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Myocardial infarction and other co-morbidities in patients with chronic obstructive pulmonary disease: a Danish Nationwide Study of 7.4 million individuals

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Aims Myocardial infarction is nominally the most important co-morbidity in patients with chronic obstructive pulmonary disease, and the one with the greatest potential for treatment and prevention to improve the overall prognosis of chronic obstructive pulmonary disease patients. We assessed the extent of myocardial infarction and other co-morbidities in individuals with chronic obstructive pulmonary disease in the general population.

Methods and results We used individual participant data for the entire Danish population from 1980 through 2006, comprising 140 million person-years of follow-up. We used information from four national Danish registries with 100% follow-up and detected ever-diagnosed chronic obstructive pulmonary disease ($n = 313\,958$) and incident cases of a first myocardial infarction ($n = 422\,344$), lung cancer ($n = 116\,629$), hip fracture ($n = 53\,756$), depression ($n = 93\,038$), and diabetes mellitus ($n = 292\,228$). Multivariate adjusted hazard ratios for life-time association with ever-diagnosed chronic obstructive pulmonary disease were 1.26 (95% CI 1.25–1.27) for myocardial infarction, 2.05 (2.03–2.08) for lung cancer, 2.12 (2.07–2.17) for hip fracture, 1.74 (1.70–1.77) for depression, and 1.21 (1.20–1.23) for diabetes mellitus, compared with controls; these risk estimates were highest in women and the youngest age groups. Before the first hospitalization with chronic obstructive pulmonary disease, multivariate adjusted odds ratios were 1.47 (1.44–1.49) for myocardial infarction, 3.68 (3.52–3.84) for lung cancer, 1.16 (1.13–1.18) for hip fracture, 1.88 (1.80–1.96) for depression, and 1.16 (1.13–1.18) for diabetes mellitus, compared with matched controls. Corresponding values after a chronic obstructive pulmonary disease hospitalization were 0.74 (0.73–0.76), 1.48 (1.45–1.51), 1.23 (1.20–1.27), 1.21 (1.18–1.24), and 0.83 (0.81–0.85), respectively.

Conclusion Chronic obstructive pulmonary disease was associated with higher rates of myocardial infarction, lung cancer, diabetes, hip fracture, and depression, but the strength of these associations was modified after a first admission for chronic obstructive pulmonary disease. These associations may be related to common genetic and/or lifestyle/environmental risk factors, and therefore these factors are likely to have an adverse health impact rather than chronic obstructive pulmonary disease *per se*.

Keywords Myocardial infarction • Chronic obstructive pulmonary disease • Comorbidity • Epidemiology

Introduction

Myocardial infarction is nominally the most important co-morbidity in patients with chronic obstructive pulmonary disease.[1,2] Chronic obstructive pulmonary disease is currently the fourth leading cause of death worldwide, and has a rising mortality rate:[3] it has been estimated that by the year 2020 chronic obstructive pulmonary disease will be the third leading cause of death. Presence of chronic obstructive pulmonary disease as well as myocardial infarction and other co-morbidities contributes to

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poor health outcome in chronic obstructive pulmonary disease patients, and therefore treatment and prevention of myocardial infarction and other co-morbidities may have beneficial effects towards the overall prognosis of chronic obstructive pulmonary disease patients.[4] Co-morbidities of chronic obstructive pulmonary disease, such as myocardial infarction, lung cancer, hip fracture, depression, and diabetes mellitus, has been reported in smaller studies of patients,[1,2,5–7] studies prone to selection bias; however, the extent of association between chronic obstructive pulmonary disease and myocardial infarction and other co-morbidities in the general population is unknown. Hence, powerful and selection bias-free assessment of prospective associations of chronic obstructive pulmonary disease with the risk of myocardial infarction and other co-morbidities should yield better understanding of the aetiological processes underlying any such associations.

The aim of this nationwide study based on individual participant data was to examine life-time association and development before and after a chronic obstructive pulmonary disease hospitalization of myocardial infarction and other co-morbidities in patients with chronic obstructive pulmonary disease. For this purpose, we examined the association of chronic obstructive pulmonary disease with myocardial infarction, lung cancer, hip fracture, depression, and diabetes mellitus in those with and without chronic obstructive pulmonary disease in the entire Danish population from 1980 through 2006. We chose to include these five co-morbidities because they all are recognized as potential chronic obstructive pulmonary disease co-morbidities,[1,2,5–7] because myocardial infarction, lung cancer, and hip fracture (as a clinical marker of osteoporosis) are relatively hard endpoints unlikely to be given to patients during a hospitalization without proper diagnostic tests, and because diabetes mellitus and depression may demonstrate the spectrum of co-morbidities in chronic obstructive pulmonary disease patients. Other potential co-morbidities were not included because of questionable diagnostic validity in national registries (e.g. left ventricular heart failure, peripheral arterial disease, and stroke), or because such data are not available nationwide (e.g. dyslipidaemia and hypertension). As a negative control, we examined association between chronic obstructive pulmonary disease and a diagnosis of multiple sclerosis, because multiple sclerosis does not share any risk factors with chronic obstructive pulmonary disease. We used information from the national Danish Patient Registry, the national Danish Causes of Death Registry, and the national Danish Civil Registration System and Statistics Denmark. These registries were all complete from 1980 through 2006.

Methods

We used individual participant data for the entire Danish population from the beginning of 1980 through the end of 2006 comprising 7.4 million individuals and 140 million person-years of follow-up.[8] The national Danish Civil Registration System records all births, deaths, emigrations, and immigrations in Denmark, recorded by the civil registration number, which is unique to every person living in Denmark and includes information on age and sex.[9] These studies were approved by Herlev Hospital, Copenhagen University Hospital and Statistics Denmark; in Denmark, approval by ethical committees of such anonymous nationwide studies is not necessary.

Endpoints: myocardial infarction, lung cancer, diabetes mellitus, hip fracture, depression, and multiple sclerosis

Information on diagnoses of myocardial infarction, lung cancer, hip fracture, depression, diabetes mellitus, and multiple sclerosis was drawn from the national Danish Patient Registry (66–94% of events) and the national Danish Causes of Death Registry (6–34% of events); multiple sclerosis acted as a negative control.

The national Danish Patient Registry records information on discharge diagnoses from all public and private Danish hospitals including outpatients, using the unique civil registration number. Records include admission date and diagnoses according to the WHO International Classification of Diseases (ICD8 until 1993, hereafter ICD10). All individuals with records of myocardial infarction (ICD8 410; ICD10 I21), lung cancer (ICD8 162; ICD10 C34), hip fracture (ICD8 820; ICD10 S720–S722), depression (ICD8 296, 300.49; ICD10 F31–F39), diabetes mellitus (ICD8 249, 250; ICD10 E10–E14), and multiple sclerosis (ICD8 340; ICD10 G35) from 1980 through 2006 were used in the study as incident endpoints.

The national Danish Causes of Death Registry records information on death date and causes of death for all deaths in Denmark using the unique civil registration number, reported by hospitals and general practitioners. All individuals with records of causes of death diagnoses (using ICD8 and ICD10 codes as described above) for myocardial infarction, lung cancer, hip fracture, depression, diabetes mellitus, and multiple sclerosis from 1980 through 2006 were also used in the study as incident endpoints.

Chronic obstructive pulmonary disease

Information on chronic obstructive pulmonary disease was drawn from the national Danish Patient Registry and the national Danish Causes of Death Registry, as described above. All individuals with records of hospitalization and/or death with diagnosed chronic obstructive pulmonary disease (ICD8 491, 492; ICD10 J41–J44) from 1980 through 2006 were used to identify individuals suffering from chronic obstructive pulmonary disease. ICD8 496 was never implemented in the Danish ICD8 version. The ICD8 version was used until the end of 1993 while the ICD9 version was never implemented in Denmark before the start of the ICD10 version.

Other covariates

Statistics Denmark covering all persons living in Denmark records information on descent, educational level, and geographical residency, using the unique civil registration number.

Statistical analysis

Statistical analyses were performed using STATA 11.0 MP software, using individual participant data. We have previously conducted similar studies,[8,10] each of which was validated by running parallel statistical analyses with similar results. Age-standardized incidence rates were calculated according to the WHO World Standard population.[11] We assessed the association between chronic obstructive pulmonary disease and myocardial infarction, lung cancer, hip fracture, depression, diabetes mellitus, and multiple sclerosis in three different ways, all of which were decided *a priori*.

First, we assessed the prevalence of these co-morbidities stratified by 10-year age groups, in those with and without chronic obstructive

pulmonary disease. Differences in disease prevalence were tested with Chi-square tests.

Secondly, we assessed life-time association by following all persons living in Denmark from 1980, birth date, or immigration (which ever came last) to a disease event, death, emigration, or end of 2006 (whichever came first); when individuals first emigrated and later immigrated back to Denmark, they were still included in the analysis. For these analyses, we used Kaplan–Meier curves, log-rank tests, and Cox regression models with age as the timescale, which implies that age is automatically adjusted for. Cox proportional hazards ratios were calculated as measures for relative risk. Models were left truncated (1980 or at immigration) with delayed entry, and individuals were censored at events, death, permanent emigration, or end of follow-up. Assessment of the proportional hazards assumption was done graphically, and showed no major violations. Multivariate models were adjusted for age, sex, descent, geographical residency, and educational level. In the sensitivity analyses using Cox regression as described above, we excluded individuals with a diagnosis of chronic obstructive pulmonary disease before age 30 and 40 years. Finally, for the overall analyses, we also calculated odds ratios using logistic regression analysis as described below.

Thirdly, we assessed whether individuals hospitalized with chronic obstructive pulmonary disease have increased or decreased risk of development of myocardial infarction, lung cancer, hip fracture, depression, and diabetes mellitus before and after a hospitalization with chronic obstructive pulmonary disease using a nested case–control design; we excluded individuals diagnosed with chronic obstructive pulmonary disease and the relevant co-morbidity during the same hospitalization, as well as individuals who only had chronic obstructive pulmonary disease diagnosed at their death certificate. For co-morbidities before a chronic obstructive pulmonary disease hospitalization, chronic obstructive pulmonary disease cases were matched by birth year, age at chronic obstructive pulmonary disease hospitalization, and sex with up to five general population controls, creating matched subsets of up to six individuals. Logistic regression analysis adjusted multivariate as described above, and then compared the risk of myocardial infarction and other co-morbidities before the date of chronic obstructive pulmonary disease hospitalization (all events of the relevant co-morbidity after this date were excluded). For co-morbidities after a chronic obstructive pulmonary disease hospitalization, chronic obstructive pulmonary disease cases were matched similarly to five population controls; however, cases and controls with the relevant co-morbidity before the date of chronic obstructive pulmonary disease hospitalization were excluded. Risk of myocardial infarction and other co-morbidities was calculated using logistic and Cox regression, adjusted multivariate as described above. Time at risk started at 'time of chronic obstructive pulmonary disease hospitalization' for both cases and controls in Cox regression analyses in nested case–control studies.

Results

We included the entire Danish population in a 27-year-follow-up period from 1980 through 2006, comprising 7 419 791 individuals in total and 140 million person-years of follow-up. Baseline characteristics are shown in *Table 1*. We identified 313 958 individuals with chronic obstructive pulmonary disease, 422 344 individuals with myocardial infarction, 116 629 individuals with lung cancer, 53 756 individuals with hip fracture, 93 038 individuals with depression, 292 228 individuals with diabetes mellitus, and 5064 individuals with multiple sclerosis. The median age at diagnosis was 68 years (61–79) [median (inter-quartile range)] for chronic obstructive pulmonary disease, 70 years (61–80) for myocardial infarction, 69 years (62–76) for lung cancer, 81 years (76–88) for hip fracture, 67 years (55–80) for depression, 65 years (56–76) for diabetes mellitus, and 63 years (54–71) for multiple sclerosis.

Prevalence of myocardial infarction and other co-morbidities

Calculation of prevalence of co-morbidities by 10-year age groups in those with and without chronic obstructive pulmonary disease allows a look at unadjusted data. For these calculations, we included the entire Danish population from 1980 through 2006.

For myocardial infarction and diabetes mellitus, a higher prevalence among those with vs. without chronic obstructive pulmonary disease was observed before age 70 years, for depression this was observed before age 90 years, while for lung cancer and hip fracture this was observed for all age groups (*Figure 1*); however, prevalence of multiple sclerosis did not differ between those with and without chronic obstructive pulmonary disease.

Life-time association of chronic obstructive pulmonary disease with myocardial infarction and other co-morbidities

Calculation of life-time association provides a measure of relative risk of co-morbidities in those ever vs. never hospitalized or dead with diagnosed chronic obstructive pulmonary disease, but does not provide clues to causality. For these calculations, we included the entire Danish population from 1980 through 2006.

Cumulative incidence by age of myocardial infarction, lung cancer, hip fracture, depression, and diabetes mellitus were all substantially higher among those ever diagnosed with chronic obstructive pulmonary disease ($n = 313\,958$) than among controls ($n = 7\,105\,833$) (all log-rank $P < 10^{-300}$; *Figure 2*); however, this was not the case for cumulative incidence of multiple sclerosis, and therefore measures of relative risk were not calculated for multiple sclerosis.

Multivariate adjusted hazard ratios from Cox regression for life-time association with chronic obstructive pulmonary disease were 1.26 (95% CI 1.25–1.27) for myocardial infarction, 2.05 (2.03–2.08) for lung cancer, 2.12 (2.07–2.17) for hip fracture, 1.74 (1.70–1.77) for depression, and 1.21 (1.20–1.23) for diabetes mellitus, compared with controls (*Table 2*). The corresponding odds ratios from logistic regression were similar.

Only very few individuals received a diagnosis of chronic obstructive pulmonary disease before the age of 40 years, and almost none before the age of 30 years (except for a few cases in the very early childhood ages) (*Figure 3*). When we excluded individuals with chronic obstructive pulmonary disease diagnosed before age 30 and 40 years, the risk estimates were only attenuated slightly. When stratifying by descent and geographical residency, we found only minor changes in risk estimates (*Table 3*). However, when stratifying by sex and age at study entry, we found higher risk estimates for women and the youngest age groups.

Table 1 Baseline characteristics of individuals ever diagnosed with chronic obstructive pulmonary disease vs. controls in the entire Danish population from 1980 through 2006, comprising 7.4 million individuals

	Chronic obstructive pulmonary disease	Controls
Age, years	55 (46–66)	26 (1.2–42)
Gender		
Male	173 591 (55%)	3 532 790 (50%)
Female	140 367 (45%)	3 573 042 (50%)
Age group, years		
<30	22 718 (7%)[a]	4 344 171 (61%)
30–39	28 394 (9%)	838 277 (12%)
40–49	53 941 (17%)	548 690 (8%)
50–59	86 553 (28%)	492 345 (7%)
60–69	73 469 (23%)	438 531 (6%)
70–79	39 203 (12%)	310 450 (4%)
80–89	9110 (3%)	119 808 (2%)
≥90	570 (0.2%)	13 561 (0.2%)
Descent		
Danish	303 298 (97%)	6 255 264 (89%)
Other	10 341 (3%)	751 088 (11%)
Geographical residency		
Country side and towns	116 457 (37%)	2 785 668 (40%)
Cities, 12 000–100 000 inhabitants	79 239 (25%)	1 811 263 (26%)
Cities, >100 000 inhabitants	118 200 (38%)	2 431 107 (35%)
Level of education		
Unknown, including children[b]	132 241 (43%)	2 197 311 (32%)
Primary school	111 766 (36%)	1 819 365 (26%)
High school	1947 (1%)	355 389 (5%)
Vocational	48 618 (16%)	1 525 675 (22%)
Short academic education	3351 (1%)	210 824 (3%)
Medium academic education	8588 (3%)	531 399 (8%)
Long academic education	2764 (1%)	331 870 (5%)

Baseline characteristics were at study entry in 1980, at birth if born after 1980, or at immigration if after 1980. Values are numbers (percent) or median (interquartile range) for age. Information on descent, geographical residency, and level of education is not available on all individuals, and therefore numbers vary slightly.
[a]Number of individuals who at study entry were <30 years and who developed chronic obstructive pulmonary disease during the following 27 years: median age at chronic obstructive pulmonary disease diagnosis was 34 years (IQR; 25–47) in those <30 years at study entry.
[b]Information on education was not available if completed prior to 1980 or abroad.

Myocardial infarction and other co-morbidities developed before and after hospitalization with chronic obstructive pulmonary disease

Calculation of the risk of acquiring co-morbidities before and after the first hospitalization with chronic obstructive pulmonary disease is different from assessing life-time association as reported above. In *Figure 2* and *Table 2*, we examine risk of myocardial infarction and other co-morbidities as a function of ever-diagnosed chronic obstructive pulmonary disease. Therefore, the relative differences in age of onset of chronic obstructive pulmonary disease, myocardial infarction and other co-morbidities will not be visible in these illustrations, which conversely is the case in *Figure 1* and *Table 4*. For the calculations in *Table 4*, we compared individuals hospitalized with chronic obstructive pulmonary disease to year of birth, age at chronic obstructive pulmonary disease hospitalization, and sex-matched general population controls. Follow-up after a chronic obstructive pulmonary disease hospitalization for the nested case–control study was 3.2 and 17.1 million person-years for chronic obstructive pulmonary disease cases and controls in the analyses for myocardial infarction.

Multivariate adjusted odds ratios from logistic regression in chronic obstructive pulmonary disease patients before the first hospitalization with chronic obstructive pulmonary disease were 1.47 (1.44–1.49) for myocardial infarction, 3.68 (3.52–3.84) for lung cancer, 1.16 (1.13–1.18) for hip fracture, 1.88 (1.80–1.96) for depression, and 1.16 (1.13–1.18) for diabetes mellitus, compared with matched controls (*Table 4*). The corresponding odds ratios after a chronic obstructive pulmonary disease hospitalization were 0.74 (0.73–0.76) for myocardial infarction, 1.48 (1.45–1.51) for lung cancer, 1.23 (1.20–1.27) for hip fracture, 1.21 (1.18–1.24) for depression, and 0.83

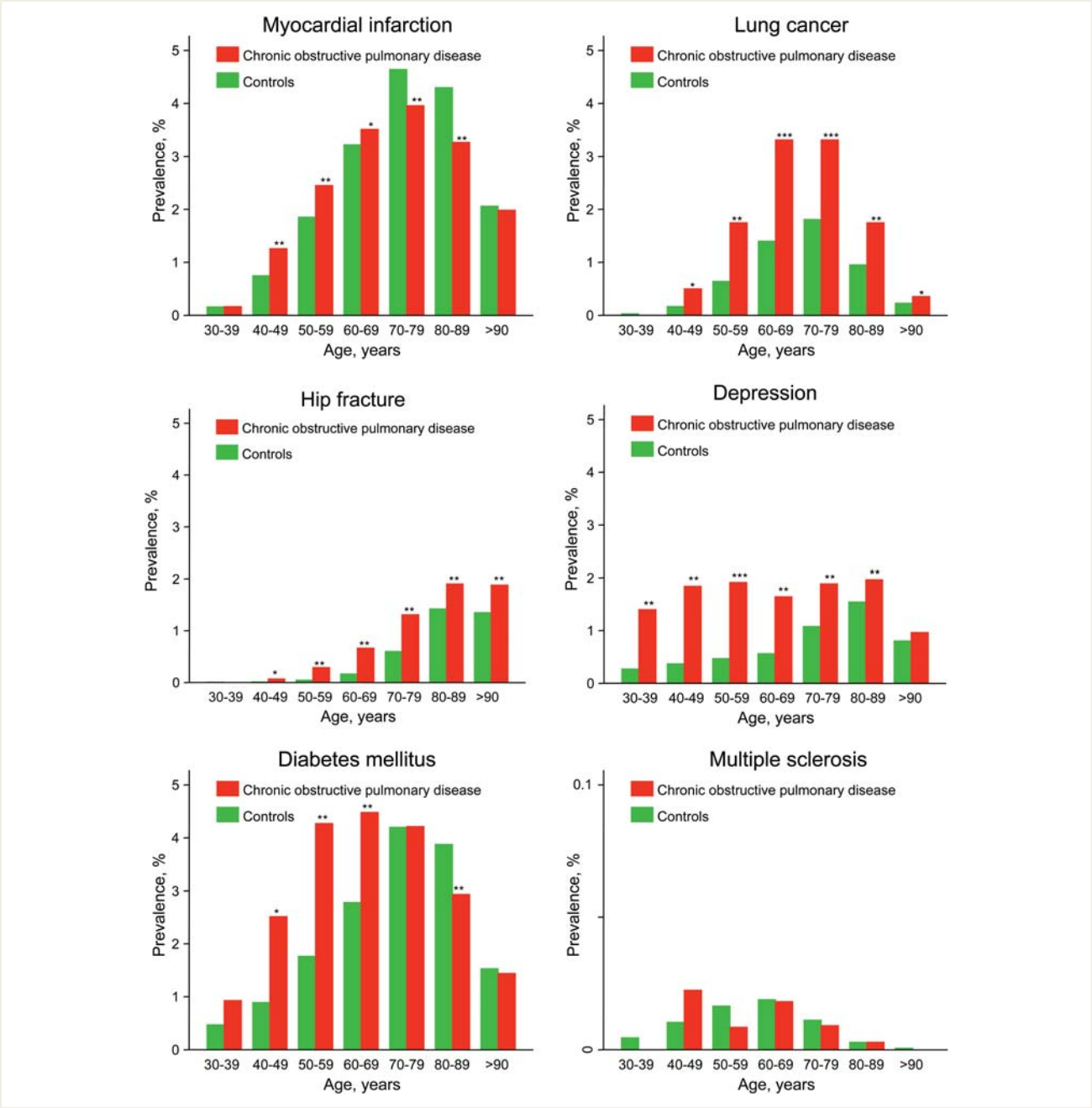

Figure 1 Prevalence of first event of myocardial infarction, lung cancer, hip fracture, depression, diabetes mellitus, and multiple sclerosis, among those with and without chronic obstructive pulmonary disease in the Danish population from 1980 through 2006. Note, that the *y*-axis for multiple sclerosis deviates. *P*-values are Chi-square tests. * $P < 0.05$, ** $P < 0.001$, *** $P < 10^{-100}$.

(0.81–0.85) for diabetes mellitus, compared with matched controls (*Table 4*). The hazard ratios from Cox regression after a chronic obstructive pulmonary disease hospitalization were similar to the corresponding logistic regression odds ratios.

Discussion

Epidemiological association is not necessarily a direct pathogenetical/pathophysiological linkage. Given this reservation for the interpretation of our data, in this nationwide cohort study we observed that ever diagnosed chronic obstructive pulmonary disease associated with life-time risk increases of one quarter for myocardial infarction, double the risk for lung cancer and hip fracture, three quarters for depression, and one fifth for diabetes. Before a chronic obstructive pulmonary disease hospitalization, all these values were also elevated; however, after a chronic obstructive pulmonary disease hospitalization, only risk of future lung cancer, hip fracture, and depression remained elevated,

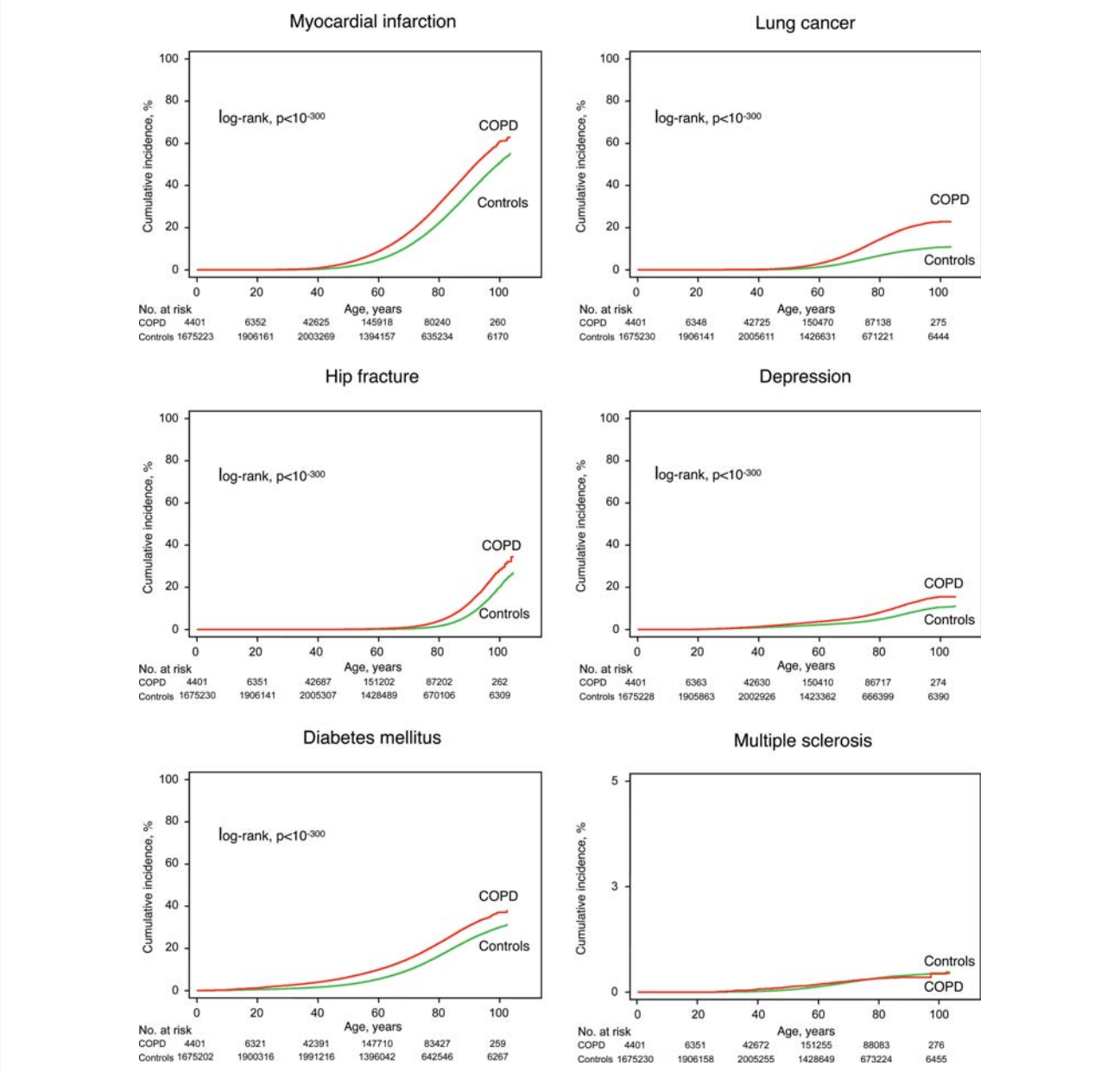

Figure 2 Lifetime cumulative incidence of first myocardial infarction and other co-morbidities among individuals with and without ever diagnosed chronic obstructive pulmonary disease. Kaplan–Meier cumulative incidence of first event of myocardial infarction, lung cancer, hip fracture, depression, diabetes mellitus, and multiple sclerosis according to ever diagnosed chronic obstructive pulmonary disease. The entire Danish population from 1980 through 2006, comprising 7 418 953 individuals, was studied. Note, that the *y*-axis for multiple sclerosis deviates.

while risk of future myocardial infarction and diabetes mellitus was reduced by one fifth. Also, risk estimates were highest among women and among those of younger age groups at study entry. These questions have never previously been addressed in a nationwide study based on individual participant data.

Mechanistically, the most reliable hypothesis to justify the linkage between chronic obstructive pulmonary disease and co-morbidities is that they share common genetic and/or lifestyle/environmental risk factors. However, there are different alternative suggestions as to the cause for association between chronic obstructive pulmonary disease and its co-morbidities, including inflammation.[1,12–15]

For myocardial infarction, the likely explanation of the life-time association with chronic obstructive pulmonary disease is common risk factors like smoking and other known lifestyle and/or environmental risk factors such as poor diet, sedentary lifestyle, and low socioeconomic class. In accordance with previous studies,[16] our results suggested that individuals with no previous myocardial infarction at the first hospitalization with chronic obstructive pulmonary disease will be less likely to develop myocardial infarction at a later stage. In contrast to our findings, other studies have found increased risk of myocardial infarction in chronic obstructive pulmonary disease patients.[16–18] Our

Table 2 Life-time association of chronic obstructive pulmonary disease with a first myocardial infarction, lung cancer, hip fracture, depression, and diabetes mellitus in the entire Danish population from 1980 through 2006

	Chronic obstructive pulmonary disease (n = 313 958)		Controls (n = 7 105 833)		Odds/hazard ratio (95% CI)	
	n	Age-standardized incidence rates per 10 000 person-years	n	Age-standardized incidence rates per 10 000 person-years	Age adjusted	Multivariate adjusted
Myocardial infarction	57 129	27.2	365 215	17.7		
Logistic regression, all					1.25 (1.24–1.26)	1.27 (1.26–1.28)
Cox regression, all					1.30 (1.29–1.31)	1.26 (1.25–1.27)
After age 30 years					1.28 (1.27–1.30)	1.25 (1.24–1.26)
After age 40 years					1.21 (1.20–1.22)	1.20 (1.19–1.21)
Lung cancer	24 408	10.3	92 221	4.5		
Logistic regression, all					2.19 (2.16–2.23)	2.31 (2.27–2.35)
Cox regression, all					2.08 (2.05–2.11)	2.05 (2.03–2.08)
After age 30 years					2.05 (2.02–2.08)	2.03 (2.00–2.06)
After age 40 years					1.91 (1.89–1.94)	1.92 (1.89–1.95)
Hip fracture	9608	3.3	44 148	1.6		
Logistic regression, all					1.59 (1.55–1.62)	1.64 (1.60–1.68)
Cox regression, all					2.11 (2.06–2.16)	2.12 (2.07–2.17)
After age 30 years					2.10 (2.05–2.15)	2.12 (2.07–2.16)
After age 40 years					2.07 (2.02–2.11)	2.08 (2.04–2.13)
Depression	11 172	7.5	81 866	4.5		
Logistic regression, all					1.54 (1.50–1.57)	1.58 (1.54–1.61)
Cox regression, all					1.73 (1.70–1.77)	1.74 (1.70–1.77)
After age 30 years					1.73 (1.69–1.77)	1.79 (1.75–1.82)
After age 40 years					1.72 (1.68–1.76)	1.76 (1.72–1.80)
Diabetes mellitus	32 577	7.5	259 651	4.5		
Logistic regression, all					1.21 (1.19–1.22)	1.21 (1.19–1.22)
Cox regression, all					1.24 (1.22–1.25)	1.21 (1.20–1.23)
After age 30 years					1.20 (1.19–1.21)	1.18 (1.17–1.20)
After age 40 years					1.14 (1.12–1.15)	1.13 (1.12–1.15)

Multivariate adjusted hazard ratios were adjusted for age, sex, descent, geographical residency, and level of education. Incidence rates were age-standardized according to the WHO standard population.

findings may be due to either selection bias, increased medical surveillance (patients admitted for chronic obstructive pulmonary disease could be more tightly controlled than otherwise), and/or change of lifestyle after hospitalization with a diagnosis of chronic obstructive pulmonary disease. Also, chronic obstructive pulmonary disease patients could have myocardial infarction before patients without chronic obstructive pulmonary disease, as supported by the present data. Importantly, smoking could explain at least partially the association between chronic obstructive pulmonary disease and myocardial infarction, and could explain the 'protection' of an admission for chronic obstructive pulmonary disease (patients could be more likely to quit smoking after an admission).

For lung cancer, the association with chronic obstructive pulmonary disease is well established.[19–22] In the present study, the 105% increased life-time risk and 66% increased risk of lung cancer after the first hospitalization with chronic obstructive pulmonary disease are in accordance with previous studies.[18] The most likely factor to cause both diseases is smoking.

For hip fracture/osteoporosis, the association with chronic obstructive pulmonary disease detected in our study agrees with that observed in several previous studies, even in milder stages of chronic obstructive pulmonary disease.[23] Our results are in concordance with these previous findings with a high prevalence of osteoporosis for all age groups. Chronic obstructive pulmonary disease patients have several risk factors for hip fracture/osteoporosis, like age, limited physical activity, low body mass index, smoking, malnutrition, and use of corticosteroids.[24,25]. Additionally, systemic corticosteroids remain the most common cause of drug related osteoporosis, while the effect of long-term use of inhaled corticosteroids remains unclear.[23,26,27]

For depression, and in concordance with the present study, anxiety and depression are frequently associated with chronic obstructive pulmonary disease, and appears to be more prevalent

in chronic obstructive pulmonary disease patients than in other chronic diseases.[28–30] As the depression diagnoses used in this study are hospitalizations with depression, the mild cases of depression are not likely to be included in our study. Due to their physical impairment, individuals with chronic obstructive pulmonary disease are frequently isolated from many social activities,[31] which could lead to depression. Depression has shown to predict fatigue, shortness of breath, and disability in individuals with chronic obstructive pulmonary disease.[29]

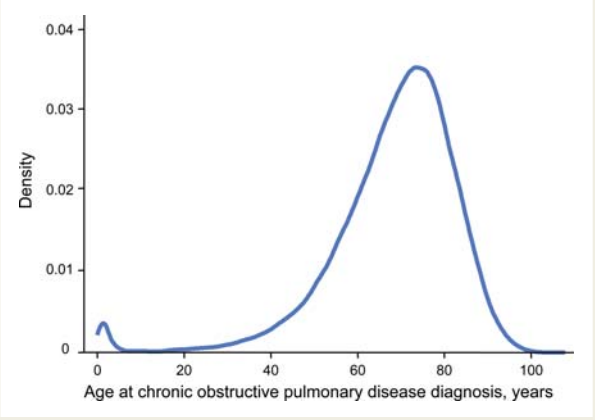

Figure 3 Age at chronic obstructive pulmonary disease diagnosis. Distribution of hospitaizations or deaths with chronic obstructive pulmonary disease as relative densities as a function of age at diagnosis in the entire Danish population from 1980 through 2006.

For diabetes mellitus like for myocardial infarction, lifestyle risk factors may play a common role in the development of both chronic obstructive pulmonary disease and diabetes mellitus.[32] Also, reduced lung function is a risk factor for development of diabetes and inflammatory mediators are elevated in both conditions.[33] Use of both inhaled and systemic steroids may influence the treatment of diabetes in chronic obstructive pulmonary disease patients, but this is not well established, conversely it is uncertain if tighter glucose control can improve chronic obstructive pulmonary disease outcome.[34] Our results suggested that individuals with no previous diabetes mellitus at first hospitalization with chronic obstructive pulmonary disease will be less likely to receive a diagnosis of diabetes mellitus at a later stage. Like for myocardial infarction after a hospitalization with chronic obstructive pulmonary disease, this may be due to either selection bias, increased medical surveillance, and/or change of lifestyle after a chronic obstructive pulmonary disease hospitalization.

Our subanalyses and stratified analyses support the validity of our results, as the risk estimates in the different statistical models only differed slightly. The sensitivity analyses restricted to individuals above 30 and 40 years, also only attenuated risk estimates slightly. Also, higher risk estimates among study entry younger age groups support the findings, as co-morbidity at

Table 3 Risk of a first myocardial infarction and other co-morbidities in the entire Danish population, stratified by baseline characteristics

	Myocardial infarction	Lung cancer	Hip fracture	Depression	Diabetes mellitus
All	1.26 (1.25–1.27)	2.05 (2.03–2.08)	2.12 (2.07–2.17)	1.74 (1.70–1.77)	1.21 (1.20–1.23)
Sex					
Male	1.17 (1.16–1.18)	1.76 (1.73–1.79)	1.97 (1.91–2.05)	1.52 (1.47–1.57)	1.21 (1.19–1.23)
Female	1.55 (1.52–1.57)	2.55 (2.49–2.61)	2.25 (2.19–2.32)	1.89 (1.84–1.94)	1.27 (1.25–1.29)
Age group, years					
30–39	2.34 (2.26–2.44)	3.91 (3.71–4.12)	5.99 (5.17–6.93)	3.17 (2.99–3.35)	2.25 (2.17–2.33)
40–49	1.75 (1.71–1.79)	2.57 (2.49–2.66)	4.62 (4.27–4.99)	2.57 (2.46–2.69)	1.68 (1.64–1.72)
50–59	1.25 (1.23–1.28)	1.79 (1.75–1.84)	2.96 (2.83–3.10)	1.83 (1.76–1.89)	1.17 (1.14–1.20)
60–69	1.05 (1.03–1.06)	1.63 (1.59–1.68)	1.86 (1.79–1.93)	1.37 (1.31–1.43)	0.98 (0.96–1.01)
70–79	1.05 (1.03–1.08)	1.79 (1.71–1.87)	1.55 (1.48–1.63)	1.09 (0.98–1.21)	0.94 (0.91–0.98)
80–89	0.95 (0.90–1.00)	1.53 (1.33–1.77)	1.38 (1.25–1.51)	0.80 (0.53–1.20)	0.96 (0.88–1.05)
Descent					
Danish	1.26 (1.25–1.27)	2.05 (2.02–2.08)	2.12 (2.07–2.17)	1.74 (1.71–1.78)	1.21 (1.20–1.23)
Other	1.47 (1.39–1.55)	2.24 (2.04–2.45)	2.10 (1.83–2.42)	1.68 (1.51–1.86)	1.29 (1.21–1.36)
Geographical residency					
Country side and towns	1.23 (1.21–1.25)	2.21 (2.16–2.27)	2.12 (2.04–2.20)	1.74 (1.68–1.80)	1.24 (1.21–1.26)
Cities, 12 000–100 000 inhabitants	1.31 (1.29–1.34)	2.08 (2.02–2.15)	2.21 (2.11–2.31)	1.79 (1.72–1.87)	1.24 (1.21–1.27)
Cities, >100 000 inhabitants	1.25 (1.23–1.27)	1.88 (1.84–1.92)	2.04 (1.97–2.11)	1.64 (1.59–1.69)	1.16 (1.14–1.18)

Values represent multivariate adjusted hazard ratios, adjusted for age, sex, descent, geographical residency, and level of education.

Table 4 Myocardial infarction, lung cancer, hip fracture, depression, and diabetes mellitus before and after a hospitalization with chronic obstructive pulmonary disease in nested case–control studies within the entire Danish population from 1980 through 2006

	Odds/hazard ratio (95% CI)	
	Age adjusted	**Multivariate adjusted**
Myocardial infarction		
Logistic regression		
Before chronic obstructive pulmonary disease	1.53 (1.50–1.56)	1.47 (1.44–1.49)
After chronic obstructive pulmonary disease	0.64 (0.63–0.65)	0.74 (0.73–0.76)
Cox regression		
After chronic obstructive pulmonary disease	0.86 (0.85–0.87)	0.83 (0.82–0.84)
Lung cancer		
Logistic regression		
Before chronic obstructive pulmonary disease	3.81 (3.65–3.98)	3.68 (3.52–3.84)
After chronic obstructive pulmonary disease	1.31 (1.29–1.34)	1.48 (1.45–1.51)
Cox regression		
After chronic obstructive pulmonary disease	1.72 (1.69–1.75)	1.66 (1.63–1.70)
Hip fracture		
Logistic regression		
Before chronic obstructive pulmonary disease	1.19 (1.16–1.21)	1.16 (1.13–1.18)
After chronic obstructive pulmonary disease	1.18 (1.15–1.21)	1.23 (1.20–1.27)
Cox regression		
After chronic obstructive pulmonary disease	1.39 (1.35–1.43)	1.40 (1.36–1.44)
Depression		
Logistic regression		
Before chronic obstructive pulmonary disease	1.85 (1.77–1.92)	1.88 (1.80–1.96)
After chronic obstructive pulmonary disease	1.18 (1.15–1.21)	1.21 (1.18–1.24)
Cox regression		
After chronic obstructive pulmonary disease	1.17 (1.14–1.21)	1.20 (1.16–1.23)
Diabetes mellitus		
Logistic regression		
Before chronic obstructive pulmonary disease	1.19 (1.16–1.21)	1.16 (1.13–1.18)
After chronic obstructive pulmonary disease	0.77 (0.76–0.79)	0.83 (0.81–0.85)
Cox regression		
After chronic obstructive pulmonary disease	0.83 (0.81–0.84)	0.81 (0.80–0.83)

Multivariate adjusted odds/hazard ratios were adjusted for age, sex, descent, geographical residency, and level of education. For these calculations, we here compared individuals with chronic obstructive pulmonary disease to year of birth, age at chronic obstructive pulmonary disease hospitalization, and sex-matched general population controls.

older age may partly confound the associations. In the stratified analyses, there was a tendency towards higher risk estimates for women for all endpoints, possibly caused by different lifestyle including smoking in Danish women and men, although this is only speculative. We used multiple sclerosis as a negative control, because this disease does not share risk factors with chronic obstructive pulmonary disease, and thus indirectly support that the positive associations observed between chronic obstructive pulmonary disease and myocardial infarction and other co-morbidities are real.

Limitations of the present study include the fact that these results are mainly for whites of Danish descent, and therefore our results may not necessarily apply to other ethnic groups or to countries with a substantial different life-style than the Danish. Another potential limitation is misclassification of diagnoses. Audits and/or other types of data-quality control are not performed periodically on nationwide registry data. Therefore, the dates for the first diagnosis of chronic obstructive pulmonary disease may be arbitrary as well as the attribution of chronic obstructive pulmonary disease as the cause for the hospitalization. This may be an important limitation of the study, in particular because both chronic obstructive pulmonary disease diagnosis and chronic obstructive pulmonary disease hospitalizations were not prospectively defined but left to the judgement of the attending physicians. Nevertheless, a review of medical records for 1581 patients with a chronic obstructive pulmonary disease

hospitalization in the national Danish Patient Registry showed a positive predictive value for chronic obstructive pulmonary disease of 92%.[35] Diagnoses of myocardial infarction[36,37] and diabetes mellitus[38] have likewise been validated in the registries. For depression, the validity of the diagnosis is highest for severe and moderate type of depression and decreases for mild depression.[39] Finally, hip fracture almost always leads to a hospitalization in Denmark. The study is also limited by the fact that we can only investigate individuals with hospitalization diagnoses for chronic obstructive pulmonary disease including outpatients, which implies that these individuals most likely suffer from a severe form of chronic obstructive pulmonary disease. Individuals with less severe chronic obstructive pulmonary disease, who are not hospitalized, are in this study a part of the control group and possibly will tend to underestimate our risk estimates. Also, individuals with chronic obstructive pulmonary disease and co-morbidities have higher hospitalization rate,[40] therefore patients in this study may have a higher fraction of co-morbidities than in individuals with less severe chronic obstructive pulmonary disease. Another limitation, due to the design of the study, is that we were unable to describe baseline treatment, and therefore we have no information as to whether admissions modify this baseline treatment. Also, we were unable to describe important baseline lifestyle risk factors like smoking, cholesterol levels, glucose levels, body mass index, low high-density lipoprotein cholesterol levels, hypertension, and so on. It is likewise a limitation that we have no information available on sequelae or severity of chronic obstructive pulmonary disease in individual patients in our national databases. An additional limitation is that we did not examine yet other potential chronic obstructive pulmonary disease comorbidities including smoking associated cancers like those in oesophagus, larynx, mouth, throat, kidney, bladder, and pancreas or yet other diseases like left ventricular heart failure, peripheral vascular disease, atrial arrhythmias, and stroke. Finally, there may be some unrecognized bias that cannot be accounted for by statistical adjustment.

In this population-based study, chronic obstructive pulmonary disease was associated with higher rates of myocardial infarction, lung cancer, hip fracture, depression, and diabetes but the strength of these associations was modified after a first admission for chronic obstructive pulmonary disease. These associations may be related to common genetic and/or lifestyle/environmental risk factors, and therefore these factors are likely to have an adverse health impact rather than chronic obstructive pulmonary disease *per se*.

Authors and contributors

Database handling and statistical analyses were by B.F.S., M.D., and B.G.N. All three authors contributed to analyses and interpretation of data. B.F.S. wrote the first draft of the paper, which was revised and finally accepted by the other authors.

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CARDIOVASCULAR FLASHLIGHT

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Danon disease presenting as severe myocardial hypertrophy

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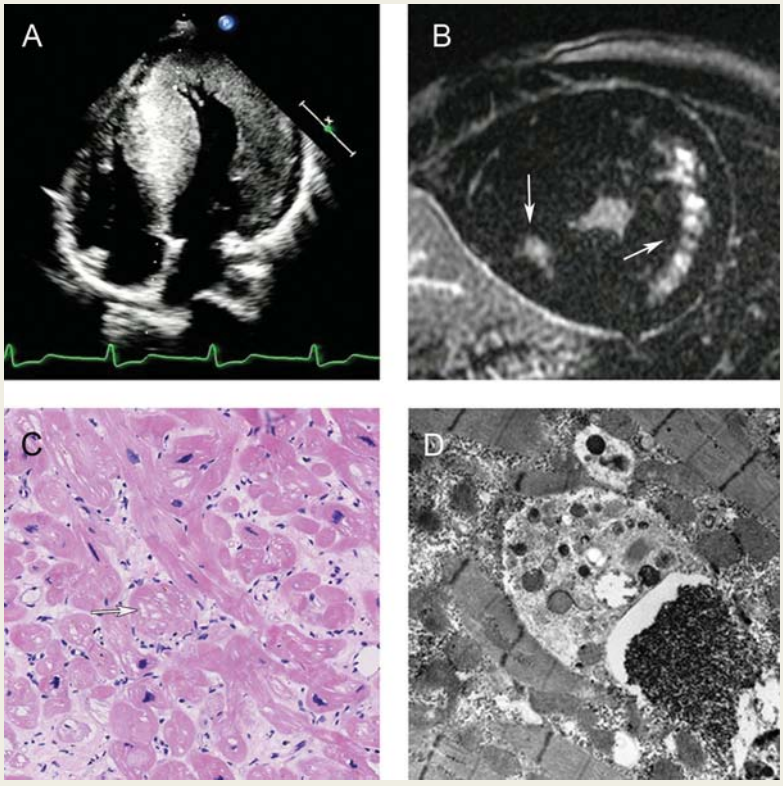
A 15-year-old boy presented with abnormal electrocardiogram on regular examination, which showed left ventricular hypertrophy and a Wolff–Parkinson–White pre-excitation pattern. Clinical examination displayed mild limb muscle weakness and atrophy and slight mental retardation. Laboratory testing revealed increased plasma creatine kinase concentration. Transthoracic echocardiography showed massive left ventricular hypertrophy (interventricular septum 25 mm and left ventricular lateral wall 24 mm) (*Panel A*). Cardiac magnetic resonance found late gadolinium enhancement in the left ventricular wall (*Panel B*, arrows). Endomyocardial biopsy was performed and light microscopy showed diffuse myocyte hypertrophy and intracytoplasmic vacuoles (*Panel C*, arrow). Electron microscopy showed sparse glycogen particles, myelin-like lamellar material, granular debrisin, and the autophagic vacuoles (*Panel D*). Genetic analysis identified a mutation in the exon 6 of lysosome-associated membrane protein-2 (LAMP2) gene.



The final diagnosis was Danon's disease, an X-linked lysosomal disease due to a primary deficiency of LAMP2. The absence of LAMP2 leads to an accumulation of autophagic vacuoles, mainly in the heart and skeletal muscle cells. The characteristics of Danon's disease include childhood onset, male predominance, hypertrophic cardiomyopathy, mild myopathy, and mental retardation. Unfortunately, there is no causal therapy for Danon's disease. As the disease progresses, the only remaining therapeutic option is cardiac transplantation.