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.[41,42]

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 in relation to 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.[43,44]

Limitations

The diagnosis of asthma in the included subjects was based on 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[45] 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 may have 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.[46]

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 only including participants without a previous diagnosis of asthma and only included 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.[47,48]

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 influences mortality risk.

As the number of events in this cohort study was not substantial, there is a risk of under and overestimating the importance of the identified risk factors. Therefore, the results of this study cannot stand on their own, yet it provides 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?

Abbreviations:

BMI = Body Mass Index

DCH = Diet Cancer and Health Cohort

HR = Hazard Ratio

OR = Odds Ratio

Declarations

Ethics approval and consent to participate: 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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Competing interests: ODT, ZJA, and CSU have no perceived conflicts of interest in relation to this study.

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

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

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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	< 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

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/m2)	1.00	-
	Overweight (25-30 kg/m2)	1.56 (0.93-2.63)	-
	Obese (≥ 30 kg/m2)	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 -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.

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