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This is the peer reviewed version of the following article:

Wastesson, Jonas W; Morin, Lucas; Laroche, Marie-Laure; Johnell, Kristina. "How Chronic Is Polypharmacy in Old Age? A Longitudinal Nationwide Cohort Study". *J Am Geriatr Soc.* 2019 67(3):455–462.

which has been published in final form at

<http://dx.doi.org/10.1111/jgs.15717>

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How chronic is polypharmacy in old age? A longitudinal nationwide cohort study

Running title: The chronicity of polypharmacy

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Impact statement:

We certify that this novel clinical investigation provides original research about the chronicity of polypharmacy in a large and unselected cohort of older adults. A deeper understanding of the dynamic nature of polypharmacy is an important addition to the current literature.

Word count:

Abstract 244

Full text 2997

1 **Abstract**

2 **OBJECTIVE:** To evaluate the chronicity of polypharmacy among older adults, and to
3 identify factors associated with chronic polypharmacy.

4 **DESIGN:** Longitudinal cohort study using register data.

5 **SETTING:** Nationwide, Sweden.

6 **PARTICIPANTS:** All 711,432 older adults (≥ 65 years) living in Sweden with 5 or more
7 prescription drugs in October 2010 were included and followed-up until December 2013.
8 Mean age at baseline was 77 (SD, 7.8) years, 59% were women, and 7% lived in nursing
9 homes.

10 **MEASUREMENT:** Monthly changes in the exposure to polypharmacy. Data regarding
11 prescription drug use were extracted from the Swedish Prescribed Drugs Register.

12 **RESULTS:** Overall, 82% were continuously exposed to polypharmacy during ≥ 6 months,
13 and 74% during ≥ 12 months. The proportion of individuals who remained exposed until the
14 end of the study was 55%. Among the 21,361 individuals who had not been exposed to
15 polypharmacy during the 6-month period before baseline (i.e. with a new episode of
16 polypharmacy), only 30% remained exposed for ≥ 6 months. The proportion of older adults
17 who spent at least 80% of their follow-up time with polypharmacy was substantially higher
18 among prevalent polypharmacy users at baseline than among those with a new polypharmacy
19 episode (80% vs 24%, $p < 0.01$). Factors associated with chronic polypharmacy included
20 higher age, female gender, living in an institution, chronic multimorbidity, and multi-dose
21 dispensing.

22 **CONCLUSION:** Polypharmacy is most often chronic, although a substantial share of older
23 adults experience short, recurring episodes of polypharmacy and are thus exposed to its
24 potential harms in a transient rather than persistent manner.

25 **Keywords:** duration; drugs; epidemiology; medication; polypharmacy

26 **Introduction**

27 Multimorbidity is common among older adults and often results in multiple medication use.
28 Polypharmacy (commonly defined as the concurrent use of 5 or more drugs)¹ is a concern
29 because it has been linked to an array of negative health outcomes.²⁻⁶ The prevalence of
30 polypharmacy has increased in most countries during the last decades⁷⁻¹¹. In the United
31 States, it is estimated that about 40% of people aged 65 years or older use ≥ 5 drugs
32 concomitantly.⁷ Yet few studies have documented the longitudinal development of
33 polypharmacy over time, and little is known about the proportion of older adults who are
34 chronically exposed to polypharmacy. Prior studies suggest that older adults tend to persist
35 with polypharmacy over time.¹²⁻¹⁶ Factors such as higher age, female gender, high BMI,
36 smoking and chronic conditions are associated with higher odds of remaining on
37 polypharmacy.¹⁶ However, these studies were based on survey data with several years
38 between each wave. The use of prescription drugs by older adults can fluctuate, and episodes
39 of polypharmacy can occur sporadically. Newly diagnosed chronic conditions and temporary
40 changes in health status (e.g. post-operative pain, infections) can for instance prompt an
41 increase in the number of drugs, while deprescribing and lack of adherence can shorten the
42 medication list.

43 Understanding the chronicity of polypharmacy is important for a number of reasons¹⁷. First,
44 most definitions of polypharmacy do not consider whether the exposure to polypharmacy is
45 chronic or transient.^{18,19} Yet, this has implications for evaluating the quality of drug
46 prescribing since short-term exposure to polypharmacy as a response to acute events is often
47 clinically appropriate. Second, various interventions have been implemented to reduce the

48 prevalence and the harms of polypharmacy. Most of these interventions have proven
49 unsuccessful.^{20,21} Potentially because polypharmacy may not always be a chronic and
50 persistent hazard,²² making it difficult to provide tailored interventions at the right time for
51 older adults¹⁸. Third, observational studies aiming at establishing a causal association
52 between polypharmacy and subsequent health outcomes have seldom considered
53 polypharmacy as a time-varying or cumulative exposure based on the assumption that
54 polypharmacy is by definition chronic.²³ Yet, until now, this assumption has remained
55 untested and there exists no consensual definition of what constitutes *chronic*
56 *polypharmacy*.¹⁹ Our aim was thus twofold: i) to evaluate the degree of chronicity of
57 polypharmacy among older adults in Sweden, and ii) to identify factors associated with
58 chronic rather than transient polypharmacy.

59

60 **Methods**

61 **Study population**

62 We used register data with nationwide coverage in Sweden to create a longitudinal cohort of
63 older adult (≥ 65 years) who were exposed to ≥ 5 drugs in October 2010. Study participants
64 were followed prospectively until December 2013, i.e. for up to 37 months. The Swedish
65 Prescribed Drug Register was linked to the National Patient Register, the National Cause of
66 Death Register, and the Social Services Register, as described elsewhere.²⁴ We excluded
67 individuals who died during the first 12 months of follow-up, as people at the end of life
68 might have specific clinical needs.²⁵ The selection of the study population is presented in
69 Supplementary materials Figure S1.

70 **Outcome measurement: polypharmacy**

71 Data regarding prescription drug use were extracted from the Swedish Prescribed Drugs
72 Register, which collects information about all prescription drugs delivered in pharmacies in
73 Sweden.²⁶ Exposure periods were constructed for each dispensed drug based on: (i) the date
74 of drug dispensing, (ii) the number of dispensed defined daily doses, and (iii) the prescribed
75 daily dose as reported by the prescriber.^{27,28} We then calculated the number of different drugs
76 used in each 30-day window, i.e. distinct substances according to the 5th level of Anatomical
77 Therapeutic Chemical (ATC) classification system. As illustrated in Figure S2, individuals
78 were considered as exposed to polypharmacy during a given month when the number of
79 drugs was ≥ 5 .

80 To distinguish “chronic” from “transient” polypharmacy exposure, we used the different
81 approaches illustrated in Figure 1. Health problems are usually defined as “chronic” when
82 they persist over time without any measurable interruptions (e.g. diabetes, heart failure). To
83 reflect this, we calculated the *duration* of polypharmacy as the number of consecutive months
84 spent with ≥ 5 different drugs. We considered the first episode, starting at baseline and
85 stopping when the patient was no longer exposed to polypharmacy for at least 2 months. In
86 other words, interruptions in polypharmacy exposure were discarded if they lasted ≤ 1 month.
87 This ‘grace period’ was used to reduce the influence of irregular drug refill patterns.
88 Chronicity of polypharmacy was calculated as the proportion of individuals who remained
89 exposed for ≥ 6 months and ≥ 12 months.

90 Other health problems do not persist over time without any measurable interruption, but can
91 still be considered as chronic if people are experiencing them more often than not (e.g.
92 chronic pain, psoriasis). The underlying assumption is that some conditions occur so
93 frequently that their impact on people’s everyday life is constant although their onset appears
94 as a series of discrete events. In order to mirror this second scenario, we calculated the
95 *fraction of time with polypharmacy* by dividing the number of months with polypharmacy
96 (numerator) by the total number of months of available follow-up (denominator). The
97 numerator did include grace periods. We then defined chronic polypharmacy users as older
98 adults who had a fraction of time with polypharmacy $\geq 80\%$ (e.g. at least 30 months out of 37
99 for those surviving the complete follow-up). This is similar to how drug adherence is
100 calculated using the medication possession ratio.²⁹

101 [Figure 1 about here]

102 **Other covariates**

103 *Living arrangement* at baseline was defined as ‘community-dwelling’ or ‘living in
104 institution’, using data from the Social Services Register. *Multimorbidity* was assessed using
105 a validated assessment tool (5), which captures 60 distinct chronic diseases using data from
106 the national patient register during the 3 years prior to baseline, as well as data about specific
107 medications dispensed during the same period. This variable was defined as the number of
108 chronic conditions, with ≥ 5 conditions as the maximum value. *Multi-dose dispensing* (in
109 Swedish, *ApoDos*) refers to drugs administered through portion packed plastic pouches. It is
110 especially common among older adults living in nursing homes in Sweden.³⁰

111 **Statistical analysis**

112 We calculated the duration of polypharmacy for each individual, and identified those who
113 remained exposed for ≥ 6 and ≥ 12 consecutive months. To account for left censoring we
114 stratified the population according to their exposure to polypharmacy during the 6-month
115 period *before* baseline. Since we excluded older adults who died during the first year of
116 follow-up, outcome measurement was not affected by right censoring (i.e. survival).
117 However, the persistence of polypharmacy throughout the entire follow-up was analyzed
118 with Kaplan-Meier survival functions accounting for mortality. We then measured the
119 fraction of time with polypharmacy as the number of months spent with polypharmacy
120 divided by the total number of months of available follow-up. The proportion of older adults
121 who had a fraction of time with polypharmacy $\geq 80\%$ was reported with percentages. Since
122 this indicator is proportional to the contributing time of each individual, it is not affected by
123 mortality selection. We analyzed factors associated with a high fraction of time with

124 polypharmacy using multivariate logistic regression models adjusted for age, sex, living
125 arrangement, number of chronic conditions, dispensing regimen and number of drugs at
126 baseline. All estimates from the logistic regression are calculated as predicted probabilities
127 and presented as percentages (with 95% confidence intervals) using the margins command in
128 Stata version 14.1 (StataCorp, College Station, TX). Predicted probabilities can be compared
129 across models and can be interpreted as adjusted proportions conditional on the covariates.³¹
130 Post hoc, we stratified the analysis by dispensing regimen to investigate the combined effect
131 of living arrangement and dispensing regimen. In sensitivity analyses, the fraction of time
132 with polypharmacy was categorized using a lower cut-off value (50% instead of 80%), which
133 has previously been used as a definition of chronic polypharmacy³²

134 **Ethical approval**

135 Data were anonymized and the Regional Ethical Review Board in Stockholm approved the
136 study (2013/1941-31/3 and 2015/1319-32).

137

138 **Results**

139 Out of 1,752,022 older adults (≥ 65 years) alive at baseline, 769,286 were exposed to
140 polypharmacy. After excluding 57,854 individuals who died during the first 12 months of
141 follow-up, the study population thus consisted of 711,432 older adults (Supplementary Figure
142 S1). This represents 44% of the population aged ≥ 65 years in Sweden. Mean age at baseline
143 was 77.4 years (SD 7.8), 59.1% were women. About 3% ($n=21,361$) of study participants
144 started a new episode of polypharmacy, i.e. had not been exposed to polypharmacy during the
145 6-month period before baseline (Table 1). Persons with a new episode of polypharmacy were
146 on average younger, had fewer chronic conditions and used fewer drugs at baseline (Table
147 S1).

148 [Table 1]

149 Polypharmacy was often long lasting. Overall, 82.3% of participants were exposed to
150 polypharmacy for ≥ 6 months, and 74.3% for ≥ 12 months. Among older adults with a new
151 polypharmacy episode, these proportions were 29.8%, and 18.6%, respectively (Table 2). The
152 proportion of individuals who remained exposed to polypharmacy until the end of follow-up
153 was 55.3% in the total study population, but only 9.3% among people who had not been
154 exposed to polypharmacy before baseline. Among the 317,478 older adults who discontinued
155 polypharmacy, 76.3% experienced at least one more episode of polypharmacy during the
156 follow-up period (Table S2). As shown in Figure 2, polypharmacy persisted for a longer time
157 among older adults aged 75 or older than among younger individuals. Episodes of
158 polypharmacy were also longer among individuals with a higher number of medications at
159 baseline (Figure S3).

160 [Table 2]

161 [Figure 2]

162 During follow-up, we observed 21.2 million person-months with polypharmacy out of a total
163 of 25.3 million person-months of follow-up. The average fraction of time with polypharmacy
164 was thus 84%, ranging from 80% among individuals aged 65–74 years to 89% among those
165 aged 95 years and older. Table 3 shows the proportion of older adults with a high fraction of
166 time with polypharmacy, i.e. exposed to polypharmacy for $\geq 80\%$ of follow-up. In the total
167 study population, 79.9% of older adults had a high fraction of time with polypharmacy,
168 compared with 23.6% among persons with a new polypharmacy episode at baseline. After
169 adjustment for potential confounders, this proportion increased with age, as well as with
170 multi-dose drug dispensing compared with ordinary prescriptions (adjusted predicted
171 probability 93% vs 78%, $p < 0.01$). The proportion of nursing home residents with a high
172 fraction of time with polypharmacy was higher than among community dwellers (90.7% vs
173 79.1%). However, after adjustment for other covariates, this association was reversed
174 (predicted probability 76.7% vs. 80.1%). In post-hoc analysis, we explored the interaction
175 between living arrangement and drug dispensing scheme. This showed that community-
176 dwellers with multi-dose dispensing were in fact more likely to have a high fraction of time
177 with polypharmacy than persons living in institution (Table S3). In sensitivity analyses where
178 the fraction of time with polypharmacy was calculated without the one month grace period
179 which yielded similar numbers, and using a cut-off value of $\geq 50\%$ which left the association
180 with other covariates largely unaffected although a larger proportion of older adults were
181 classified as chronic polypharmacy users (Table S4 and S5).

183 **Discussion**

184 This large longitudinal cohort study tracking monthly changes in drug utilization among
185 older adults in Sweden shows that polypharmacy (concurrent use of ≥ 5 drugs) is often a
186 chronic state. This was demonstrated with two complementary approaches.

187 First, when focusing on the *duration* of polypharmacy episodes, our data clearly show that
188 polypharmacy is persistent for a majority of older adults. About 75% of the individuals with
189 polypharmacy at baseline remained exposed to polypharmacy for at least 12 consecutive
190 months. Moreover, even though persons with a new polypharmacy episode at baseline were
191 more likely to discontinue polypharmacy in the short term, more than three quarters of the
192 people who stopped polypharmacy eventually transitioned back to polypharmacy before the
193 end of the study period. This suggests that polypharmacy is often a chronic state, however a
194 substantial share of older adults experience short episodes of polypharmacy and are thus
195 exposed to its potential harms in a transient rather than persistent manner. This is especially
196 true among those who are prescribed 3 to 4 medications for the management of chronic
197 diseases (and who are likely to fluctuate around the threshold of 5 drugs used to define
198 polypharmacy).

199 Another way to assess the longitudinal exposure to polypharmacy is to investigate the
200 proportion of months that older adults spend with polypharmacy. Contrary to *duration*, which
201 measures the length of continuous and uninterrupted polypharmacy episodes and is therefore
202 particularly sensitive to grace periods and right censoring (e.g. survival), the *fraction of time*
203 *with polypharmacy* describes the burden of polypharmacy with respect to the available
204 follow-up time. This approach is comparable to the methodology proposed by Franchi et al.,

205 for defining chronic polypharmacy users, which consists in measuring the proportion of
206 individuals exposed to polypharmacy at least 6 out of 12 months.³² In the present study, we
207 found that 80% of older adults had a high *fraction of time with polypharmacy* (i.e. spent
208 $\geq 80\%$ of follow-up with polypharmacy), which is indicative of a chronic exposure. Risk
209 factors associated with high fraction of time with polypharmacy included higher age, female
210 gender, living in institution, chronic multimorbidity, and multi-dose dispensing^{33–35}. When
211 using the same cut-off value as Franchi et al.³² – namely being exposed to polypharmacy
212 during more than 50% of the available months – 42% of older adults who started a new
213 polypharmacy episode at baseline had chronic polypharmacy in our study. An unexpected
214 finding was that the adjusted probability of spending a large proportion of months with
215 polypharmacy was higher among people residing in the community than in nursing homes.
216 However, more detailed analyses revealed that this association was mostly driven by multi-
217 dose dispensing – the small share of persons living in the community with multi-dose drug
218 dispensing had the largest fraction of time with polypharmacy. The finding that people with
219 multi-dose dispensing spend a higher fraction of time with polypharmacy is in agreement
220 with previous Swedish studies showing that persons with multi-dose dispensing have fewer
221 changes made to their drug regimens (e.g. dose adjustments, drug discontinuations and newly
222 prescribed drugs)^{30,36}. One suggested reason for the fewer changes is that prescribers have the
223 possibility to renew all drugs at once, which is not possible with ordinary prescriptions³⁶.

224 There currently exists no consensual definition of polypharmacy, but two aspects have been
225 widely discussed: the number of drugs that defines polypharmacy in a clinically meaningful
226 way,^{37,38} and the criteria that would allow for drawing the line between appropriate and
227 inappropriate polypharmacy.²⁰ These two dimensions – the *intensity* and the *composition* of

228 polypharmacy – are indeed important. However, only few studies have made a distinction
229 between chronic and transient polypharmacy.¹⁹ Our study shows that exposure to
230 polypharmacy is not always stable over time, and that transient polypharmacy episodes are
231 not uncommon. The notion of *temporality* should thus be better accounted for in the future.
232 Observational studies that have investigated the association between polypharmacy and
233 negative health outcomes have seldom considered polypharmacy as a time-varying
234 exposure.^{2,39} Yet, doing so would considerably improve the assessment of harms of
235 polypharmacy and could potentially elucidate the question whether the effect of
236 polypharmacy is cumulative (i.e. longer exposure to polypharmacy leads to an accumulated
237 risk of adverse effects) or if polypharmacy is hazardous even if exposure is short-lasting. The
238 potential cumulative hazard of polypharmacy was recently highlighted in a British study,
239 which demonstrated that the associations between polypharmacy and physical and cognitive
240 capabilities was more pronounced among older adults with a long-term exposure to
241 polypharmacy.²³

242 ***Strengths and limitations***

243 The main strength of this study is that it includes the entire population of older adults aged
244 ≥ 65 years with polypharmacy in Sweden, followed up for 3 years. The monthly assessments
245 of polypharmacy exposure provides better time resolution of the fluctuations in
246 polypharmacy status than earlier survey-based studies with longer time periods between
247 survey waves.^{12–16,23} There are some notable limitations to the study. First, we assessed
248 monthly exposure to polypharmacy rather than weekly or even daily exposure periods, which
249 could overlook some of the fluctuations in drug use. The choice of monthly time windows
250 was dictated by the considerable computation power required to calculate concurrent drug

251 exposure for a population of 700,000 individuals over 3 years with a more detailed time
252 resolution. It should also be noted that drugs used in hospitals are not recorded in the Swedish
253 Prescribed Drug Register, and a one-month stay in hospital could thus result in a change in
254 polypharmacy because of not filling new prescriptions. Additionally, over the counter drugs
255 are not recorded in the Swedish Prescribed Drug Register, this most likely leads to an
256 underestimation of the individual burden of polypharmacy. Adherence to different
257 medications could lead to misclassification of the exposure to polypharmacy in this study:
258 our data do not provide information about drugs that were prescribed but never dispensed or
259 whether the dispensed drugs were actually consumed. Our results should be interpreted in the
260 light of this limitation. To reduce the risk of overestimating short-term fluctuations, we only
261 considered polypharmacy to be discontinued if two consecutive months were spent without
262 polypharmacy. Second, we calculated the number of drugs by summing together all distinct
263 ATC codes including medications intended for short-term use that do not contribute to
264 chronic polypharmacy. However, considering all prescribed drugs reflects the natural course
265 of polypharmacy in the older population. Fourth, we tried to isolate people with a new
266 episode of polypharmacy at baseline from those who had already been exposed. This is
267 because incident polypharmacy users have been proposed as a promising target for future
268 interventions.²³ However, because we could only construct a 6-month *washout* period before
269 baseline, we cannot be certain that these individuals have a truly incident episode of
270 polypharmacy. Last, polypharmacy is often a result of multimorbidity. We were able to
271 account for the number of chronic conditions at baseline. However, future studies should also
272 investigate how severity of different conditions affects chronicity of polypharmacy.

273 In conclusion, in this longitudinal study of more than half a million older people followed for
274 up to three years, we found that that about 75% of the persons with polypharmacy were
275 exposed to polypharmacy for at least 12 consecutive months. A large majority of older adult
276 was also exposed to polypharmacy for more than 80% of the total study months. Our results
277 therefore suggest that polypharmacy is most often chronic, but that a substantial share of
278 older adults experience short, recurring episodes of polypharmacy and are thus exposed to its
279 potential harms in a transient rather than persistent manner. This highlights the need to
280 consider polypharmacy as a dynamic state in both epidemiological studies and in clinical
281 practice.

282

283 **ACKNOWLEDGMENTS**

284 **Financial Disclosure:** This work was supported by the Swedish Research Council (2015-
285 03618.). The sponsor had no role in the design or writing of the study.

286 **Conflict of Interest:** Authors have no conflicts of interest to report.

287 **Author Contributions:** All authors contributed to the study design, interpretation of
288 findings, writing and review of the manuscript. Jonas W Wastesson and Lucas Morin
289 performed analyses.

290 **Sponsor's Role:** The sponsor had no role in the design, methods, subject recruitment, data
291 collections, analysis and preparation of paper.

292

Elements of Financial/Personal Conflicts	*Author 1		Author 2		Author 3		Author 4	
	JWW		LM		MLL		KJ	
	Yes	No	Yes	No	Yes	No	Yes	No
Employment or Affiliation		X		X		X		X
Grants/Funds		X		X		X		X
Honoraria		X		X		X		X
Speaker Forum		X		X		X		X
Consultant		X		X		X		X
Stocks		X		X		X		X
Royalties		X		X		X		X
Expert Testimony		X		X		X		X
Board Member		X		X		X		X
Patents		X		X		X		X
Personal Relationship		X		X		X		X

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313 **Supplementary material**

314 Brief title: Supplementary analyses of chronicity of polypharmacy

315

313 **Figure captions**

314 **Figure 1.** Fictitious example of two persons followed from baseline until the end of the study
315 period, i.e. for a follow-up time of 37 months in total. Each square represents 1 month. The
316 washout period of 6 months before baseline is used to distinguish persons who were already
317 exposed to polypharmacy before baseline (Person A) from those who started a new
318 polypharmacy episode at baseline (Person B). Each episode of polypharmacy starts at the
319 first month of exposure, and ends when the person remains unexposed for at least 2
320 consecutive months (grace period). In this example, both persons are considered as having a
321 first episode of polypharmacy that persisted for 7 months, followed by 2 other episodes of
322 polypharmacy. The fraction of time with polypharmacy is calculated as the number of
323 months with polypharmacy – including grace periods – divided by the total number of
324 months of available follow-up. In this example, the fraction of time with polypharmacy is
325 equal to $33 \div 37$ (89.2%). Thus, considering a cut-off value of $\geq 80\%$, these persons are defined
326 as chronic polypharmacy users.

327

328 **Figure 2:** Kaplan-Meier survival functions. Solid-line curves denotes the persistence of
329 polypharmacy with a 2-month grace period. Dotted-line curves denotes the persistence of
330 polypharmacy with no grace period (sensitivity analysis). Vertical dashed lines indicate
331 polypharmacy exposure at 6 and 12 months, respectively.

332

313 **Table 1.** Characteristics of older adults with polypharmacy at baseline (Sweden, 2010)

Sex, No (%)	
Men	291,175 (40.9%)
Women	420,257 (59.1%)
Age	
Mean (SD)	77.4 (7.8)
No (%)	
65-74 years	300,810 (42.3%)
75-84 years	273,069 (38.4%)
85-94 years	129,715 (18.2%)
95 years +	7,838 (1.1%)
Living arrangement, No (%)	
Community	658,693 (92.6%)
Institution	52,739 (7.4%)
Number of chronic conditions	
Mean (SD)	3.7 (2.6)
No (%)	
0	41,256 (5.8%)
1	102,904 (14.5%)
2	122,735 (17.2%)
3	116,609 (16.4%)
4	98,338 (13.8%)
≥5	229,590 (32.3%)
Drug dispensing scheme, No (%)	
Ordinary prescription	611,123 (85.9%)
Multi-dose dispensing	100,309 (14.1%)
Number of drugs at baseline	
Mean (SD)	8.0 (3.1)
No (%)	
5	149,247 (21.0%)
6	128,527 (18.1%)
7	105,530 (14.8%)
8	83,972 (11.8%)
9	65,710 (9.2%)
≥10	178,446 (25.1%)
Polypharmacy during the 6-month period before baseline, No (%)	
No	21,361 (3.0%)
Yes	690,071 (97.0%)
Death during follow-up, No (%)	

Between 12 and 24 months	54,476 (7.7%)
Between 25 and 37 months	57,027 (8.0%)
Survived follow-up	599,792 (84.3%)

Table 2. Persistence of polypharmacy (≥ 5 drugs) among older adults in Sweden.

	Entire cohort (n=711,432)		Older adults with a new polypharmacy episode at baseline (n=21,361)	
	≥ 6 months	≥ 12 months	≥ 6 months	≥ 12 months
	%	%	%	%
Total	82.3	74.3	29.8	18.6
Sex				
Men	81.8	73.2	31.9	19.9
Women	82.7	75.0	28.2	17.6
Age				
65-74 years	78.1	68.5	26.8	15.6
75-84 years	84.2	76.7	33.0	21.6
85-94 years	87.8	82.0	36.5	25.6
95 years +	88.6	83.2	29.5	17.0
Living arrangement				
Community	81.4	73.0	29.4	18.1
Institution	93.7	90.5	48.4	37.9
Number of chronic conditions				
0	65.2	53.3	20.5	11.5
1	73.2	62.4	25.2	14.7
2	77.4	67.7	29.9	18.2
3	81.2	72.2	34.0	21.7
4	84.8	77.0	36.3	24.2
≥ 5	91.7	86.7	44.1	31.5
Drug dispensing scheme				
Ordinary prescription	80.2	71.2	29.1	17.8
Multi-dose dispensing	95.5	93.0	51.4	41.8
Number of drugs at baseline				
5	55.0	41.8	23.4	13.7
6	76.1	64.3	35.1	21.5
7	86.7	77.7	46.5	31.2
8	92.0	85.4	56.2	40.3
9	95.0	90.2	69.1	56.6
≥ 10	97.8	95.5	78.4	67.3
Death during follow-up				
Between 12 and 24 months	90.5	85.9	43.8	34.6
Between 25 and 37 months	89.4	84.4	41.6	29.8
Survived follow-up	80.9	72.3	28.6	17.4

^a Duration of polypharmacy was calculated as the number of consecutive months with polypharmacy, with a 2-month grace period (see *methods* for more information) .

Table 3. Proportion of older adults with a high fraction of time with polypharmacy ($\geq 80\%$) during follow-up

	Entire cohort (n=711,432)			Older adults with a new polypharmacy episode at baseline (n=21,361)		
	Crude %	Adjusted % ^a	95% CI	Crude %	Adjusted % ^a	95% CI
Total	79.9	79.9	(79.8-80.0)	23.6	23.6	(23.1-24.2)
Sex						
Men	79.3	80.5	(80.4-80.6)	24.5	24.4	(23.6-25.2)
Women	80.0	79.5	(79.4-79.6)	22.9	23.0	(22.3-23.7)
Age						
65-74 years	74.8	77.7	(77.6-77.8)	19.5	20.5	(19.8-21.2)
75-84 years	82.5	81.6	(81.5-81.7)	27.8	27.1	(26.1-28.1)
85-94 years	86.1	82.7	(82.5-82.9)	33.2	29.4	(27.5-31.2)
95 years +	85.9	81.1	(80.2-82.0)	31.0	22.3	(15.7-28.8)
Living arrangement						
Community	79.1	80.1	(80.0-80.2)	23.1	23.4	(22.9-24.0)
Institution	90.7	76.7	(76.1-77.3)	47.2	29.4	(25.1-33.7)
Number of chronic conditions						
0	60.6	75.5	(75.2-75.8)	15.3	17.4	(16.1-18.7)
1	69.5	78.0	(77.8-78.2)	18.7	20.1	(19.0-21.1)
2	74.4	78.7	(78.5-78.9)	23.8	24.1	(22.9-25.2)
3	78.5	79.6	(79.4-79.8)	27.1	26.0	(24.6-27.4)
4	82.8	81.1	(80.9-81.4)	30.8	28.5	(26.6-30.4)
≥ 5	90.5	84.1	(83.9-84.3)	37.5	31.8	(29.8-33.8)
Drug dispensing scheme						
Ordinary prescription	77.8	79.1	(79.0-79.2)	22.7	23.0	(22.4-23.6)
Multi-dose	92.8	87.9	(87.6-88.2)	50.6	39.9	(35.7-44.1)
Number of drugs at baseline						
5	51.6	55.8	(55.6-56.1)	19.1	19.5	(18.9-20.2)
6	72.1	74.1	(73.8-74.3)	26.7	26.4	(25.1-27.6)
7	83.7	84.2	(84.0-84.4)	35.2	34.2	(32.0-36.5)
8	90.1	89.8	(89.6-90.0)	41.2	38.0	(34.4-41.6)
9	93.8	93.3	(93.1-93.5)	61.4	55.3	(49.6-61.0)
≥ 10	97.2	96.6	(96.5-96.7)	63.3	56.5	(49.4-63.5)

^a Probabilities mutually adjusted for the other covariates in the table.