

Supplementary Material

This appendix is provided by the authors to give readers additional information about their study.

Figure S1 – Overview of the study design

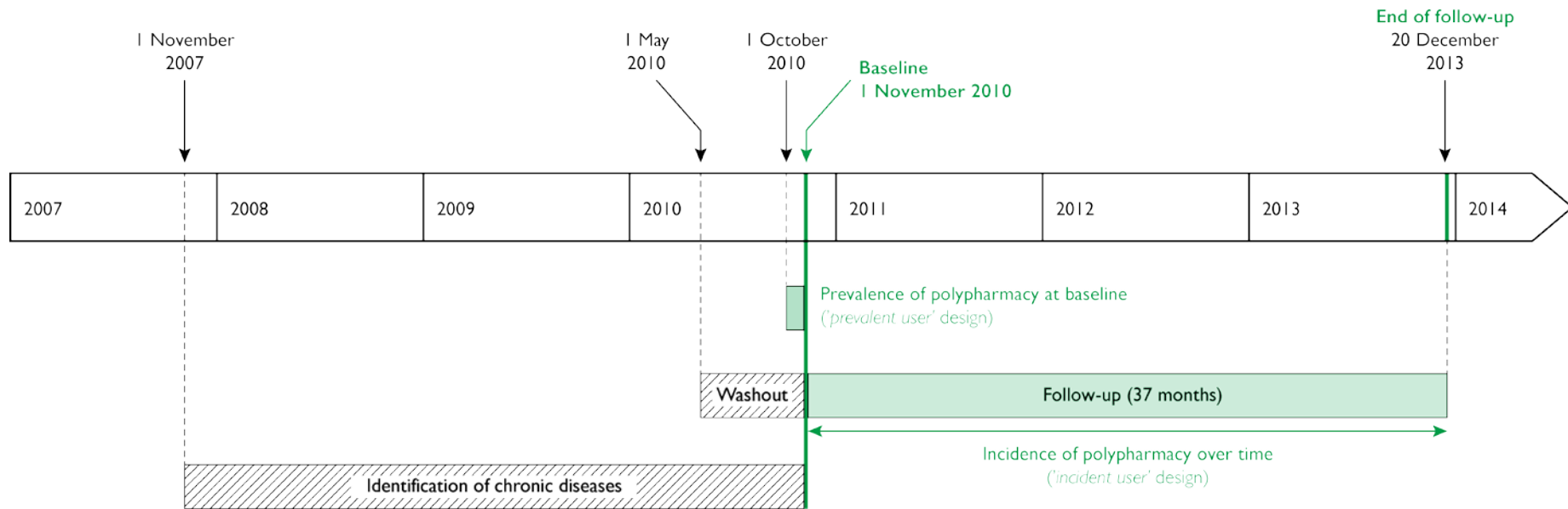
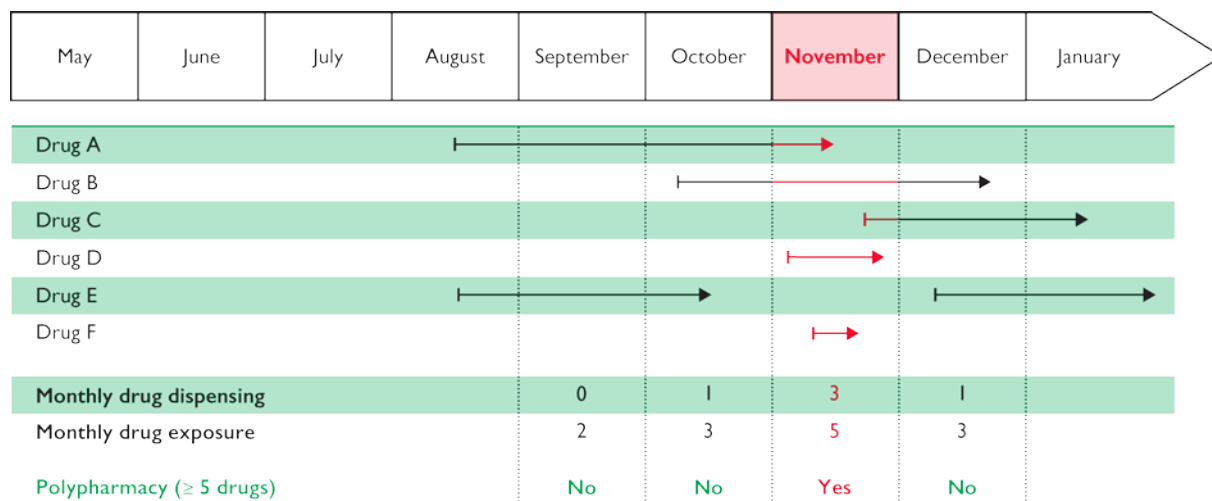


Figure S2 – Calculation of monthly drug exposure in the Swedish Prescribed Drugs Register



Tick marks represent the date of drug dispensing (“start date”), horizontal lines represent the estimated duration of drug exposure, and arrows represent the end of drug exposure (“end date”).

Table S1 – Characteristics of older adults not exposed to excessive polypharmacy (≥ 10 drugs) during the 6-month washout period before baseline

	No. (%)
Total	1 438 437
Sex	
Men	668 824 (46.5%)
Women	769 613 (53.5%)
Age, years	
Mean (SD)	74.4 (7.6)
No. (%)	
65 to 74 years	829 870 (57.7%)
75 to 84 years	430 419 (29.9%)
85 to 94 years	165 881 (11.5%)
95 years and older	12 267 (0.9%)
Living arrangement	
Community	1 390 021 (96.6%)
Nursing home	48 416 (3.4%)
Number of chronic diseases	
Mean (SD)	1.8 (1.8)
No. (%)	
0	428 925 (29.8%)
1	356 518 (24.8%)
2	252 591 (17.6%)
3	166 091 (11.5%)
4	104 135 (7.2%)
≥ 5	130 177 (9%)
Drug dispensing scheme	
Ordinary prescriptions	1 366 289 (95%)
Multi-dose dispensing	72 148 (5.0%)
Time to death	
>12 months	1 395 667 (97.0%)
≤ 12 months	42 770 (3.0%)
Level of education^a	
Primary education	509 698 (35.4%)
Lower secondary education	97 280 (6.8%)
Upper secondary education	516 418 (35.9%)
Higher education	284 269 (19.8%)

^a Missing values for the level of education: $n=30,772$

Table S2 – Proportion of older adults exposed to polypharmacy according to various cut-off points

	≥2 drugs	≥3 drugs	≥4 drugs	≥5 drugs	≥6 drugs	≥7 drugs	≥8 drugs	≥9 drugs	≥10 drugs
Total cohort	74.0%	63.9%	53.8%	44.0%	35.1%	27.4%	21.0%	15.8%	11.7%
Sex									
Men	70.5%	60.3%	50.2%	40.4%	31.6%	24.1%	18.1%	13.3%	9.6%
Women	76.9%	66.8%	56.7%	47.0%	38.0%	30.1%	23.4%	17.9%	13.4%
Age, years									
65 to 74 years	65.2%	53.3%	42.4%	32.8%	24.9%	18.5%	13.7%	10.0%	7.3%
75 to 84 years	81.8%	73.1%	63.2%	53.0%	43.1%	34.0%	26.3%	19.9%	14.8%
85 to 94 years	89.2%	82.8%	74.8%	65.5%	55.5%	45.5%	36.3%	28.2%	21.2%
95 years and older	89.1%	83.3%	76.0%	67.0%	57.1%	46.8%	37.1%	28.3%	20.9%
Level of education									
Primary education	78.7%	69.8%	60.1%	50.3%	40.9%	32.4%	25.1%	19.1%	14.2%
Lower secondary education	73.7%	63.4%	53.1%	43.3%	34.5%	26.9%	20.7%	15.6%	11.5%
Upper secondary education	73.1%	62.6%	52.1%	42.3%	33.4%	25.9%	19.7%	14.8%	10.9%
Higher education	68.1%	56.2%	45.3%	35.6%	27.4%	20.7%	15.3%	11.3%	8.2%
Living arrangement									
Community	72.8%	62.3%	51.9%	42.0%	33.0%	25.4%	19.1%	14.2%	10.4%
Nursing home	95.3%	92.5%	88.0%	81.7%	73.8%	64.6%	54.7%	44.8%	35.5%
Number of chronic diseases									
0	39.7%	26.7%	16.7%	9.7%	5.3%	2.8%	1.5%	0.8%	0.4%
1	69.6%	54.7%	40.7%	28.6%	18.9%	11.9%	7.2%	4.2%	2.4%
2	83.3%	71.6%	58.5%	45.4%	33.4%	23.4%	15.7%	10.2%	6.4%
3	91.0%	82.9%	72.3%	59.9%	47.2%	35.4%	25.5%	17.7%	11.8%
4	94.9%	89.6%	81.8%	71.5%	59.6%	47.5%	36.2%	26.6%	18.8%
≥5	98.1%	96.1%	92.6%	87.2%	79.8%	70.8%	60.9%	50.9%	41.2%
Drug dispensing scheme									
Ordinary prescriptions	71.7%	60.8%	50.1%	40.0%	31.0%	23.4%	17.3%	12.7%	9.1%
Multi-dose dispensing	98.9%	97.1%	93.7%	88.0%	80.3%	71.0%	60.6%	50.2%	40.2%
Time to death									
>12 months	73.2%	62.8%	52.4%	42.6%	33.6%	26.0%	19.6%	14.6%	10.7%
≤12 months	92.1%	88.0%	82.5%	75.6%	67.5%	59.0%	50.1%	41.7%	33.6%

Table S3 – Prevalence of and factors associated with excessive polypharmacy at baseline

	Cohort	Excessive polypharmacy (≥ 10 medications)	
	No. individuals	Prevalence (%)	Adj. OR (95% CI) ^a
Total cohort	1 742 336	203 698 (11.7%)	–
Sex			
Men	782 503	75 394 (9.6%)	1
Women	959 833	128 304 (13.4%)	1.45 (1.44–1.47)
Age, years			
65 to 74 years	936 163	68 222 (7.3%)	1
75 to 84 years	551 710	81 628 (14.8%)	1.11 (1.10–1.12)
85 to 94 years	237 086	50 220 (21.2%)	1.03 (1.01–1.04)
95 years and older	17 377	3628 (20.9%)	0.84 (0.80–0.88)
Living arrangement			
Community	1 652 329	171 739 (10.4%)	1
Nursing home	90 007	31 959 (35.5%)	1.07 (1.05–1.09)
Number of chronic diseases			
0	432 537	1737 (0.4%)	1
1	373 378	8938 (2.4%)	5.48 (5.20–5.77)
2	284 124	18 117 (6.4%)	14.31 (13.61–15.05)
3	206 689	24 470 (11.8%)	27.16 (25.84–28.55)
4	148 141	27 806 (18.8%)	45.38 (43.18–47.70)
≥ 5	297 467	122 630 (41.2%)	130.2 (124.02–136.65)
Drug dispensing scheme			
Ordinary prescriptions	1 595 776	144 852 (9.1%)	1
Multi-dose dispensing	146 560	58 846 (40.2%)	2.85 (2.80–2.90)
Time to death			
>12 months	1 665 908	177 999 (10.7%)	1
≤ 12 months	76 428	25 699 (33.6%)	1.50 (1.47–1.53)
Level of education			
Primary education	641 947	91 092 (14.2%)	1
Lower secondary education	117 615	13 520 (11.5%)	0.94 (0.92–0.96)
Upper secondary education	618 285	67 544 (10.9%)	0.93 (0.93–0.95)
Higher education	326 724	26 839 (8.2%)	0.80 (0.79–0.82)

^a Logistic regression model including all presented covariates as independent variables. Because of missing values for the level of education (n=37 765), adjusted odds ratios (OR) and 95% confidence intervals (CI) are calculated for a subset of 1 704 571 individuals (97.8% of total)

Figure S3 – Age-specific prevalence of polypharmacy (≥ 5 drugs) at baseline, by living arrangement and drug dispensing

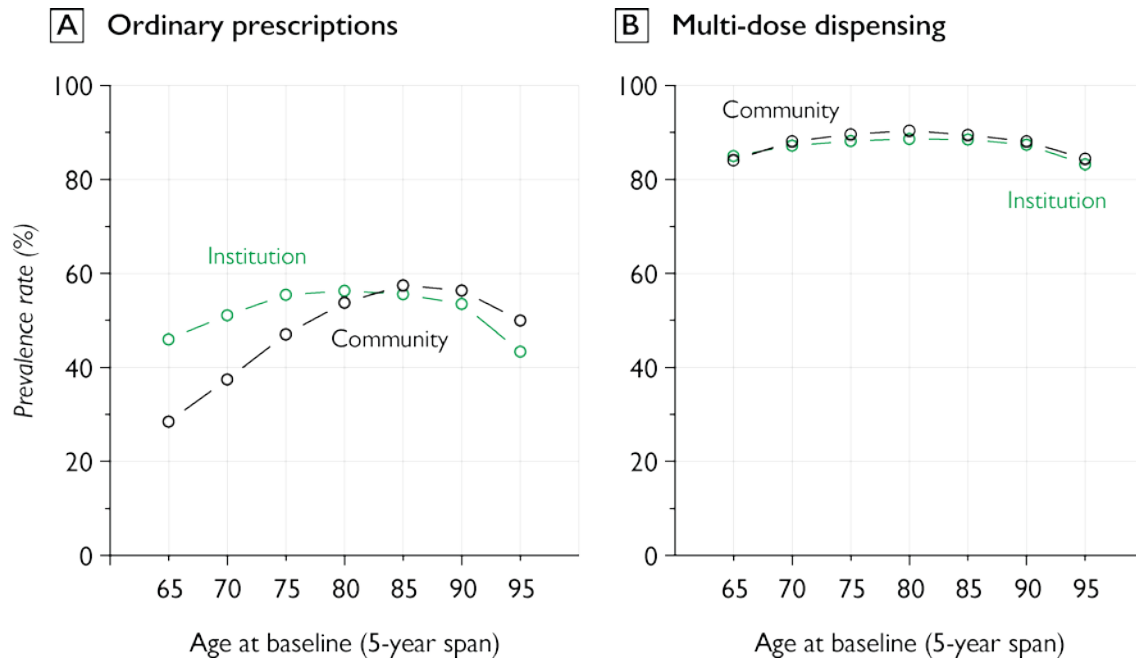


Figure S4 – Age-specific prevalence of excessive polypharmacy (≥ 10 drugs) at baseline, by living arrangement and drug dispensing

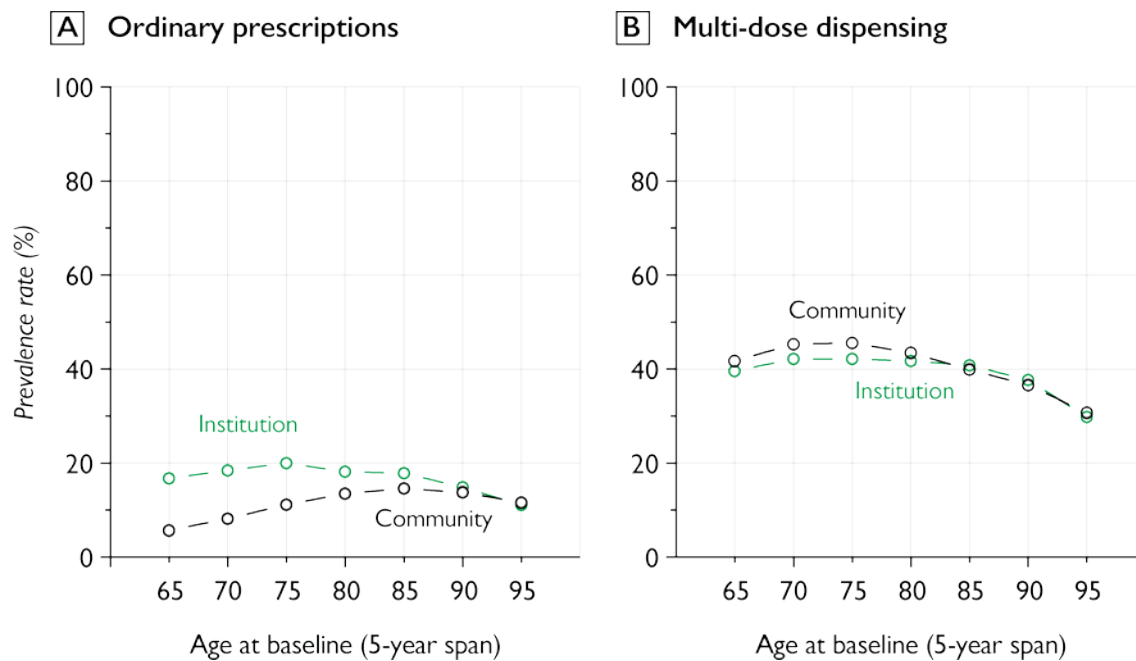


Table S4 – Sensitivity analysis: prevalence of polypharmacy and excessive polypharmacy after removing antiinfectives (ATC code J)

	Mean number of prescription drugs	Prevalence rate (%)	
	Mean (SD)	≥5 drugs	≥10 drugs
Total cohort	4.5 (3.9)	43.4	11.2
Sex			
Men	4.1 (3.7)	39.8	9.2
Women	4.8 (3.9)	46.3	12.8
Age, years			
65 to 74 years	3.6 (3.6)	32.2	6.9
75 to 84 years	5.3 (3.9)	52.4	14.2
85 to 94 years	6.3 (4.0)	65.0	20.4
95 years and older	6.3 (3.8)	66.3	19.9
Living arrangement			
Community	4.3 (3.8)	41.3	9.9
Nursing home	8.1 (4.1)	81.2	34.4
Number of chronic diseases			
0	1.6 (2.0)	9.4	0.4
1	3.2 (2.6)	27.9	2.2
2	4.4 (3.0)	44.5	6.0
3	5.5 (3.2)	59.0	11.2
4	6.5 (3.4)	70.7	17.8
≥5	8.8 (4.1)	86.7	39.8
Drug dispensing scheme			
Ordinary prescriptions	4.1 (3.6)	39.3	8.6
Multi-dose dispensing	8.8 (3.9)	87.7	39.0
Time to death			
>12 months	4.4 (3.8)	41.9	10.2
≤12 months	7.7 (4.5)	74.9	32.3
Level of education			
Primary education	5.0 (4.0)	49.8	13.6
Lower secondary education	4.5 (3.9)	42.6	11.0
Upper secondary education	4.4 (3.8)	41.6	10.4
Higher education	3.8 (3.6)	34.9	7.8

Figure S5 – Sensitivity analysis: prevalence of polypharmacy according to the number of therapeutic subgroups and to the number of chemical substances

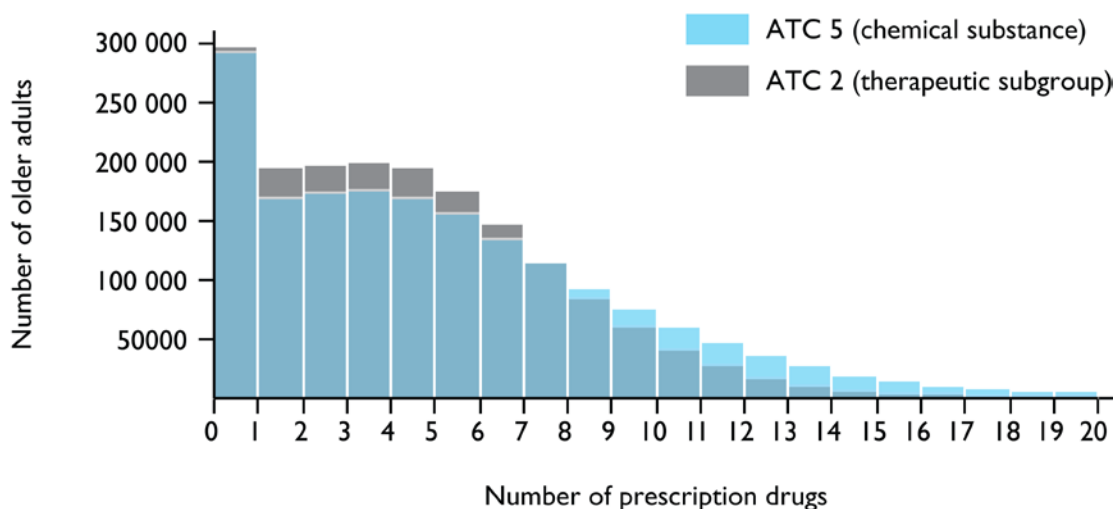
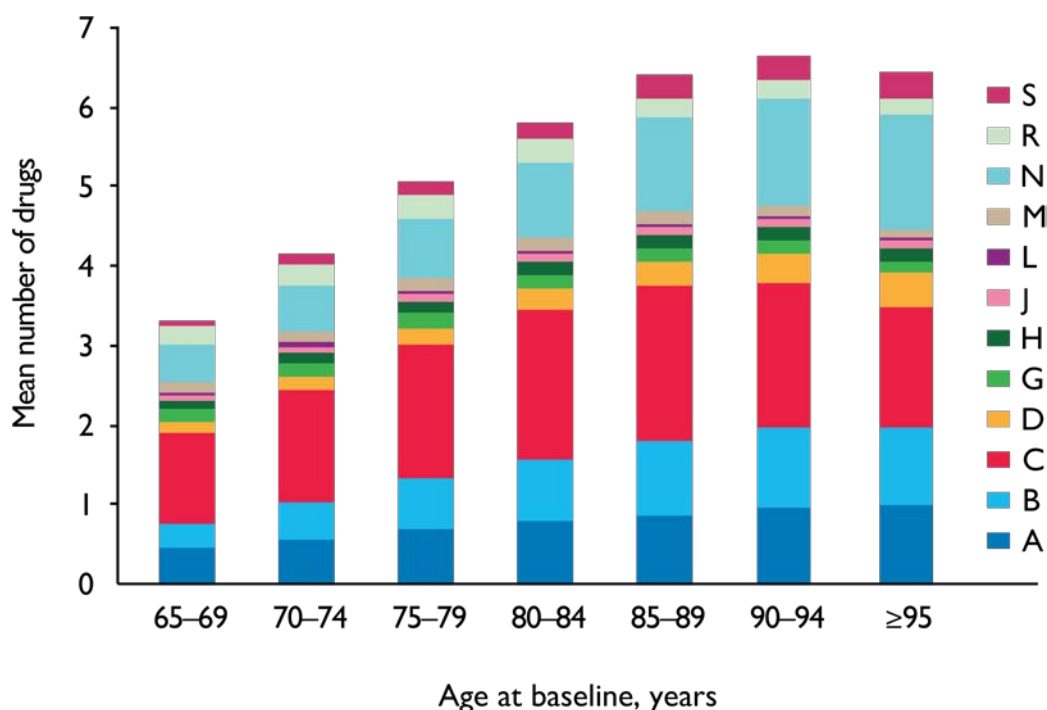


Figure S6 – Mean number of drugs at from different therapeutic groups baseline, by age



Note figure S8: Therapeutic groups are presented according to the ATC classification system. Please consult <https://www.whocc.no/> for additional information about ATC.

Table S5 – Incidence of excessive polypharmacy (≥ 10 medications) during follow-up

	Person-years ^a	Failures ^b	Incidence rate	Hazard ratio	
				Model 1 ^c	Model 2 ^d
	No.	No.	Per 100 p-year	HR (95% CI)	HR (95% CI)
Total cohort	3 808 624	306 196	8.0 (8.0–8.1)	–	–
Sex					
Men	1 788 817	132 548	7.4 (7.4–7.4)	1	1
Women	2 019 807	173 648	8.6 (8.6–8.6)	1.13 (1.12–1.14)	1.13 (1.12 - 1.14)
Age, years					
65 to 74 years	2 346 735	130 552	5.6 (5.5–5.6)	1	1
75 to 84 years	1 089 584	117 402	10.8 (10.7–10.8)	1.48 (1.47–1.49)	1.40 (1.39 - 1.41)
85 to 94 years	352 221	55 030	15.6 (15.5–15.8)	1.87 (1.85–1.89)	1.60 (1.58 - 1.62)
95 years and older	20 085	3212	16.0 (15.4–16.6)	1.99 (1.92–2.06)	1.46 (1.4 - 1.51)
Living arrangement					
Community	3 732 275	290 253	7.8 (7.7–7.8)	1	1
Nursing home	76 349	15 943	20.9 (20.6–21.2)	1.22 (1.20–1.24)	0.86 (0.84 - 0.87)
Number of chronic diseases					
0	1 277 303	29 600	2.3 (2.3–2.3)	1	1
1	996 253	55 967	5.6 (5.6–5.7)	2.28 (2.25–2.31)	2.28 (2.24 - 2.31)
2	657 241	60 913	9.3 (9.2–9.3)	3.6 (3.55–3.65)	3.59 (3.54 - 3.64)
3	400 398	53 204	13.3 (13.2–13.4)	5.02 (4.94–5.09)	4.97 (4.9 - 5.04)
4	231 880	40 816	17.6 (17.4–17.8)	6.45 (6.36–6.55)	6.34 (6.24 - 6.44)
≥ 5	245 550	65 696	26.8 (26.6–27)	9.41 (9.28–9.54)	9.05 (8.92 - 9.18)
Drug dispensing scheme					
Ordinary prescriptions	3 689 811	276 592	7.5 (7.5–7.5)		1
Multi-dose dispensing	118 814	29 604	24.9 (24.6–25.2)		1.58 (1.56 - 1.61)
Time to death					
>12 months	3 789 561	296 196	7.8 (7.8–7.8)		1
≤ 12 months	19 063	10 000	52.5 (51.4–53.5)		2.94 (2.88 - 3.01)
Level of education					
Primary education	1 294 958	124 953	9.6 (9.6–9.7)		1
Lower secondary education	259 263	20 292	7.8 (7.7–7.9)		0.94 (0.92 - 0.95)
Upper secondary education	1 387 419	105 704	7.6 (7.6–7.7)		0.93 (0.92 - 0.93)
Higher education	788 771	48 918	6.2 (6.1–6.3)		0.81 (0.80 - 0.82)

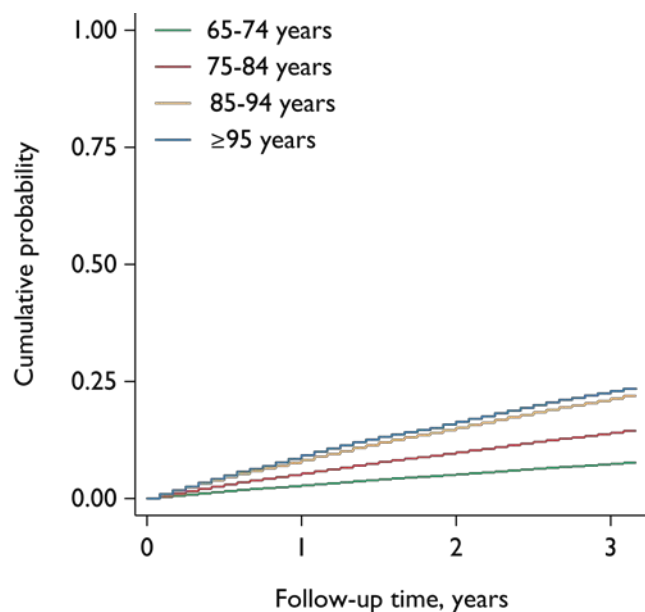
^a Contributing time (in years) of older adults free of excessive polypharmacy at baseline (n=1 438 437)

^b First period of exposure to polypharmacy ('single-failure' incident cases)

^c Cox proportional hazard regression model including sex, age and number of chronic diseases as independent variables.

^d Cox proportional hazard regression model including all covariates presented in the table. Because of missing values for the level of education (n=30 772; 2.1%), results from Model 2 are based on a subset of 1 407 665 (97.9%) individuals.

Figure S7 – Cumulative incidence of excessive polypharmacy (≥ 10 drugs) during follow-up



*Kaplan-Meier failure function adjusted for sex, living arrangement, number of chronic diseases at baseline, drug dispensing scheme, level of education and time to death ($n=1\ 407\ 665$)

Table S6 – Incidence rate of polypharmacy (≥ 5 drugs) according to the number of prescription drugs at baseline

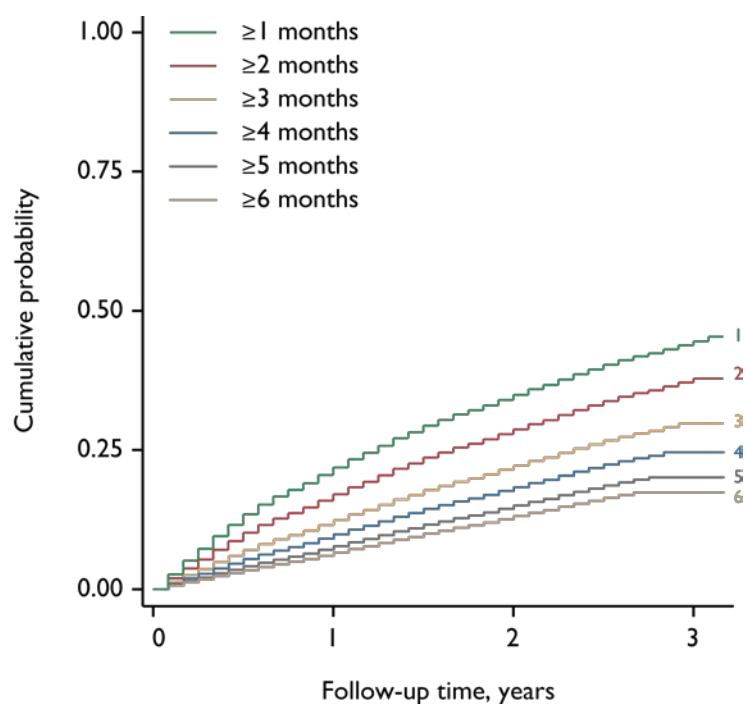
Number of drugs at baseline	Person-years	Failures	Incidence rate ^a
	No.	No.	Per 100 person-year
0 drug	776415	57830	7.4 (7.3–7.5)
1 drug	401874	58741	14.6 (14.5–14.7)
2 drugs	333155	83234	25.0 (24.8–25.2)
3 drugs	220498	93869	42.6 (42.3–42.8)
4 drugs	91619	70030	76.4 (75.9–77.0)

^a Adjusted for age, sex, living arrangement, number of chronic diseases at baseline, drug dispensing scheme, level of education and time to death.

Table S7 – Incidence rate of polypharmacy (≥ 5 drugs) according to the duration of the first polypharmacy episode

Duration of polypharmacy	Person-years ^a	Failures ^b	Incidence rate
	No.	No.	Per 100 person-year
≥ 1 month	1 823 560	363 704	19.9 (19.8–20.0)
≥ 2 months	1 947 738	302 959	15.6 (15.5–15.7)
≥ 3 months	2 071 804	237 707	11.5 (11.4–11.6)
≥ 4 months	2 143 822	195 892	9.1 (9.0–9.2)
≥ 5 months	2 205 124	159 972	7.3 (7.2–7.4)
≥ 6 months	2 240 148	138 243	6.2 (6.1–6.3)

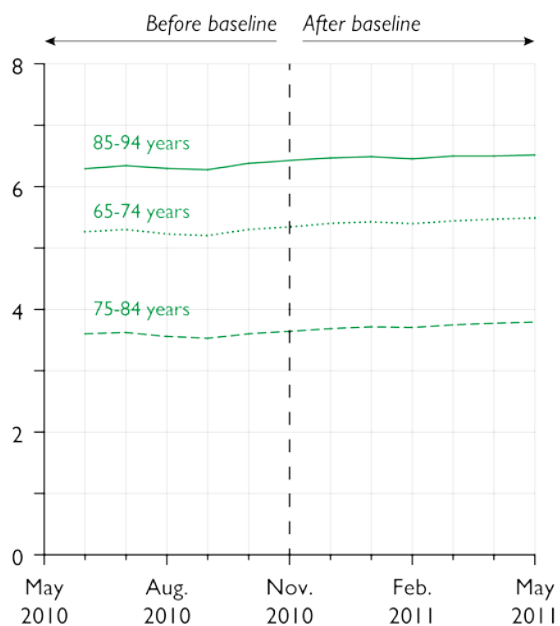
Figure S8 – Incidence rate of polypharmacy (≥ 5 drugs) according to the duration of the first polypharmacy episode



* Curves represent the unadjusted Kaplan-Meier failure functions

Figure S9 – Variation in the number of prescribed drugs during the 6 months before and 6 months after baseline

A Mean number of prescribed drugs



B Prevalence rate of polypharmacy (≥ 5 drugs)

