

SUPPLEMENTARY MATERIEL

e-Table 1: Distribution of anticholinergic drug classes by anticholinergic potency

<i>Anticholinergic drug class</i>	<i>ATC classification level</i>	<i>Number of different ATC levels</i>	<i>ACB-1</i>	<i>ACB-2/3</i>
Antihistamines	R06A	10	7	3
Opioids	N02A	4	4	0
Alimentary tract and metabolism drugs	A	4	4	0
Anxiolytic drugs	N05B	4	3	1
Antidepressant drugs	N06A	9	2	7
Cardiovascular system drugs	C	14	14	0
Antipsychotic drugs	N05A	11	4	7
Other anticholinergic drugs		15	5	10
<i>Total</i>		71	43 (61%)	28 (39%)

ACB, Anticholinergic Cognitive Burden scale; ATC, Anatomical Therapeutic Chemical classification system.

e-Table 2: Relation between cumulative exposure to anticholinergic drugs over a 3-year period and z-scores on cognitive function tests according to age groups (n=34 267)

Cumulative exposure to AC treatment		Episodic memory				Verbal fluency				Executive functions					
		Free recall		Delayed free recall		Semantic fluency		Phonemic fluency		DSST		TMT-A		TMT-B	
		Estimate (Std. Error)		Estimate (Std. Error)		Estimate (Std. Error)		Estimate (Std. Error)		Estimate (Std. Error)		Estimate (Std. Error)			
45 to 64 years (n=27010)															
No delivery	14289	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
0_3 months	8347	-0.008 (0.006)		-0.015 (0.006)	*	-0.039 (0.006)	***	-0.003 (0.006)		-0.012 (0.006)	*	0.002 (0.006)		-0.008 (0.006)	
3_12 months	2680	-0.052 (0.009)	***	-0.048 (0.009)	***	-0.059 (0.010)	***	-0.007 (0.010)		0.000 (0.009)		0.007 (0.010)		-0.015 (0.010)	
1_3 years	1282	-0.016 (0.013)		-0.032 (0.013)	*	-0.058 (0.013)	***	0.016 (0.013)		-0.037 (0.013)	**	-0.050 (0.013)	***	-0.014 (0.013)	
>3 years	412	-0.139 (0.022)	***	-0.134 (0.022)	***	-0.047 (0.023)	*	-0.059 (0.023)	**	-0.221 (0.022)	***	-0.160 (0.023)	***	-0.183 (0.023)	***
65 years and older (n=7257)															
No delivery	3806	Ref		Ref		Ref		Ref		Ref		Ref		Ref	
0_3 months	2090	0.006 (0.013)		0.024 (0.013)		0.035 (0.012)	**	0.020 (0.012)		0.001 (0.011)		0.007 (0.010)		0.014 (0.010)	
3_12 months	705	-0.048 (0.019)	*	-0.018 (0.020)		0.044 (0.018)	*	0.001 (0.018)		-0.096 (0.017)	***	-0.019 (0.015)		-0.032 (0.016)	*
1_3 years	504	0.035 (0.022)		0.009 (0.023)		0.009 (0.021)		-0.024 (0.021)		-0.073 (0.020)	***	-0.083 (0.018)	***	-0.071 (0.019)	***
>3 years	152	-0.026 (0.039)		-0.106 (0.041)	**	-0.026 (0.036)		-0.066 (0.037)		-0.126 (0.034)	***	-0.181 (0.031)	***	-0.111 (0.032)	***

Each value is the adjusted cognitive z-score difference between two groups.

AC, anticholinergic drug; DSST, Digit Symbol Substitution Test; TMT, A and B, Trail Making Test; SE, standard error

¹Lifestyle variables: living with a partner, smoking status, alcohol consumption, physical activity, body mass index

²Health status variables: self-rated health status, depressive symptoms, diabetes, respiratory diseases, cardiovascular diseases, osteoarticular disease, hypercholesterolemia, and cancer.

P value: *, 0.01 to 0.05; **, 0.001 to 0.01; ***, < 0.001

e-Table 3: Sensitivity analysis of associations linking cumulative anticholinergic drug exposure over the 3 years before cognitive testing and z-scores on cognitive tests, adjusted on lifestyle^a and health status^b variables, excluding participants with antipsychotics deliveries (n=33 949)

<i>Cumulative AC exposure</i>		<i>Episodic memory</i>		<i>Verbal fluency</i>		<i>Executive functions</i>		
		<i>Immediate free recall</i>	<i>Delayed free recall</i>	<i>Semantic fluency</i>	<i>Phonemic fluency</i>	<i>DSST</i>	<i>TMT-A</i>	<i>TMT-B</i>
		Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
<i>Adjusted on lifestyle^a and health status^b variables</i>								
<i>None</i>	18 095	Ref	Ref	Ref	Ref	Ref	Ref	Ref
<i><3 months</i>	10 390	-0.014 (0.012)	-0.016 (0.012)	-0.021 (0.012)	0.000 (0.012)	-0.002 (0.012)	-0.013 (0.012)	-0.015 (0.012)
<i>3-12 months</i>	3322	-0.057 (0.019) **	-0.047 (0.019) *	-0.037 (0.019)	-0.005 (0.019)	-0.028 (0.019)	-0.009 (0.019)	-0.026 (0.019)
<i>1-3 years</i>	1682	0.019 (0.026)	0.003 (0.026)	-0.023 (0.026)	0.017 (0.026)	-0.020 (0.026)	-0.037 (0.026)	-0.006 (0.026)
<i>>3 years</i>	460	-0.049 (0.048)	-0.050 (0.048)	0.013 (0.048)	-0.035 (0.048)	-0.104 (0.048) *	-0.097 (0.048) *	-0.089 (0.048)

Each value is the adjusted cognitive z-score difference between two groups.

AC, anticholinergic drug; DSST, Digit Symbol Substitution Test; TMT, A and B, Trail Making Test

^a Lifestyle variables: living with a partner, smoking status, alcohol consumption, physical activity, body mass index

^b Health status variables: self-rated health status, depressive symptoms, diabetes, respiratory diseases, cardiovascular diseases, osteoarticular disease, hypercholesterolemia, and cancer.

P values: 0.05 to 0.10; *, 0.01 to 0.05; **, 0.001 to 0.01; ***, < 0.001

e-Table 4: Associations linking cumulative exposure to anticholinergic drugs over a 3-year period and z-scores on cognitive function tests according to anticholinergic class¹, adjusted on lifestyle² and health status³ variables (n=30315), “analysis restricted on ACB-1 drugs”.

Cumulative AC exposure			Episodic memory		Verbal fluency		Executive functions		
			Immediate free recall	Delayed free recall	Semantic fluency	Phonemic fluency	DSST	TMT-A	TMT-B
			Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)	Estimate (SE)
Antihistamines	None	24230	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	5670	0.020 (0.007) **	0.004 (0.007)	-0.010 (0.007)	0.012 (0.007)	0.014 (0.007) *	0.024 (0.007) ***	0.031 (0.007) ***
	≥ 1 year	415	0.048 (0.022) *	0.050 (0.022) *	-0.038 (0.022)	0.022 (0.022)	0.056 (0.022) *	0.036 (0.022)	0.081 (0.022) ***
Opioids	None	26486	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	3793	-0.038 (0.008) ***	-0.041 (0.008) ***	-0.002 (0.008)	-0.010 (0.008)	-0.003 (0.008)	-0.002 (0.008)	-0.014 (0.008)
	≥ 1 year	36	-0.208 (0.074) **	-0.018 (0.074)	0.076 (0.075)	0.162 (0.075) *	-0.016 (0.074)	0.134 (0.074)	-0.003 (0.075)
Alimentary tract and metabolism drugs	None	26670	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	3594	0.017 (0.008) *	0.012 (0.008)	-0.003 (0.008)	-0.005 (0.008)	0.009 (0.008)	-0.017 (0.008) *	-0.027 (0.008) ***
	≥ 1 year	51	0.134 (0.063) *	-0.065 (0.062)	-0.115 (0.063)	-0.133 (0.063) *	-0.146 (0.062) *	-0.197 (0.063) **	-0.276 (0.063) ***
Anxiolytic drugs	None	28596	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	1643	-0.048 (0.012) ***	-0.045 (0.012) ***	-0.035 (0.012) **	0.001 (0.012)	-0.004 (0.011)	-0.017 (0.012)	-0.012 (0.012)
	≥ 1 year	76	-0.095 (0.052)	-0.157 (0.051) **	0.021 (0.052)	0.019 (0.052)	-0.103 (0.051) *	-0.098 (0.052)	-0.119 (0.052) *
Antidepressant drugs	None	29881	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	265	-0.001 (0.028)	0.022 (0.028)	0.052 (0.028)	0.107 (0.028) ***	0.069 (0.028) *	0.090 (0.028) **	0.058 (0.028) *

	≥ 1 year	169	0.068 (0.035)	-0.047 (0.035)	0.103 (0.035) **	0.070 (0.035) *	-0.087 (0.035) *	-0.141 (0.035) ***	-0.114 (0.035) **
Cardiovascular system drugs	None	29579	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	410	-0.092 (0.022) ***	0.001 (0.022)	-0.020 (0.022)	0.032 (0.022)	-0.046 (0.022) *	-0.090 (0.022) ***	-0.075 (0.022) ***
	≥ 1 year	326	0.076 (0.025) **	0.139 (0.025) ***	0.042 (0.025)	0.001 (0.025)	-0.097 (0.025) ***	-0.116 (0.025) ***	-0.043 (0.025)
Antipsychotics	None	30247	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	50	-0.249 (0.063) ***	-0.245 (0.063) ***	-0.151 (0.064) *	-0.262 (0.064) ***	-0.286 (0.063) ***	-0.018 (0.063)	-0.356 (0.064) ***
	≥ 1 year	18	-0.210 (0.105) *	-0.496 (0.105) ***	-0.700 (0.106) ***	-0.378 (0.106) ***	-0.968 (0.105) ***	-0.761 (0.105) ***	-0.627 (0.106) ***
Other AC drugs	None	28235	Ref	Ref	Ref	Ref	Ref	Ref	Ref
	<1 year	1963	-0.022 (0.011) *	-0.040 (0.011) ***	0.008 (0.011)	-0.005 (0.011)	-0.025 (0.011) *	-0.056 (0.011) ***	-0.017 (0.011)
	≥ 1 year	117	0.040 (0.041)	0.017 (0.041)	-0.055 (0.042)	0.101 (0.042) *	-0.072 (0.041)	-0.078 (0.041)	-0.045 (0.042)

Values are given as the adjusted difference between two groups in terms of cognitive z-score.

AC, anticholinergic drug; DSST, Digit Symbol Substitution Test; TMT, A and B, Trail Making Test; ATC, Anatomical Therapeutic Chemical classification system; ACB, Anticholinergic Cognitive Burden scale.

¹Drug classes of anticholinergic agents were determined based on the ATC classification level.

²Lifestyle variables: living with a partner, smoking status, alcohol consumption, physical activity, body mass index.

³Health status variables: self-rated health status, depressive symptoms, diabetes, respiratory diseases, cardiovascular diseases, osteoarticular disease, hypercholesterolemia, and cancer.

P value: *, 0.01 to 0.05; **, 0.001 to 0.01; ***, < 0.001