

## Supplemental Content

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**e-figure 1.** Time trend of pollutant levels and autoimmune diseases, as detected by hospitalizations and ER visits. Rome, 2006-2014

### e-Appendix:

#### Data Collection Instruments

##### Details about data registries

**Regional Pharmacy Drug Sales Registry** contains individual records for each medical prescription written by general practitioners of the National Health Service and dispensed at public or private pharmacies in the entire Lazio region (where Rome is located), complete with the date of dispensing.

**Regional Hospital Discharge Registry** contains individual records for each hospitalization occurring in public hospitals and private clinics in the entire Lazio region (where Rome is located)

complete with dates of both hospital admission and discharge, and with both primary and up to five secondary diagnoses at discharge.

***Emergency Room Visit Registry*** contains individual records for each access occurring in public hospitals and private clinics in the whole region complete with date of access and up to five health problems identified as suspected diagnoses (one principal and four secondary).

All of these registries contain the identification characteristics of each subject. However, though the information are individual in many of these sources, they are made anonymous thanks to an individual regional code that identifies (anonymously but univocally) each subject, allowing record linkages between registries and between repeated registrations in each registry, without disclosing patient identity.

***Co-payment exemption registry*** is a special register for specific diseases amenable of exemption from co-payment of monetary contribution to the National Health Service.

**e-Table 1. Autoimmune diseases and ICD-9 codes**

<b><u>DISEASE</u></b>	<b><u>CODE</u></b>
<b>Autoimmune thyroiditis</b>	<b>245.2</b>
Hashimoto's	245.2
Lymphocytic	245.2
Lynfoid	245.2
Lymphomatosis	245.2
<b>Other CNS disorders</b>	
Multiple sclerosis	340
<b>Inflammatory diseases of the skin and subcutaneous tissue</b>	
Psoriasis (excluding arthropatic)	696.1
<b>Connective tissue diseases</b>	
Systemic lupus erythematosus	710.0
<b>Inflammatory arthropathies</b>	
Rheumatoid arthritis	714.0



**e-Table 2. Sequelae and complications in the study of autoimmune diseases.**

<b>AUTOIMMUNE DISEASES WITH THEIR COMPLICATIONS</b>	<b>ICD-9<sup>TH</sup> CODES</b>
<b>Autoimmune thyroiditis</b>	
Hypothyroidism	244
Non-Hodgkins lymphoma (rarely)	200, 202
<b>Systemic lupus erythematosus</b>	
Chronic glomerulonephritis	282.8
Acute or chronic nephritis	583.8
Renal failure	584, 585
Atherosclerosis	440.9
Ischemic stroke	434.9
Cerebral hemorrhage	431
Cardio vascular diseases	410-411; 426-427; 428; 427.1, 427.41, 427.42, 427.5, 428.1, 429.5, 429.6, 429.71, 429.79, 429.81, 518.4, 780.2, 785.51, 414.10, 423.0 as primary diagnosis with 410-411 as secondary diagnosis
Myocarditis	422
Thrombocytopenia	287.5
Interstitial pneumonia	515
Interstitial lung disease	516.3
Pleurisy	511.0
Pleural effusion	511.9
Pulmonary hypertension	416
<b>Rheumatoid arthritis</b>	
Ischemic heart diseases	410-411 o (427.1, 427.41, 427.42, 427.5, 428.1, 429.5, 429.6, 429.71, 429.79, 429.81, 518.4, 780.2, 785.51, 414.10, 423.0) as primary diagnosis with 410-411 as secondary diagnosis
Pericarditis	420
Epilepsy	345
Chronic glomerulonephritis	582
Acute or chronic nephritis	583
Renal failure	594, 585
Interstitial pneumonia	515

Pulmonary fibrosis	516.3
Chronic bronchiolitis obliterans	491.8
Rheumatoid lung disease	714.81
Pulmonary hypertension	416

### **Psoriasis**

Psoriatic arthritis	696.0
Non-Hodgkins lymphoma	200.0, 202.0.
Ischemic heart diseases	410-4011 o (427.1, 427.41, 427.42, 427.5, 428.1, 429.5, 429.6, 429.71, 429.79, 429.81, 518.4, 780.2, 785.51, 414.10, 423.0) as secondary disease with 410-411 as primary disease
Hypertension	401, 405
Atrial fibrillation	427.3
Metabolic syndrome	277.7
Crohn's disease or colon regional enteritis	555.1, 555.9
Non-alcoholic fatty liver disease	571.8
Depression	311

### **Multiple sclerosis**

NONE

**e-Table 3 Specific drugs for treatment of autoimmune diseases**

<b>DISEASES specific drugs</b>	<b>WHO ATC codes</b>	<b>notes</b>
<b>AUTOIMMUNE THYROIDITIS</b>		
<i>systemic hormonal preparations</i>		
levothyroxine sodium	H03AA01	
<i>mineral supplement</i>		
selenium		not marketed in Italy
<b>SYSTEMIC LUPUS ERYTHEMATOSUS</b>		
<i>corticosteroids</i>		
for systemic use	H02	
dermatologic preparations	D07	
inhalants	R03BA	
<i>analgesics</i>		
acetylsalicylic acid	N02BA01, N02BA51	
<i>antimalarials</i>		
hydroxychloroquine	P01BA02	
<i>immunomodulating agents (immunosuppressants)</i>		
belimumab	L04AA26	authorized in Italy in 2013
azathioprine	L04AX01	OFF-LABEL
mycophenolic acid	L04AA06	OFF-LABEL
<i>(monoclonal antibodies)</i>		
rituximab	L01XC02	OFF-LABEL
<i>(antimetabolites)</i>		
methotrexate	L01BA01	OFF-LABEL
<b>RHEUMATOID ARTHRITIS</b>		
<i>analgesics</i>		
paracetamol	N02BE01	
opioids	N02A	
<i>anti-inflammatory and anti-rheumatic products</i>		
ibuprofen	M01AE01	
naproxen	M01AE02	
coxibs	M01AH	
<i>corticosteroids</i>		
for systemic use	H02	
dermatologic preparations	D07	
inhalants	R03BA	
<i>antimalarials</i>		
hydroxychloroquine	P01BA02	
<i>immunomodulating (antimetabolites)</i>		
methotrexate	L01BA01	

## PSORIASIS

### *Antipsoriatics*

for topical use D05A

for systemic use D05B

### *Corticosteroids*

for systemic use H02

dermatologic preparations D07

inhalants R03BA

### *Vitamins*

vitamin D A11CC, A11CB

### *immunomodulating agents (immunosuppressants)*

apremilast not marketed in Italy

#### **calcineurin inhibitors**

ciclosporin L04AD01

#### **(TNF- $\alpha$ ) inhibitors**

adalimumab L04AB04

etanercept L04AB01

infliximab L04AB02

#### **interleukin inhibitors**

ustekinumab L04AC05

secukinumab not marketed in Italy

#### *(antimetabolites)*

methotrexate L01BA01

## MULTIPLE SCLEROSIS

### *immunomodulating agents (immunosuppressants)*

azathioprine L04AX01

alemtuzumab L04AA34

fingolimod L04AA27 OFF-LABEL authorized in Italy in 2013

teriflunomide L04AA31 OFF-LABEL authorized in Italy in 2013

#### **interleukin inhibitors**

daclizumab not marketed in Italy

ozanimod none not marketed in Italy

#### *(monoclonal antibodies)*

rituximab L01XC02

#### *(immunostimulants)*

interferon alfa2 L03AB05

### *other nervous system drugs*

laquinimod not marketed in Italy

dimethyl fumarate N07XX09 OFF-LABEL authorized in Italy in 2011

### *corticosteroids for exacerbation*

glucocorticoids H02AB

**e-Table 4. Effects on hospitalizations and medicine prescriptions following daily increases of 10 µg/m<sup>3</sup> of PM<sub>10</sub>, PM<sub>2.5</sub> and NO<sub>2</sub>, in patients with autoimmune diseases, Rome, 2006-2014**

THYROIDITIS	PM <sub>10</sub> <sup>b</sup>		PM <sub>2.5</sub> <sup>b</sup>		NO <sub>2</sub> <sup>b</sup>	
	N <sup>a</sup>	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )
<b>Hospitalizations</b>	1,808					
Lag 0-1		-0.66 (-5.27;4.17)	0.26 (-6.47;7.48)	-0.12 (-4.65;4.63)		
Lag 0-5		0.74 (-5.08;6.91)	-1.12 (-9.51;8.04)	-0.13 (-6.03;6.13)		
<b>Medication changes<sup>d</sup></b>						
<b>Levothyroxine</b>						
Any	55,987					
Lag 0-1		<b>1.66</b> (0.9;2.44)	<b>3.31</b> (2.21;4.42)	<b>2.11</b> (1.41;2.81)		
Lag 0-5		-0.31 (-1.25;0.64)	0.18 (-1.16;1.54)	0.6 (-0.26;1.47)		
increasing dose	20,641					
Lag 0-1		<b>1.45</b> (0.12;2.8)	<b>2.84</b> (0.96;4.75)	<b>3.42</b> (2.15;4.71)		
Lag 0-5		<b>-1.91</b> (-3.53;-0.27)	-1.72 (-3.99; 0.59)	0.50 (-1.05; 2.08)		
reducing refill time	41,825					
Lag 0-1		<b>2.11</b> (1.41;2.81)	<b>2.42</b> (1.21;3.64)	<b>1.93</b> (1.13;2.74)		
Lag 0-5		0.6 (-0.26;1.47)	0.51 (-0.99;2.03)	0.34 (-0.65;1.35)		
SYSTEMIC LUPUS ERYTHEMATOSUS	PM <sub>10</sub> <sup>b</sup>		PM <sub>2.5</sub> <sup>b</sup>		NO <sub>2</sub> <sup>b</sup>	
	N <sup>a</sup>	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )	% IR <sup>c</sup> (95% CI <sup>c</sup> )
<b>Hospitalizations</b>	2,821					
Lag 0-1		-1.65 (-5;1.82)	-0.51 (-5.36;4.59)	1.98 (-1.3;5.37)		
Lag 0-5		-3.42 (-7.55;0.88)	-4.44 (-10.32;1.82)	1.78 (-2.35;6.09)		
<b>Medication changes<sup>d</sup></b>						
<b>Corticosteroids</b>						
Any	7,942					
Lag 0-1		<b>2.51</b> (0.55;4.51)	<b>3.55</b> (0.7;6.49)	<b>2.23</b> (0.39;4.1)		
Lag 0-5		0.53 (-1.91;3.03)	1.92 (-1.65;5.61)	1.3 (-1;3.65)		
increasing dose	2,699					
Lag 0-1		2.28 (-1.18;5.85)	3.32 (-1.62;8.51)	1.61 (-1.7;5.03)		
Lag 0-5		1.29 (-3.03;5.81)	4.15 (-2.16;10.87)	1.63 (-2.51;5.94)		
reducing refill time	5,628					
Lag 0-1		1.96 (-0.36;4.34)	2.49 (-0.88;5.97)	1.87 (-0.29;4.08)		
Lag 0-5		-0.38 (-3.26;2.59)	0.27 (-3.92;4.64)	0.99 (-1.72;3.76)		
administration route	1,062					
Lag 0-1		4.38 (-1.38;10.48)	<b>8.57</b> (0.06;17.81)	5.26 (-0.36;11.19)		
Lag 0-5		2.51 (-4.66;10.22)	7.66 (-2.94;19.4)	3.53 (-3.56;11.14)		
<b>Oral Corticosteroids</b>						
Any	6,279					
Lag 0-1		<b>2.41</b> (0.19;4.69)	3.1 (-0.14;6.45)	<b>2.06</b> (0;4.17)		
Lag 0-5		0.35 (-2.42;3.21)	1.54 (-2.5;5.76)	1.34 (-1.24;3.99)		
increasing dose	2,353					
Lag 0-1		1.22 (-2.47;5.05)	2.06 (-3.23;7.63)	0.66 (-3.74;5.26)		
Lag 0-5		0.93 (-3.72;5.8)	3.46 (-3.31;10.69)	0.52 (-3.5;4.71)		



**Table 4. (cont.1) Effects on hospitalizations and medicine prescriptions**

educing refill time	4,533			
Lag 0-1		2.38 (-0.24;5.07)	2.84 (-0.99;6.81)	2.22 (-0.19;4.69)
Lag 0-5		-0.52 (-3.76;2.83)	-0.13 (-4.84;4.8)	1.2 (-1.81;4.31)
<b>Hydroxicloroquine</b>				
Any	3,107			
Lag 0-1		<b>4.11</b> (0.87;7.47)	<b>8.86</b> (3.93;14.03)	<b>4.94</b> (1.89;8.08)
Lag 0-5		2.95 (-1.12;7.18)	<b>6.33</b> (0.22;12.82)	3.65 (-0.15;7.59)
increasing dose	699			
Lag 0-1		4.04 (-3.46;12.12)	7.67 (-3.37;19.97)	4.7 (-2.15;12.03)
Lag 0-5		-3.02 (-12.09;6.99)	-5.04 (-18.05;10.03)	2.63 (-6.22;12.32)
reducing refill time	2,646			
Lag 0-1		<b>4.51</b> (1.01;8.13)	<b>9.73</b> (4.38;15.35)	<b>4.93</b> (1.62;8.35)
Lag 0-5		3.78 (-0.62;8.37)	<b>7.9</b> (1.25;14.98)	3.53 (-0.57;7.8)
<b>RHEUMATOID ARTHRITIS</b>	<b>N<sup>a</sup></b>	<b>PM10<sup>b</sup></b>	<b>PM2.5<sup>b</sup></b>	<b>NO2<sup>b</sup></b>
		<b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>	<b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>	<b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>
<b>Hospitalizations</b>	5,836			
Lag 0-1		2.27 (-0.15;4.75)	1.25 (-2.19;4.81)	0.51 (-1.76;2.84)
Lag 0-5		1.2 (-1.79;4.28)	-0.27 (-4.56;4.21)	1.79 (-1.11;4.78)
<b>Medication changes<sup>d</sup></b>				
<b>Corticosteroids</b>				
Any	59,463			
Lag 0-1		<b>0.93</b> (0.18;1.68)	<b>1.57</b> (0.49;2.66)	<b>1.31</b> (0.62;2.01)
Lag 0-5		-0.72 (-1.65;0.22)	-0.81 (-2.12;0.51)	-0.08 (-0.94;0.79)
increasing dose	11,961			
Lag 0-1		<b>2.34</b> (0.65;4.07)	<b>3.86</b> (1.39;6.39)	<b>2.73</b> (1.11;4.37)
Lag 0-5		-0.05 (-2.17;2.11)	0.79 (-2.22;3.89)	0.81 (-1.2;2.87)
reducing refill time	49,270			
Lag 0-1		<b>0.83</b> (0.01;1.66)	<b>1.39</b> (0.19;2.59)	<b>1.08</b> (0.32;1.85)
Lag 0-5		-0.76 (-1.79;0.27)	-0.99 (-2.43;0.48)	-0.25 (-1.2;0.71)
administration route	6,066			
Lag 0-1		0.28 (-2.1;2.72)	1.42 (-1.98;4.94)	1.58 (-0.75;3.96)
Lag 0-5		-1.76 (-4.7;1.28)	-1.45 (-5.58;2.87)	-1.46 (-4.32;1.48)
<b>Oral Corticosteroids</b>				
Any	48,330			
Lag 0-1		<b>1.05</b> (0.22;1.89)	<b>1.75</b> (0.54;2.97)	<b>1.24</b> (0.47;2.02)
Lag 0-5		-0.76 (-1.8;0.28)	-0.92 (-2.39;0.56)	-0.16 (-1.12;0.8)
increasing dose	9,626			
Lag 0-1		<b>2.94</b> (1.01;4.9)	<b>4.93</b> (2.11;7.83)	<b>2.94</b> (1.12;4.79)
Lag 0-5		0 (-2.4;2.46)	1.47 (-1.97;5.03)	0.83 (-1.43;3.15)
reducing refill time	45,918			
Lag 0-1		<b>0.98</b> (0.12;1.84)	<b>1.59</b> (0.35;2.84)	<b>1.15</b> (0.36;1.95)
Lag 0-5		-0.74 (-1.81;0.33)	-1.01 (-2.51;0.52)	-0.28 (-1.26;0.72)

**Table 4. (cont.2) Effects on hospitalizations and medicine prescriptions**

<b>NSAIDs</b>				
Any	50,004			
Lag 0-1		<b>0.88</b> (0.07;1.7)	<b>2.29</b> (1.11;3.48)	<b>1.84</b> (1.09;2.6)
Lag 0-5		-0.67 (-1.68;0.35)	0.37 (-1.07;1.84)	0.35 (-0.59;1.29)
increasing dose	14226			
Lag 0-1		1.42 (-0.11;2.98)	<b>3.39</b> (1.14;5.69)	<b>2.04</b> (0.59;3.51)
Lag 0-5		-1 (-2.91;0.96)	0.2 (-2.56;3.03)	0.39 (-1.4;2.22)
reducing refill time	43,185			
Lag 0-1		<b>0.94</b> (0.06;1.82)	<b>2.08</b> (0.81;3.36)	<b>1.7</b> (0.89;2.52)
Lag 0-5		-0.52 (-1.62;0.58)	0.3 (-1.26;1.88)	0.26 (-0.75;1.27)
<b>PSORIASIS</b>				
	<b>N<sup>a</sup></b>	<b>PM10<sup>b</sup></b> <b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>	<b>PM2.5<sup>b</sup></b> <b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>	<b>NO2<sup>b</sup></b> <b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>
<b>Hospitalizations</b>	6,676			
Lag 0-1		-0.12 (-2.38;2.2)	-0.7 (-3.93;2.64)	-0.32 (-2.48;1.89)
Lag 0-5		-1.15 (-3.96;1.74)	-1.38 (-5.47;2.88)	0.15 (-2.61;2.99)
<b>Medication changes<sup>d</sup></b>				
<b>Corticosteroids</b>				
Any	23,732			
Lag 0-1		0.48 (-0.69;1.67)	<b>1.77</b> (0.05;3.52)	<b>1.72</b> (0.61;2.85)
Lag 0-5		-0.65 (-2.13;0.85)	0.52 (-1.58;2.67)	0.99 (-0.4;2.41)
increasing dose	1,500			
Lag 0-1		-0.32 (-5.25;4.85)	0.27 (-6.7;7.77)	2.99 (-1.99;8.22)
Lag 0-5		-0.97 (-7.3;5.8)	-1.04 (-9.74;8.5)	2.62 (-3.8;9.48)
reducing refill time	22,454			
Lag 0-1		0.71 (-0.5;1.94)	<b>2.14</b> (0.37;3.95)	<b>1.75</b> (0.6;2.91)
Lag 0-5		-0.23 (-1.75;1.32)	1.14 (-1.03;3.36)	1.12 (-0.32;2.58)
administration route	581			
Lag 0-1		-4.37 (-11.89;3.8)	-3.41 (-14.19;8.71)	3.08 (-5.06;11.92)
Lag 0-5		<b>-10.5 (-19.6;-0.3)</b>	-11.12 (-23.48;3.24)	-0.94 (-10.92;10.16)
<b>Anti-psoriasis drugs</b>				
Any	30,610			
Lag 0-1		0.93 (-0.22;2.09)	<b>1.73</b> (0.07;3.41)	<b>1.75</b> (0.68;2.83)
Lag 0-5		-0.1 (-1.53;1.35)	0.44 (-1.58;2.52)	1.01 (-0.32;2.37)
increasing dose	4,607			
Lag 0-1		-0.42 (-3.25;2.5)	-0.35 (-4.31;3.77)	1.21 (-1.47;3.97)
Lag 0-5		0.79 (-2.75;4.47)	1.25 (-3.7;6.47)	2.69 (-0.76;6.26)
reducing refill time	27,031			
Lag 0-1		0.85 (-0.38;2.09)	1.71 (-0.06;3.52)	<b>1.82</b> (0.67;2.97)
Lag 0-5		-0.31 (-1.85;1.25)	0.19 (-1.98;2.42)	0.83 (-0.6;2.28)
administration route	4,533			
Lag 0-1		2.38 (-0.24;5.07)	2.84 (-0.99;6.81)	2.22 (-0.19;4.69)

Lag 0-5                      -0.52 (-3.76;2.83)                      -0.13 (-4.84;4.8)                      1.2 (-1.81;4.31)

**Table 4. (cont.3) Effects on hospitalizations and medicine prescriptions**

<b>Biological</b>				
Any	5,171			
Lag 0-1		1.64 (-0.99;4.34)	<b>4.04</b> (0.21;8.01)	2.16 (-0.35;4.73)
Lag 0-5		1.26 (-2.03;4.67)	3.1 (-1.59;8.01)	0.66 (-2.46;3.87)
increasing dose	1,161			
Lag 0-1		4.05 (-1.7;10.13)	8.15 (-0.05;17.02)	5.37 (-0.29;11.35)
Lag 0-5		3.94 (-3.25;11.66)	10.05 (-0.59;21.84)	3.81 (-3.26;11.4)
reducing refill time	4,789			
Lag 0-1		1.27 (-1.47;4.09)	3.56 (-0.43;7.7)	1.76 (-0.85;4.44)
Lag 0-5		1.25 (-2.18;4.8)	2.74 (-2.14;7.86)	0.49 (-2.75;3.85)
<b>MULTIPLE SCLEROSIS</b>	<b>PM10<sup>b</sup></b>		<b>PM2.5<sup>b</sup></b>	<b>NO2<sup>b</sup></b>
	<b>N<sup>a</sup></b>	<b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>	<b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>	<b>% IR<sup>c</sup> (95% CI<sup>c</sup>)</b>
<b>Hospitalizations</b>	4,338			
Lag 0-1		0.2 (-2.52;3)	-0.22 (-4.19;3.92)	0.06 (-2.62;2.81)
Lag 0-5		0.26 (-3.11;3.76)	-1.07 (-6.06;4.19)	-1.2 (-4.56;2.27)
<b>Medication changes<sup>d</sup></b>				
<b>Corticosteroids</b>				
Any	4,420			
Lag 0-1		-0.47 (-3.3;2.44)	-0.65 (-4.68;3.55)	0.63 (-2.02;3.37)
Lag 0-5		-1.86 (-5.34;1.75)	-3.18 (-8.08;1.98)	-0.52 (-3.84;2.9)
increasing dose	3,745			
Lag 0-1		-1.67 (-4.81;1.57)	-1.78 (-6.19;2.84)	-2 (-4.98;1.08)
Lag 0-5		<b>-4.41</b> (-8.26;-0.41)	-4.22 (-9.6;1.48)	-1.69 (-5.45;2.21)
reducing refill time	3,339			
Lag 0-1		-2.02 (-5.27;1.34)	-2.57 (-7.17;2.25)	0.94 (-2.16;4.12)
Lag 0-5		-2.93 (-6.95;1.26)	-4.35 (-9.99;1.65)	0.09 (-3.79;4.13)
administration route	779			
Lag 0-1		6.4 (-0.94;14.29)	<b>11.08</b> (0.33;22.98)	3.13 (-3.92;10.7)
Lag 0-5		3.43 (-5.73;13.48)	7.21 (-5.7;21.89)	-1.15 (-9.69;8.19)

<sup>a</sup> N is the number of hospitalizations and prescriptions in autoimmune patients.

<sup>b</sup> PM<sub>10</sub>= particulate matter with aerodynamic diameter < 10 microns.

PM<sub>2.5</sub>= particulate matter with aerodynamic diameter 2.5 microns.

NO<sub>2</sub>= nitrogen dioxide.

<sup>c</sup> % IR=percent increase of risk; CI=confidence interval.

<sup>d</sup> Medication changes :

any = any prescription for which changes of dose or refill timing or both were observed,

increasing dose = a positive difference between the dose in a prescription and the previous same substance, for the same patient,

reducing refill time = a shorter elapsed time interval between a two consecutive refills, with respect to the preceding time interval,

administration route = changing pharmaceutical form for a faster / higher internal dose in a prescription of a substance with respect to the preceding one (from cutaneous or nasal or inhalation, to oral, to subcutaneous injection).

**e-Table 5. Effects on hospitalisations and ER visits in autoimmune patients, including incident cases (2006-2012) among exacerbations, for 10 µg/m<sup>3</sup> increase of PM<sub>10</sub>, PM<sub>2.5</sub> and NO<sub>2</sub>. Rome. 2006-2014**

	N	PM <sub>10</sub>			PM <sub>2.5</sub>			NO <sub>2</sub>		
		% IR	95%CI		% IR	95%CI		% IR	95%CI	
<b>Autoimmune thyroiditis</b>	7572									
Lag 0-1		0.64	-1.74	3.07	1.01	-2.46	4.60	1.94	-0.44	4.38
Lag 0-5		0.15	-2.90	3.29	-0.89	-5.32	3.75	2.68	-0.47	5.93
<b>SLE</b>	3686									
Lag 0-1		-0.68	-3.63	2.37	0.43	-3.85	4.90	2.46	-0.46	5.45
Lag 0-5		-2.00	-5.66	1.81	-2.72	-8.00	2.86	2.36	-1.33	6.20
<b>Rheumatoid arthritis</b>	9940									
Lag 0-1		<b>2.05</b>	0.09	4.05	1.95	-0.87	4.84	0.95	-0.89	2.82
Lag 0-5		1.46	-0.97	3.96	1.57	-2.00	5.27	1.54	-0.82	3.96
<b>Psoriasis</b>	10103									
Lag 0-1		-0.32	-2.20	1.59	-0.35	-3.05	2.43	-0.48	-2.27	1.35
Lag 0-5		-1.20	-3.55	1.20	-1.02	-4.48	2.58	-0.04	-2.35	2.32
<b>Multiple sclerosis</b>	6071									
Lag 0-1		0.55	-1.83	3.00	0.54	-2.95	4.15	-0.15	-2.46	2.22
Lag 0-5		0.30	-2.67	3.37	-0.34	-4.77	4.30	-1.02	-3.95	2.01

**e-Table 6. Effects on drug assumptions in patients with autoimmune diseases for 10 µg/m<sup>3</sup> daily increase in PM<sub>10</sub>, PM<sub>2.5</sub> and NO<sub>2</sub> levels by using individual controls. Rome, 2006-2014**

Tyrhoiditis	PM10 <sup>b</sup>			PM2.5 <sup>b</sup>			NO2 <sup>b</sup>			
	N <sup>a</sup>	% IR <sup>c</sup> (95% CI <sup>c</sup> )			% IR <sup>c</sup> (95% CI <sup>c</sup> )			% IR <sup>c</sup> (95% CI <sup>c</sup> )		
<b>Medication changes<sup>d</sup></b>										
<b>Levothyroxine</b>										
Any	71,623									
Lag 0-1		<b>1.05</b>	0.34	1.76	<b>1.95</b>	0.92	2.99	<b>1.84</b>	1.19	2.50
Lag 0-5		-1.01	-1.87	-0.13	-1.23	-2.46	0.02	0.45	-0.35	1.26
increasing dose	17,038									
Lag 0-1		<b>0.81</b>	-0.63	2.27	1.79	-0.28	3.91	<b>1.84</b>	1.19	2.50
Lag 0-5		-2.03	-3.79	-0.23	-1.76	-4.25	0.80	0.45	-0.35	1.26
reducing refill time	65,139									
Lag 0-1		<b>1.04</b>	0.29	1.78	<b>1.91</b>	0.83	3.00	<b>1.82</b>	1.14	2.50
Lag 0-5		-0.88	-1.79	0.04	-1.19	-2.48	0.12	0.46	-0.38	1.30
<b>Systemic Lupus Erythematosus</b>										
<b>Medication changes<sup>d</sup></b>										
<b>Corticosteroids</b>										
Any	9,914									
Lag 0-1		<b>1.12</b>	-0.69	2.97	<b>3.04</b>	0.43	5.72	<b>2.36</b>	0.68	4.07
Lag 0-5		-0.33	-2.56	1.96	0.97	-2.22	4.26	0.57	-1.50	2.68
increasing dose	2,471									
Lag 0-1		2.29	-1.28	5.99	4.23	-0.90	9.63	<b>3.55</b>	0.06	7.16
Lag 0-5		2.25	-2.30	7.01	5.50	-1.12	12.56	2.51	-1.83	7.04
reducing refill time	8,620									
Lag 0-1		0.93	-1.02	2.92	2.39	-0.41	5.27	<b>2.32</b>	0.51	4.16
Lag 0-5		-0.78	-3.19	1.68	-0.11	-3.51	3.40	0.32	-1.91	2.60
admin route change	533									
Lag 0-1		1.89	-5.70	10.09	8.48	-3.15	21.49	4.91	-2.62	13.02
Lag 0-5		1.27	-8.28	11.81	7.90	-6.45	24.46	3.57	-5.66	13.71
<b>Oral Corticosteroids</b>										
Any	8,993									
Lag 0-1		0.83	-1.08	2.78	2.47	-0.26	5.28	<b>2.01</b>	0.25	3.80
Lag 0-5		-0.60	-2.95	1.80	0.42	-2.91	3.86	0.21	-1.95	2.43
increasing dose	2,248									
Lag 0-1		1.77	-1.99	5.68	3.65	-1.75	9.36	2.73	-0.90	6.49
Lag 0-5		2.50	-2.30	7.54	5.66	-1.31	13.13	1.87	-2.65	6.59
reducing refill time	8,073									

	Lag 0-1	0.50	-1.52	2.57	1.86	-1.04	4.84	2.04	0.18	3.94
	Lag 0-5	-1.33	-3.81	1.22	-0.78	-4.27	2.84	-0.02	-2.31	2.33
<b>Hydrochloroquine</b>										
	Any	4,447								
	Lag 0-1	2.47	-0.30	5.32	<b>4.23</b>	0.20	8.42	1.63	-0.89	4.22
	Lag 0-5	0.29	-3.13	3.84	0.05	-4.76	5.10	-1.06	-4.15	2.14
	increasing dose	610								
	Lag 0-1	<b>10.97</b>	2.53	20.10	<b>15.39</b>	3.07	29.19	<b>7.83</b>	0.29	15.94
	Lag 0-5	2.03	-7.90	13.05	4.70	10.29	22.20	4.53	-5.04	15.07
	admin route change	4,172								
	Lag 0-1	1.69	-1.17	4.62	3.35	-0.78	7.66	1.05	-1.55	3.71
	Lag 0-5	-0.06	-3.58	3.59	-0.07	-5.01	5.12	-1.28	-4.47	2.02

Rheumatoid arthritis	PM10 <sup>b</sup>			PM2.5 <sup>b</sup>			NO2 <sup>b</sup>		
	N <sup>a</sup>	% IR <sup>c</sup> (95% CI <sup>c</sup> )		% IR <sup>c</sup> (95% CI <sup>c</sup> )		% IR <sup>c</sup> (95% CI <sup>c</sup> )			

**Medication changes<sup>d</sup>**

**Corticosteroids**

	Any	21,052								
	Lag 0-1	<b>2.76</b>	1.49	4.04	<b>4.50</b>	2.68	6.36	<b>3.17</b>	1.93	4.42
	Lag 0-5	0.12	-1.50	1.75	0.74	-1.55	3.07	1.33	-0.26	2.94
	increasing dose	4,702								
	Lag 0-1	<b>4.64</b>	1.87	7.49	<b>7.51</b>	3.54	11.63	<b>4.36</b>	1.62	7.16
	Lag 0-5	1.10	-2.38	4.70	4.00	-1.01	9.26	2.36	-1.16	5.99
	reducing refill time	18,130								
	Lag 0-1	<b>2.89</b>	1.52	4.28	<b>4.87</b>	2.89	6.88	<b>3.24</b>	1.89	4.60
	Lag 0-5	0.43	-1.32	2.21	1.26	-1.22	3.81	1.78	0.05	3.53
	admin route change	1,630								
	Lag 0-1	-0.50	-4.91	4.11	-1.45	-7.63	5.15	1.15	-3.31	5.81
	Lag 0-5	-4.63	10.16	1.25	-8.02	15.54	0.16	-5.43	10.84	0.31

**Oral Corticosteroids**

	Any	17,734								
	Lag 0-1	<b>3.19</b>	1.80	4.61	<b>5.59</b>	3.57	7.65	<b>3.56</b>	2.21	4.94
	Lag 0-5	0.32	-1.45	2.13	1.34	-1.18	3.93	1.73	-0.01	3.49
	increasing dose	4,016								
	Lag 0-1	<b>5.44</b>	2.40	8.56	<b>9.33</b>	4.93	13.92	<b>4.70</b>	1.72	7.76
	Lag 0-5	1.36	-2.44	5.31	4.91	-0.64	10.76	2.22	-1.59	6.17
	reducing refill time	16,064								
	Lag 0-1	<b>3.00</b>	1.53	4.49	<b>5.24</b>	3.13	7.40	<b>3.34</b>	1.92	4.79
	Lag 0-5	0.30	-1.56	2.21	1.09	-1.56	3.80	1.53	-0.29	3.39

**NSAIDs**

Any	21,135									
Lag 0-1		<b>2.43</b>	1.18	3.70	<b>4.43</b>	2.62	6.27	<b>2.80</b>	1.59	4.03
Lag 0-5		-0.08	-1.67	1.53	1.47	-0.80	3.80	0.83	-0.71	2.40
increasing dose	7,234									
Lag 0-1		1.24	-0.93	3.46	<b>2.04</b>	-1.05	5.23	<b>2.16</b>	0.05	4.31
Lag 0-5		0.00	-2.78	2.85	0.18	-3.79	4.31	0.53	-2.15	3.30
reducing refill time	17,148									
Lag 0-1		<b>2.98</b>	1.58	4.39	<b>5.11</b>	3.10	7.17	<b>2.96</b>	1.60	4.34
Lag 0-5		0.42	-1.35	2.23	2.06	-0.49	4.67	1.17	-0.57	2.93

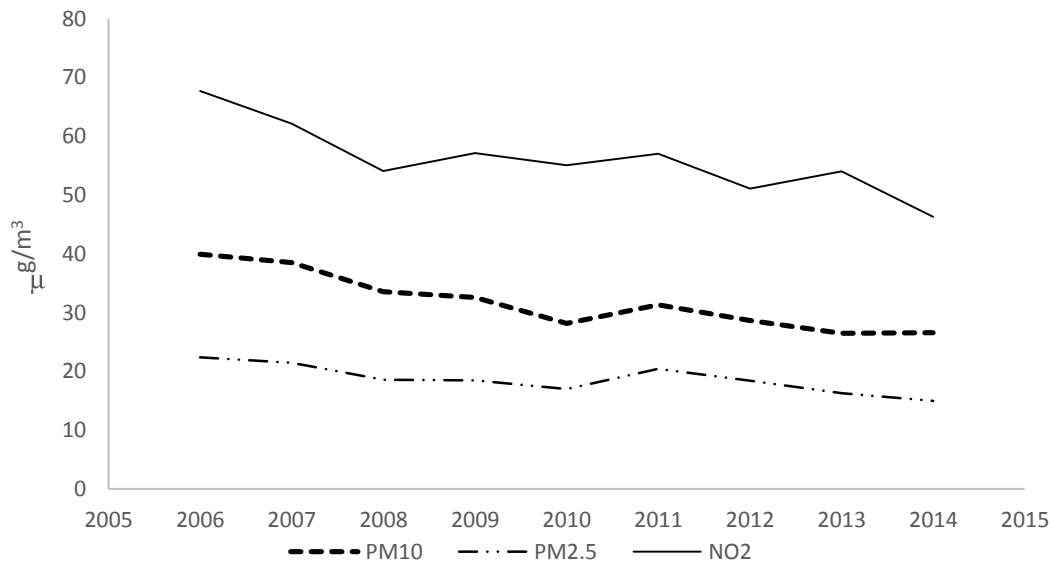
Psoriasis	N <sup>a</sup>	PM10 <sup>b</sup>			PM2.5 <sup>b</sup>			NO2 <sup>b</sup>		
		% IR <sup>c</sup>	(95% CI <sup>c</sup> )		% IR <sup>c</sup>	(95% CI <sup>c</sup> )		% IR <sup>c</sup>	(95% CI <sup>c</sup> )	
<b>Medication changes<sup>d</sup></b>										
<b>Corticosteroids</b>										
Any	30,089									
Lag 0-1		<b>1.14</b>	0.03	2.26	<b>2.20</b>	0.59	3.84	<b>2.30</b>	1.25	3.35
Lag 0-5		0.30	-1.08	1.71	0.85	-1.12	2.85	1.18	-0.12	2.49
increasing dose	4,259									
Lag 0-1		0.00	-2.69	2.77	1.00	-2.87	5.01	<b>2.88</b>	0.29	5.54
Lag 0-5		-0.55	-3.93	2.96	-0.37	-5.11	4.60	1.43	-1.82	4.79
reducing refill time	26,447									
Lag 0-1		<b>1.24</b>	0.05	2.44	<b>2.41</b>	0.68	4.16	<b>2.16</b>	1.05	3.29
Lag 0-5		0.41	-1.08	1.91	1.25	-0.86	3.41	1.18	-0.21	2.58
admin route change	2,481									
Lag 0-1		-4.37	-	3.80	-3.41	-	8.71	3.08	-5.06	11.92
Lag 0-5		<b>-10.47</b>	-	-0.27	-11.12	-	3.24	-0.94	-	10.16
<b>Anti-psoriasis drugs</b>										
Any	27,504									
Lag 0-1		0.34	-0.76	1.46	1.27	-0.32	2.88	<b>1.38</b>	0.36	2.40
Lag 0-5		-0.51	-1.88	0.88	0.16	-1.79	2.15	0.45	-0.82	1.74
<b>Biologic</b>										
Any	2,616									
Lag 0-1		2.42	-1.22	6.19	4.41	-0.73	9.83	3.39	-0.10	7.00
Lag 0-5		0.26	-4.25	4.98	2.73	-3.58	9.46	-0.53	-4.76	3.90
increasing dose	747									
Lag 0-1		6.84	-0.40	14.60	<b>11.60</b>	1.21	23.06	<b>7.31</b>	0.23	14.89
Lag 0-5		5.68	-3.37	15.58	9.94	-2.89	24.47	3.25	-5.30	12.56
reducing refill time	2,323									
Lag 0-1		1.83	-2.02	5.83	4.02	-1.39	9.73	2.91	-0.76	6.71
Lag 0-5		0.07	-4.69	5.06	2.51	-4.14	9.63	-0.65	-5.11	4.03



Multiple sclerosis		PM10 <sup>b</sup>			PM2.5 <sup>b</sup>			NO2 <sup>b</sup>		
		N <sup>a</sup>	% IR <sup>c</sup> (95% CI <sup>c</sup> )			% IR <sup>c</sup> (95% CI <sup>c</sup> )			% IR <sup>c</sup> (95% CI <sup>c</sup> )	
<b>Medication changes<sup>d</sup></b>										
<b>Corticosteroids</b>										
Any	3,445									
Lag 0-1		-1.40	-4.54	1.84	-1.33	-5.77	3.32	0.23	-2.69	3.23
Lag 0-5		<b>-4.62</b>	-8.41	-0.66	<b>-7.25</b>	-	-1.73	-2.14	-5.73	1.58
increasing dose	1,149									
Lag 0-1		-2.68	-8.11	3.08	-2.61	-	5.88	1.71	-3.76	7.48
Lag 0-5		<b>-8.09</b>	-	-1.12	<b>-10.09</b>	-	-0.15	-2.79	-9.34	4.24
reducing refill time	2,773									
Lag 0-1		-1.54	-5.04	2.10	-1.85	-6.81	3.38	-0.27	-3.51	3.09
Lag 0-5		-4.03	-8.31	0.44	<b>-6.77</b>	-	-0.48	-1.30	-5.35	2.92
admin route change	353									
Lag 0-1		1.18	-8.82	12.29	1.55	-	17.45	2.95	-6.31	13.13
Lag 0-5		-6.78	-	6.24	-6.50	-	12.25	-4.62	-	7.47

**e-Figure 1.** Time trend of pollutant levels and autoimmune diseases, as detected by hospitalizations and ER visits. Rome, 2006-2014

**Daily mean levels of air pollutants by year  
Rome, 2006-2014**



**Autoimmune patients by initial disease and by year  
Rome, 2006 - 2014**

