

ONLINE ONLY SUPPLEMENTARY MATERIAL

Statin Use and Exacerbations in Individuals With

Chronic Obstructive Pulmonary Disease

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e-Table 1. Shows details of variables from the Copenhagen General Population Study (2003-2008). These variables were included either as matching variables in the case-control design, and/or as possible confounders in multivariable analyses.

MATCHING VARIABLES	OTHER POSSIBLE CONFOUNDERS
<ul style="list-style-type: none"> • AGE: in years \pm 5 years. • GENDER: man or woman. • PULMONARY FUNCTION TESTS: according to the Global initiative for Obstructive Lung Disease (GOLD) grade of airflow limitation: <ol style="list-style-type: none"> 1. GOLD 1: forced expiratory volume in one second (FEV_1) \geq 80 percent of predicted (% predicted) based on internal reference equations from asymptomatic never smokers. 2. GOLD 2: 50% predicted \leq FEV_1 < 80 % predicted. 3. GOLD 3+4: FEV_1 < 50 % predicted. • SMOKING: reported never, former or current smoker at the examination. • CARDIOVASCULAR COMORBIDITY: yes/no variable. Defined by at least one of 4 criteria: <ol style="list-style-type: none"> 1. Ischaemic heart disease: a discharge diagnosis of ischaemic heart disease: <ol style="list-style-type: none"> a) ICD-8: 410-414 b) ICS-10: I20-I25 2. Diabetes mellitus: a discharge diagnosis of diabetes mellitus: <ol style="list-style-type: none"> a) ICD-8: 249-250 b) ICD-10: E10-E11 or E13-E14. 3. Cerebrovascular disease: reported cerebrovascular disease. 4. Regular use of diuretics: reported daily or almost daily use of diuretics. 	<ul style="list-style-type: none"> • CRP: <ol style="list-style-type: none"> 1. High: CRP > 3 mg/L 2. Low: CRP \leq 3 mg/L 3. Intermediate: 1 mg/l \square CRP \leq 3 mg/L 4. Very low: CRP \leq 1 mg/L • STATIN USE: at least one physically retrieved dispensing of statins in the three months before the exacerbation date= index date in the case-control design, or in three months before measurement of CRP. • DOSE OF STATINS: calculated in the three months described above and divided into low or high dose by a cut-point of 50% of defined daily dosages. • USE OF ALL MAINTENANCE PULMONARY MEDICATIONS: Three groups: <ol style="list-style-type: none"> 1. Long-acting β_2-agonists 2. Long-acting anti-cholinergics 3. Fixed-dose combinations of inhaled corticosteroids with long-acting β_2-agonists • DOSE OF ALL MAINTENANCE PULMONARY MEDICATIONS: calculated as described for 'DOSE OF STATINS', for three groups: <ol style="list-style-type: none"> 1. Dose of long-acting β_2-agonists 2. Dose of long-acting anti-cholinergics 3. Dose of fixed-dose combinations of inhaled corticosteroids with long-acting β_2-agonists • HEALTH BEHAVIOUR: <ol style="list-style-type: none"> 1. Regular use of vitamin pills: reported daily or almost daily use of vitamin pills, or: 2. Regular visits to their general practitioner: reported number of visits to their general practitioner larger than three times per year. • SOCIOECONOMIC STATUS: <ol style="list-style-type: none"> 1. Education: length of reported school education: <8 years/8-10 years/>10 years/>10 years+university. These categories correspond to lower primary school, higher primary school and secondary school, college, and university in Denmark. 2. Household income: low/intermediate/high, defined by categories of reported household income in Danish kroner. • ALCOHOL CONSUMPTION CATEGORIES: reported alcohol consumption categories: daily/weekly or monthly/none. • FRAILTY: reporting the feeling of not having accomplished very much recently or reporting a feeling of giving up.

e-Table 2. Anatomic Therapeutic Chemical codes used to identify dispensed medications.

DISPENSED MEDICATIONS	ANATOMIC THERAPEUTICAL CHEMICAL CODES
Statins	C10
Long-acting beta ₂ -agonists	R03AC02 R03AC03 R03CC12 R03CC13
Long-acting anti-cholinergics	R03BB04
Fixed-dose combinations of inhaled corticosteroids with long-acting beta ₂ -agonists	R03AK06 R03AK07
Oral corticosteroids	H02AB6 H02AB7
Antibiotics	J01

e-Table 3. Characteristics of variables in the Copenhagen General Population Study.

VARIABLES	COPD N=5,794		Missing data - % (N) (COPD)	1:2 matched case-control study N=1,546		Missing data - % (N) (case-control study)
	Statin use N=700	No statin N=5,094		Statin use N=320	No statin N=1226	
CRP high (>3 mg/L) - % (No.)	27.3 (191)	28.7 (1464)	0 (0)	34.4 (110)	40.0 (489)	0.2 (3)
Age – mean (SD)	70.6 (8.4)	65.6 (11.8)	0 (0)	73.1 (7.5)	70.1 (9.9)	Not relevant (selection criteria)
Men - % (No.)	53.3 (373)	46.5 (2368)	0 (0)	58.4 (187)	45.2 (554)	
FEV ₁ % of predicted – mean (SD)	79.2 (19.4)	80.3 (19.4)	0 (0)	69.5 (21.2)	69.3 (21.9)	
Comorbidity ^a - % (No.)	62.6 (438)	18.2 (928)	0 (0)	66.2 (212)	30.2 (370)	
Ischaemic heart disease - % (No.)	36.9 (258)	5.9 (301)	0 (0)	42.8 (137)	12.3 (151)	
Cerebrovascular disease - % (No.)	14.4 (100)	3.7 (188)	0.3 (19)	11.6 (37)	5.2 (63)	
Diabetes mellitus - % (No.)	12.1 (85)	1.3 (68)	0 (0)	11.2 (36)	3.3 (40)	
Regular use of diuretics - % (No.)	27.1 (180)	11.3 (560)	2.9 (170)	37.1 (115)	19.6 (233)	
Current smoking - % (No.)	31.3 (213)	39.6 (1944)	3.5 (203)	32.2 (103)	43.7 (536)	
Former smoking - % (No.)	52.1 (355)	39.9 (1957)		57.8 (185)	44.7 (548)	
GP visits regularly ^b - % (No.)	55.3 (373)	29.2 (1453)	2.6 (148)	54.9 (169)	40.2 (476)	3.6 (55)
Regular use of vitamin pills ^c - % (No.)	53.3 (355)	53.0 (2628)	3.0 (173)	52.0 (158)	57.8 (690)	3.2 (49)
Maintenance medications ^d - % (No.)	5.6 (39)	5.0 (253)	0 (0)	16.9 (54)	17.4 (213)	0 (0)
Long-acting beta ₂ -agonists - % (No.)	0.9 (6)	1.1 (54)	0 (0)	3.1 (10)	2.5 (31)	0 (0)
Long-acting anti-cholinergics - % (No.)	2.0 (14)	1.9 (98)	0 (0)	7.2 (23)	7.6 (93)	0 (0)
Fixed-dose combinations - % (No.)	3.6 (25)	3.3 (170)	0 (0)	10.6 (34)	11.4 (140)	0 (0)

COPD = Chronic Obstructive Pulmonary Disease; CRP = C-reactive protein; FEV₁ = Forced Expiratory Volume in one second; GP = general practitioner. ^aComposite (yes/no) constructed from at least one of the following criteria: a discharge diagnosis of ischaemic heart disease and/or diabetes mellitus, and/or reported cerebrovascular disease, and/or reported daily or almost daily use of diuretics. ^bReports visiting their general practitioner more than three times in the year before the examination. ^cReports a daily or almost daily use of vitamin pills. ^dUse of long-acting beta₂-agonists, and/or long-acting anti-cholinergics, and/or fixed-dose combinations of inhaled corticosteroids with long-acting beta₂-agonists in the three months before the examination, or in the three months before the index date in the case-control study.