Multimorbidity medications and poor asthma prognosis

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Supplementary material

Methods

Asthma characteristics and adverse asthma events

Current asthma was defined by the self-report of asthma symptoms or the use of asthma treatment over the previous 12 months. Late-onset asthma was defined as a disease onset (*i.e.* age at first asthma attack) after 40 years of age [E1]. COPD was defined by a positive answer to "Did a doctor ever tell you that you had one of these COPD forms: chronic bronchitis, emphysema, COPD (unspecified form)?", a definition previously validated in a cohort of health professionals in the United States [E2]. The term ACO was applied to women with both self-report of asthma and COPD. Asthma treatment level was assessed from the MGEN database (reimbursement drug database) according to the GINA (Global Initiative for Asthma) 2016 classification [E3]: 1) Step 1, no asthma maintenance therapy (*i.e.* no daily use of inhaled corticosteroids (ICS) and/or leukotriene receptor antagonists (LTRA) over the 12 months that preceded the Asthma-E3N questionnaire), 2) Step 2, low mean daily dose of ICS or LTRA or xanthines alone, 3) Step 3, either a) low mean daily dose of ICS associated with long-acting $beta_2$-agonists or LTRA or theophylline or b) medium/high mean daily dose of ICS, 4) Step 4, medium/high mean daily dose of ICS associated with long-acting $beta_2$-

agonists or high mean daily dose of ICS associated with LTRA or theophylline, 5) Step 5, add-on treatment. Steps 4 and 5 were grouped as high asthma maintenance therapy, and steps 2 and 3 as low asthma maintenance therapy. Oral corticosteroids were not included in this classification because of their wide-range of indications, particularly in the elderly, as tiotropium introduced in the GINA 2016 classification as add-on therapy for asthma with a history of exacerbations.

Asthma control was assessed by the validated Asthma Control Test (ACT), a patient-based tool relying on symptom frequency, rescue therapy use, sleep interference, activity limitation, and self-rating of control over the previous month [E4]. Women were classified into uncontrolled (ACT ≤19) and controlled asthma (ACT >19). Asthma attack was defined by a positive answer to "Have you had an asthma attack over the previous 12 months?". Asthma exacerbation was defined by the report of asthma attacks lasting at least two days in the previous 12 months. From the specific Asthma Quality of Life Questionnaire (AQLQ), which covers four domains ("symptoms", "activity limitation", "emotional function", and susceptibility to "environmental exposure") assessed over the previous two weeks, the total AQLQ score was computed as the mean of all 32 questions (a lower score being associated with a lower health-related quality of life) [E5].

Latent class analysis

Latent class analysis is a data-driven approach to identify asthma groups characterised by specific multimorbidity-related medication profiles. It estimates two sets of parameters: i) the conditional probabilities, which represent the probabilities of belonging to a cluster given specific characteristics, and ii) the posterior probabilities of cluster membership for each individual (derived from the conditional probabilities), which allow accounting for the uncertainty in the cluster membership. The number of profiles was determined using the

Akaike information criterion and the Bayesian information criterion [E6]. Latent class analysis was developed with: i) the 21 drug classes *a priori* linked to asthma-related multimorbidity grouped in ten categories (*i.e.* R03 "drugs for obstructive airway diseases" for respiratory diseases; R06 "antihistamines for systemic use" for allergy; A02 "drugs for acid related disorders" for gastro-oesophageal reflux disease; R01 "nasal preparations" for nasal polyps and rhinosinusitis; N05 "psycholeptics", N06A "antidepressants", and N06C "psycholeptics and psychoanaleptics in combination" for psychological disorders; J01 "antibacterials for systemic use", J02 "antimycotics for systemic use", J04 "antimycobacterials", and J05 "antivirals" for infections; G03 "sex hormones and modulators of the genital system" for hormonal disorders; A10 "drugs used in diabetes" for diabetes; C01 "cardiac therapy", C02 "antihypertensives", C03 "diuretics", C04 "peripheral vasodilatators", C07 "beta blocking agents", C08 "calcium channel blockers", and C09 "agents acting on the renin-angiotensin system" for cardiovascular diseases; C10 "lipid modifying agents" for dyslipidaemia which is included in metabolic syndrome), ii) drug classes linked with asthma medications identified by the network graph among women with ever-asthma and iii) three clinical and environmental factors which cannot be assessed by drug classes (body mass index for obesity, sleep apnoea syndrome, and smoking status).

Multiple imputation

Multiple imputation was performed to handle missing data derived from the Asthma-E3N questionnaire. The hypothesis of missing completely at random as missing data pattern was refuted ($p<0.0001$). The rejection of this latter hypothesis and the low proportion of missing data (10.3%) in our dataset allowed us to assume that missing data followed a missing at random mechanism, and thus to use multiple imputation to handle missing data. We conducted 20 imputations for model performance as recommended for dataset with 10% to 30% of missing information [E7].

Results

Table E1. Classification of the drug classes reimbursed in 1% or more of women with ever-asthma from the Asthma-E3N study and comparison with women without asthma.

Label		Women with ever-asthma (n=4,328)		Women without asthma (n=13,130)	
		n	(%)	n	(%)
N02B	Other analgesics and antipyretics	3,126	(72.2)	8,995	(68.5)
M01A	Antiinflammatory/antirheumatic products, non steroids	2,751	(63.6)	7,957	(60.6)
R06A	Antihistamines for systemic use	2,280	(52.7)	3,805	(29.0)
A02B	Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)	2,231	(51.5)	5,475	(41.7)
J07B	Viral vaccines	2,171	(50.2)	5,485	(41.8)
R03A	Adrenergics, inhalants	2,169	(50.1)	786	(6.0)
H02A	Corticosteroids for systemic use, plain	2,071	(47.9)	4,332	(33.0)
R01A	Decongestants and other nasal preparations for topical use	1,941	(44.8)	4,128	(31.4)
J01C	Beta-lactam antibacterials, penicillins	1,743	(40.3)	4,314	(32.9)
A11C	Vitamins A and D, including combinations of the two	1,724	(39.8)	5,125	(39.0)
M02A	Topical products for joint and muscular pain	1,476	(34.1)	4,016	(30.6)
N02A	Opioids	1,459	(33.7)	3,049	(23.2)
N05B	Anxiolytics	1,400	(32.3)	3,473	(26.5)
D08A	Antiseptics and disinfectants	1,397	(32.3)	4,197	(32.0)
C10A	Cholesterol and triglyceride reducers	1,353	(31.3)	3,876	(29.5)
J01F	Macrolides, lincosamides, and streptogramins	1,261	(29.1)	2,560	(19.5)
G03C	Estrogens	1,258	(29.1)	3,613	(27.5)
A03A	Drugs for functional bowel disorders	1,250	(28.9)	3,232	(24.6)
D07A	Corticosteroids, plain	1,222	(28.2)	3,210	(24.4)
D01A	Antifungals for topical use	1,157	(26.7)	3,303	(25.2)
A12A	Calcium	1,114	(25.7)	3,220	(24.5)
A06A	Laxatives	1,109	(25.6)	3,091	(23.5)
R03B	Other drugs for obstructive airway diseases, inhalants	1,108	(25.6)	979	(7.5)
A01A	Stomatological preparations	1,033	(23.9)	2,660	(20.3)
R05D	Couch suppressants, excluding combinations with expectorants	1,007	(23.3)	2,249	(17.1)
J01D	Other beta-lactam antibacterials	969	(22.4)	2,076	(15.8)
J01M	Quinolone antibacterials	954	(22.0)	2,318	(17.7)
B01A	Antithrombotic agents	921	(21.3)	2,872	(21.9)
S01G	Decongestants and antiallergics	911	(21.0)	1,543	(11.8)
S01A	Antiinfectives	844	(19.5)	2,323	(17.7)
M03B	Muscle relaxants, centrally acting agents	835	(19.3)	2,303	(17.5)
S01X	Other ophthalmologicals	815	(18.8)	2,377	(18.1)
N05C	Hypnotics and sedatives	807	(18.6)	2,113	(16.1)
N06A	Antidepressants	803	(18.6)	2,033	(15.5)
A03F	Propulsives	790	(18.3)	2,063	(15.7)
H03A	Thyroid preparations	775	(17.9)	1972	(15.0)

M05B	Drugs affecting bone structure and mineralisation	731	(16.9)	2,149	(16.4)
S01C	Antiinflammatory agents and antiinfectives in combination	679	(15.7)	1,783	(13.6)
Z	Others	662	(15.3)	1,786	(13.6)
C09C	Angiotensin II antagonists, plain	581	(13.4)	1,464	(11.2)
D06A	Antibiotics for topical use	575	(13.3)	1,626	(12.4)
J01X	Other antibacterials	559	(12.9)	1,551	(11.8)
A07D	Antipropulsives	535	(12.4)	1,170	(8.9)
A02A	Antiacids	519	(12.0)	1,362	(10.4)
R03D	Other systemic drugs for obstructive airway diseases	511	(11.8)	176	(1.3)
V08A	X-ray contrast media, iodinated	506	(11.7)	1,427	(10.9)
D02A	Emollients and protectives	493	(11.4)	1,290	(9.8)
N01B	Anaesthetics, local	490	(11.3)	1,341	(10.2)
J07C	Bacterial and viral vaccines, combined	482	(11.1)	1,568	(11.9)
J01R	Combinations of antibacterials	470	(10.9)	1,393	(10.6)
C07A	Beta blocking agents	463	(10.7)	2,148	(16.4)
A07B	Intestinal adsorbents	456	(10.5)	1,269	(9.7)
S01B	Antiinflammatory agents	441	(10.2)	1,207	(9.2)
C09D	Angiotensin II antagonists, combinations	437	(10.1)	1,040	(7.9)
S01E	Antiglaucoma preparations and miotics	422	(9.8)	1,354	(10.3)
J07A	Bacterial vaccines	408	(9.4)	607	(4.6)
N07C	Antivertigo preparations	396	(9.1)	1,027	(7.8)
D06B	Chemotherapeutics for topical use	380	(8.8)	1,067	(8.1)
N03A	Antiepileptics	379	(8.8)	1,075	(8.2)
C05A	Agents for treatment of haemorrhoids and anal fissures for topical use	373	(8.6)	1,049	(8.0)
C08C	Selective calcium channel blockers with mainly vascular effects	370	(8.5)	991	(7.5)
G01A	Antiinfectives and antiseptics, excluding combination with corticosteroids	319	(7.4)	636	(4.8)
C01E	Other cardiac preparations	312	(7.2)	935	(7.1)
A07X	Other antidiarrhoeals	311	(7.2)	869	(6.6)
G03D	Progestogens	301	(7.0)	882	(6.7)
S01F	Mydriatics and cycloplegics	295	(6.8)	860	(6.5)
S02C	Corticosteroids and antiinfectives in combination	292	(6.7)	721	(5.5)
V08C	Magnetic resonance imaging contrast media	292	(6.7)	795	(6.1)
J05A	Direct acting antivirals	288	(6.7)	751	(5.7)
N06D	Anti-dementia drugs	272	(6.3)	739	(5.6)
G03F	Progestogens and estrogens in combination	258	(6.0)	748	(5.7)
A10B	Blood glucose lowering drugs, excluding insulins	255	(5.9)	450	(3.4)
B05B	I.V. solutions	239	(5.5)	539	(4.1)
A04A	Antiemetics and antinauseants	235	(5.4)	634	(4.8)
C09A	Angiotensin-converting enzyme (ACE) inhibitors, plain	234	(5.4)	803	(6.1)
C08D	Selective calcium channel blockers with direct cardiac effects	232	(5.4)	277	(2.1)
A12B	Potassium	205	(4.7)	452	(3.4)
B03A	Iron preparations	204	(4.7)	410	(3.1)
A03E	Antispasmodics and anticholinergics in combination with other drugs	201	(4.6)	522	(4.0)
C01B	Antiarrhythmics, class I and III	196	(4.5)	450	(3.4)
P01A	Agents against amoebiasis and other protozoal diseases	194	(4.5)	455	(3.5)
C09B	Angiotensin-converting enzyme (ACE) inhibitors, combinations	177	(4.1)	515	(3.9)

G04B	Urologicals	177	(4.1)	430	(3.3)
C03C	High-ceiling diuretics	173	(4.0)	358	(2.7)
G03X	Other sex hormones and modulators of the genital system	160	(3.7)	436	(3.3)
J02A	Antimycotics for systemic use	158	(3.7)	234	(1.8)
C03E	Diuretics and potassium-sparing agents in combination	156	(3.6)	369	(2.8)
C01D	Vasodilatators used in cardiac diseases	144	(3.3)	361	(2.7)
M04A	Antigout preparations	144	(3.3)	353	(2.7)
A07A	Intestinal antiinfectives	142	(3.3)	259	(2.0)
S01K	Surgical aids	140	(3.2)	456	(3.5)
N02C	Antimigraine preparations	138	(3.2)	459	(3.5)
R01B	Nasal decongestants for systemic use	134	(3.1)	430	(3.3)
J01A	Tetracyclines	131	(3.0)	354	(2.7)
A12C	Other mineral supplements	123	(2.8)	276	(2.1)
C03D	Potassium-sparing agents	112	(2.6)	268	(2.0)
C04A	Peripheral vasodilatators	107	(2.5)	288	(2.2)
B03B	Vitamin B12 and folic acid	100	(2.3)	298	(2.3)
L02B	Hormone antagonists and related agents	93	(2.1)	349	(2.7)
C03B	Low-ceilng diuretics, excluding thiazides	92	(2.1)	221	(1.7)
J01E	Sulfonamides and trimethoprim	91	(2.1)	253	(1.9)
C02A	Antiadrenergic agents, centrally acting	88	(2.0)	184	(1.4)
N05A	Antipsychotics	87	(2.0)	245	(1.9)
A11H	Other plain vitamin preparations	85	(2.0)	271	(2.1)
D10A	Anti-acne preparations for topical use	83	(1.9)	225	(1.7)
J01G	Aminoglycoside antibacterials	81	(1.9)	116	(0.9)
D01B	Antifungals for systemic use	77	(1.8)	240	(1.8)
D07X	Corticosteroids, other combinations	77	(1.8)	246	(1.9)
N04B	Dopaminergic agents	77	(1.8)	239	(1.8)
D05A	Antipsoriatics for topical use	68	(1.6)	203	(1.5)
R05C	Expectorants, excluding combination with cough suppressants	68	(1.6)	70	(0.5)
N06B	Psychostimulants, agents used for ADHD and nootropics	66	(1.5)	130	(1.0)
S02A	Antiinfectives	66	(1.5)	192	(1.5)
P02C	Antinematodal agents	60	(1.4)	148	(1.1)
C07B	Beta blocking agents and thiazides	55	(1.3)	281	(2.1)
V04C	Other diagnostic agents	54	(1.2)	113	(0.9)
C03A	Low-ceiling diuretics, thiazides	51	(1.2)	132	(1.0)
L04A	Immunosuppressants	46	(1.1)	120	(0.9)
C01A	Cardiac glycosides	43	(1.0)	85	(0.6)
C01C	Cardiac stimulants, excluding cardiac glycosides	42	(1.0)	8	(0.1)

Table E2. Associations between multimorbidity-related medication profiles identified by latent class analysis and asthma characteristics and adverse asthma events among women with ever-asthma from the Asthma-E3N study.

Asthma characteristics and adverse asthma events	Crude model			Model adjusted on age			Model adjusted on asthma treatment level		
	OR (*β)	[95%CI] (*±SD)	p-value	OR (*β)	[95%CI] (*±SD)	p-value	OR (*β)	[95%CI] (*±SD)	p-value
Uncontrolled asthma									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	2.02	[1.62;2.53]	<0.0001	2.01	[1.60;2.52]	<0.0001	1.51	[1.19;1.91]	0.0006
"Predominantly metabolic multimorbidity-related medications" profile	2.59	[2.04;3.29]	<0.001	2.28	[1.78;2.90]	<0.0001	2.20	[1.72;2.81]	<0.0001
Asthma exacerbations									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	1.65	[1.18;2.31]	0.004	1.64	[1.18;2.30]	0.004	1.46	[1.08;1.99]	0.01
"Predominantly metabolic multimorbidity-related medications" profile	1.36	[0.90;2.06]	0.14	1.31	[0.90;1.93]	0.16	1.26	[0.85;1.87]	0.24
Asthma attacks									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	2.23	[1.85;2.69]	<0.0001	2.23	[1.85;2.69]	<0.0001	1.94	[1.60;2.35]	<0.0001
"Predominantly metabolic multimorbidity-related medications" profile	2.03	[1.63;2.52]	<0.0001	2.05	[1.65;2.54]	<0.0001	1.87	[1.50;2.32]	<0.0001
Total asthma quality of life score*									
"Few multimorbidity-related medications" profile	6.35	±0.02	<0.0001	6.33	±0.02	<0.0001	6.29	±0.02	<0.0001
"Predominantly allergic multimorbidity-related medications" profile	5.94	±0.03	<0.0001	5.92	±0.03	<0.0001	6.01	±0.03	<0.0001
"Predominantly metabolic multimorbidity-related medications" profile	5.86	±0.03	<0.0001	5.82	±0.03	<0.0001	5.87	±0.03	<0.0001

CI, confidence interval; OR, odds radio; SD, standard deviation.

Table E3. Associations between multimorbidity-related medication profiles identified by latent class analysis and asthma characteristics and asthma adverse events among women with current asthma from the Asthma-E3N study.

Asthma characteristics and adverse asthma events	Crude model			Model adjusted on age			Model adjusted on asthma treatment level		
	OR (*β)	[95%CI] (*±SD)	p-value	OR (*β)	[95%CI] (*±SD)	p-value	OR (*β)	[95%CI] (*±SD)	p-value
Uncontrolled asthma									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	1.76	[1.39;2.24]	<0.0001	1.76	[1.38;2.25]	<0.0001	1.38	[1.07;1.77]	0.01
"Predominantly metabolic multimorbidity-related medications" profile	2.16	[1.67;2.79]	<0.0001	1.92	[1.48;2.50]	<0.0001	1.89	[1.46;2.46]	<0.0001
Asthma exacerbations									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	1.63	[1.22;2.16]	0.0009	1.62	[1.22;2.16]	0.0009	1.46	[1.11;1.94]	0.007
"Predominantly metabolic multimorbidity-related medications" profile	1.30	[0.92;1.84]	0.13	1.28	[0.92;1.78]	0.14	1.23	[0.87;1.73]	0.23
Asthma attacks									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	1.71	[1.40;2.08]	<0.0001	1.71	[1.40;2.08]	<0.0001	1.59	[1.30;1.95]	<0.0001
"Predominantly metabolic multimorbidity-related medications" profile	1.48	[1.19;1.85]	0.0005	1.51	[1.21;1.89]	0.0002	1.42	[1.14;1.78]	0.002
Total asthma quality of life score*									
"Few multimorbidity-related medications" profile	6.08	±0.03	<0.0001	6.05	±0.03	<0.0001	6.02	±0.03	<0.0001
"Predominantly allergic multimorbidity-related medications" profile	5.72	±0.03	<0.0001	5.71	±0.03	<0.0001	5.78	±0.03	<0.0001
"Predominantly metabolic multimorbidity-related medications" profile	5.66	±0.04	<0.0001	5.72	±0.04	<0.0001	5.67	±0.04	<0.0001

CI, confidence interval; OR, odds radio; SD, standard deviation.

Table E4. Associations between multimorbidity-related medication profiles identified by latent class analysis and asthma characteristics and asthma adverse events among never-smokers from the Asthma-E3N study.

Asthma characteristics and adverse asthma events	Crude model			Model adjusted on age			Model adjusted on asthma treatment level		
	OR (*β)	[95%CI] (*±SD)	p-value	OR (*β)	[95%CI] (*±SD)	p-value	OR (*β)	[95%CI] (*±SD)	p-value
Uncontrolled asthma									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	2.51	[1.86;3.37]	<0.0001	2.36	[1.75;3.18]	<0.0001	1.85	[1.34;2.54]	0.0002
"Predominantly metabolic multimorbidity-related medications" profile	1.47	[1.03;2.10]	0.03	1.27	[0.88;1.84]	0.19	1.40	[0.98;2.02]	0.06
Asthma exacerbations									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	1.51	[1.03;2.20]	0.03	1.49	[1.02;2.19]	0.04	1.39	[0.96;2.02]	0.08
"Predominantly metabolic multimorbidity-related medications" profile	1.00	[0.65;1.54]	0.98	0.99	[0.64;1.52]	0.96	0.99	[0.65;1.53]	0.98
Asthma attacks									
"Few multimorbidity-related medications" profile	1.00	-		1.00	-		1.00	-	
"Predominantly allergic multimorbidity-related medications" profile	2.43	[1.89;3.14]	<0.0001	2.44	[1.90;3.15]	<0.0001	2.13	[1.64;2.77]	<0.0001
"Predominantly metabolic multimorbidity-related medications" profile	1.24	[0.92;1.68]	0.15	1.25	[0.92;1.69]	0.14	1.22	[0.90;1.65]	0.19
Total asthma quality of life score*									
"Few multimorbidity-related medications" profile	6.34	±0.04	<0.0001	6.30	±0.04	<0.0001	6.28	±0.04	<0.0001
"Predominantly allergic multimorbidity-related medications" profile	5.75	±0.04	<0.0001	5.75	±0.04	<0.0001	5.83	±0.04	<0.0001
"Predominantly metabolic multimorbidity-related medications" profile	6.14	±0.05	<0.0001	6.18	±0.05	<0.0001	6.10	±0.05	<0.0001

CI, confidence interval; OR, odds radio; SD, standard deviation.

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Figure Legends

Figure E1. Network-based analyses in elderly women with asthma according to disease activity: **a)** network-based analysis in women with current asthma (n=1,305 women randomly selected) and **b)** network-based analysis in women with past asthma (n=1,305). Network graphs were built from all drug classes according to the third level of the ATC classification. Node diameters represent the prevalence of use of each drug class in the population. Edge thicknesses represent the strength of the association between two drug classes estimated by the ϕ coefficient. The statistical significant links between asthma drug classes and other drug classes are highlighted.

Figure E2. Multimorbidity-related medication profiles identified by latent class analysis: **a)** "Few multimorbidity-related medications" profile (n=1,885, 43.5%); **b)** "Predominantly allergic multimorbidity-related medications" profile (n=1,419, 32.8%); and **c)** "Predominantly metabolic multimorbidity-related medications" profile (n=1,024, 23.7%).