CLINICAL RESEARCH STUDY

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Choosing Wisely? Measuring the Burden of Medications in Older Adults near the End of Life: Nationwide, Longitudinal Cohort Study

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ABSTRACT

BACKGROUND: The burden of medications near the end of life has recently come under scrutiny, because several studies suggested that people with life-limiting illness receive potentially futile treatments.

METHODS: We identified 511,843 older adults (>65 years) who died in Sweden between 2007 and 2013 and reconstructed their drug prescription history for each of the last 12 months of life through the Swedish Prescribed Drug Register. Decedents' characteristics at time of death were assessed through record linkage with the National Patient Register, the Social Services Register, and the Swedish Education Register.

RESULTS: Over the course of the final year before death, the proportion of individuals exposed to ≥10 different drugs rose from 30.3% to 47.2% (P <.001 for trend). Although older adults who died from cancer had the largest increase in the number of drugs (mean difference, 3.37; 95% confidence interval, 3.35 to 3.40), living in an institution was independently associated with a slower escalation ($\beta = -0.90$, 95% confidence interval, −0.92 to −0.87). During the final month before death, analgesics (60.8%), antithrom-botic agents (53.8%), diuretics (53.1%), psycholeptics (51.2%), and β-blocking agents (41.1%) were the 5 most commonly used drug classes. Angiotensin-converting enzyme inhibitors and statins were used by, respectively, 21.4% and 15.8% of all individuals during their final month of life.

CONCLUSION: Polypharmacy increases throughout the last year of life of older adults, fueled not only by symptomatic medications but also by long-term preventive treatments of questionable benefit. Clinical guidelines are needed to support physicians in their decision to continue or discontinue medications near the end of life.

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Under the combined effect of increased longevity, chronic multimorbidity, and single-disease clinical guidelines, the concomitant use of multiple medications has become commonplace among older adults.[1] Polypharmacy increases inappropriate drug use and drug−drug interactions and exposes older adults to serious adverse effects.[2] Yet, it is estimated that 25% to 40% of adults aged 65 years or older are prescribed at least 5 medications.[3]

When considering older people near the end of life, poly-pharmacy poses 2 problems. First, as death approaches, age-related physiologic changes are amplified by the changing metabolism, the decline of renal and hepatic functions, and the loss of body mass. As a result, pharmacokinetics and pharmacodynamics are altered, making older adults with life-limiting illness particularly vulnerable to the harmful side effects of medications.[4] Second, the accumulation of prescriptions in the context of limited life expectancy raises questions about the intended or expected benefit of the treatments.[5]

CLINICAL SIGNIFICANCE

- The burden of medications increases near the end of life (47.2% of older adults receive ≥10 prescription drugs during their last month of life).
- Polypharmacy is fueled not only by symptomatic medications but also by long-term preventive treatments of questionable benefit.
- Guidelines are needed to support physicians in their decision to continue or discontinue drug treatments near the end of life.

The burden of medications near the end of life has recently come under scrutiny, because several studies have shown that people with specific life-limiting diseases are prescribed medications whose benefit is unlikely to be achieved within their remaining lifespan.[6] However, these studies have all been conducted in selected samples of individuals who shared a common disease[7-10] or care setting[11-14] or were recruited for a clinical trial.[15] Future research and clinical guidelines need to be informed by findings that are generalizable beyond a specific illness or care setting.

This study aimed to measure the change in the prevalence of polypharmacy and to identify the most commonly used medications over the course of the last year of life of older people, using data with national coverage in Sweden.

METHODS

Study Design and Population

We conducted a nationwide, follow-back cohort study of all older adults who died at age >65 years in Sweden between January 1, 2007 and December 31, 2013. Individuals were excluded from the study population if they had no reported cause of death or had no prescription data available during the final 3 months before the date of death (Supplementary Figure 1, available online). Death certificate data were obtained from the Swedish National Board of Health and Welfare and were linked at the individual level to several other registries with national coverage: the Swedish Prescribed Drug Register, Social Services Register, National Patient Register, and Swedish Education Register. Data were anonymized, and the Regional Ethical Review Board in Stockholm approved the study (no. 2013/1941-31/3 and 2015/1319-32).

Assessment of Polypharmacy and Drug Exposure

Polypharmacy was considered as the primary outcome. Although there is no consensual definition, studies conducted in the general geriatric population typically use a threshold of ≥4 or ≥5 medications to characterize polypharmacy and ≥9 or ≥10 to describe "excessive polypharmacy."[16-18] In light of the considerable burden of chronic diseases and symptoms near the end of life,[19] we opted for the latter, more conservative cut-off. Hence polypharmacy was hereafter defined as the monthly exposure to 10 or more prescription drugs, that is, distinct substances according to the fifth level of the Anatomical Therapeutic Chemical (ATC) classification system.

Prescription drug data were derived from the Swedish Prescribed Drug Register to evaluate the total number of medications during each of the final 12 months before death. In Sweden, drug prescriptions cover a maximum period of 90 days. Drug exposure was estimated according to 1) the date of dispensing, 2) the total amount dispensed to the patient, and 3) the prescribed daily dose, as described in Supplementary Figure 2 (available online).[20,21] In addition, we calculated the prevalence of the 20 most common individual drug classes for the 12th, 6th, and final months before death. As recommended by the World Health Organization, drugs were classified by ATC code.

Descriptive Variables

Sex and age at time of death were both extracted from death certificates. International Classification of Diseases, 10th revision diagnosis codes for all contributing causes of death were categorized into 4 distinct "illness trajectories" indicative of the potential timeframe of care needs near the end of life: cancer, organ failure, prolonged dwindling, and sudden death.[22,23] Individuals were assigned a single illness trajectory using a modified version of the protocol developed by Lunney et al[24] (Supplementary Table 1, available online). When multiple causes of death indicated more than 1 illness trajectory, we applied a predefined hierarchy (ie, from cancer to prolonged dwindling to organ failure to sudden death).[25] In addition, we used a multimorbidity assessment tool recently validated in the general elderly

Table 1 Characteristics of Older Adults Who Died Between 2007 and 2013 in Sweden, by Living Arrangement

Characteristic	Community-Dwelling	Institutionalized	Total	*P* Value*
Decedents in cohort (n)	350,977	160,866	511,843	
Sex, n (%)				<.001
Men	176,490 (50.3)	57,533 (35.8)	234,023 (45.7)	
Women	174,487 (49.7)	103,333 (64.2)	277,820 (54.3)	
Age at time of death (y)				
Mean (SD)	82.6 (8.2)	87.7 (6.9)	84.2 (8.2)	<.001
n (%)				<.001
66-74	68,128 (19.4)	7621 (4.7)	75,749 (14.8)	
75-84	124,701 (35.5)	38,654 (24.0)	163,355 (31.9)	
85-94	136,847 (39.0)	90,544 (56.3)	227,391 (44.4)	
≥95	21,301 (6.1)	24,047 (14.9)	45,348 (8.9)	
Level of education,† n (%)				<.001
Primary education	177,861 (53.0)	89,458 (59.0)	267,319 (54.8)	
Secondary education	124,470 (37.1)	50,613 (33.4)	175,083 (35.9)	
Tertiary education	33,502 (10.0)	11,620 (7.7)	45,122 (9.3)	
Illness trajectory,‡ n (%)				<.001
Cancer	121,569 (34.6)	23,309 (14.5)	144,878 (28.3)	
Organ failure	143,840 (41.0)	54,758 (34.0)	198,598 (38.8)	
Prolonged dwindling	56,514 (16.1)	72,243 (44.9)	128,757 (25.2)	
Sudden death	29,054 (8.3)	10,556 (6.6)	39,610 (7.7)	
No. of chronic diseases				
Mean (SD)	5.0 (2.7)	4.7 (2.7)	4.9 (2.7)	<.001
n (%)				<.001
0	3192 (0.9)	2352 (1.5)	5544 (1.1)	
1	21,116 (6.0)	13,020 (8.1)	34,136 (6.7)	
2	39,361 (11.2)	21,137 (13.1)	60,498 (11.8)	
3	49,957 (14.2)	24,215 (15.1)	74,172 (14.5)	
4	52,361 (14.9)	23,904 (14.9)	76,265 (14.9)	
≥5	184,990 (52.7)	76,238 (47.4)	261,228 (51.0)	

SD = standard deviation.

*Pearson's χ^2 test, except for the mean age and mean number of chronic conditions (median test).

†Missing values for level of education: 24,319 (4.7% of the total cohort).

‡Illness trajectories were constructed using all the diagnoses mentioned on the death certificates (ie, both underlying and contributing causes of death). When the different causes of death indicated more than 1 illness trajectory, we applied a previously described hierarchy (ie, from cancer to prolonged dwindling to organ failure to sudden death).[25]

population[26] to provide a comprehensive account of the burden of disease near the end of life (Supplementary Table 2, available online). In brief, a total of 60 chronic diseases were identified through the National Cause of Death Register (all causes of death), the National Patient Register (inpatient and specialized outpatient diagnoses reported during the last 24 months before death), and the Swedish Prescribed Drug Register (use of specific medications in the last 24 months before death). Living arrangement of the individuals during the final year of life was categorized as "community-dwelling" or "institutionalized," using data from the Social Services Register. Level of education was used as a measure of socioeconomic position and operationalized as "primary education," "secondary education," and "tertiary education."

Statistical Analysis

Descriptive analysis was performed by calculating the proportion and means of the decedents' characteristics according to their living arrangement. Statistical differences were tested with Pearson's χ^2 for categorical variables and median test for continuous variables, with P <.001. The proportion of individuals receiving ≥10 drugs was reported together with the mean number of prescription drugs throughout the final year of life. Results comparing community-dwelling and institutionalized individuals were standardized for both sex and age by using the total population as reference.

We investigated trends in polypharmacy and in the number of prescribed drugs between the 12th month and the final month before death. Unadjusted logistic regression models were computed to calculate the odds of being exposed to polypharmacy during the final month before death compared with 12 months before, using clustered robust standard error to account for intra-individual correlation. We also identified factors independently associated with change in the number of prescribed drugs over time by means of generalized estimating equation models with identity link functions at the individual level and

unstructured correlation. The number of distinct medications was considered as a continuous dependent variable, whereas sex, age, living arrangement, number of chronic diseases, illness trajectory, and level of education were entered as independent variables. Results are presented as adjusted β coefficients with their 95% confidence intervals (CIs). In sensitivity analyses the same models were computed by removing analgesics (ATC code N02) from the total number of prescription drugs, because this class of medications is used for specific purposes near the end of life. Finally, changes in the prevalence of individual drug classes were assessed with variation rates (with 95% CI) from the 12th to the final month before death. Bivariate logistic regressions were used to assess P for trend (2-sided $\alpha = .01$). All analyses were performed with SAS JMP 12.1 (SAS Institute, Cary, NC) and Stata 14.1 (StataCorp, College Station, TX) software.

RESULTS

Study Population

Of all 545,212 older adults who died in Sweden between 2007 and 2013, 511,843 (93.9%) met our eligibility criteria. **Table 1** shows the decedents' main characteristics. Compared with community dwellers, institutionalized individuals were more often women, died at older age, and were more likely to follow a trajectory of prolonged dwindling. Overall, 51% of individuals had 5 or more diagnosed chronic conditions at time of death. The most common chronic illnesses were ischemic heart diseases (42%), hypertension (40%), congestive heart failure (38%), cancer (31%), atrial fibrillation (27%), and cerebrovascular diseases (26%).

Change in the Prevalence of Polypharmacy

The prevalence of polypharmacy increased significantly throughout the last year of life (**Figure**). Between the 12th and the final month before death, the proportion of individuals exposed to ≥10 different drugs rose from 30.3% to 47.2% (P <.001 for trend), and the mean (standard deviation) number of prescription drugs increased from 7.6 (4.4) to 9.6 (4.7). Older adults living in institutions were found to receive a greater number of medications than those living in the community (P <.001 for each of the final 12 months of life). These trends remained after excluding analgesics from the total count of prescription drugs (Supplementary Figure 3, available online). However, we found significant differences across age groups and illness trajectories (Supplementary Figure 4, available online).

Factors Associated with Change in the Number of Prescription Drugs

The magnitude of the increase in polypharmacy over the course of the last year of life varied significantly according to the decedents' characteristics (**Table 2**). Hence, the likelihood of being exposed to polypharmacy during the final month of life compared with 12 months before death was greater for individuals who died from cancer (odds ratio 3.34; 95% CI, 3.29-3.39) than for those who died from dementia or other neurodegenerative disorders (odds ratio 1.74; 95% CI,

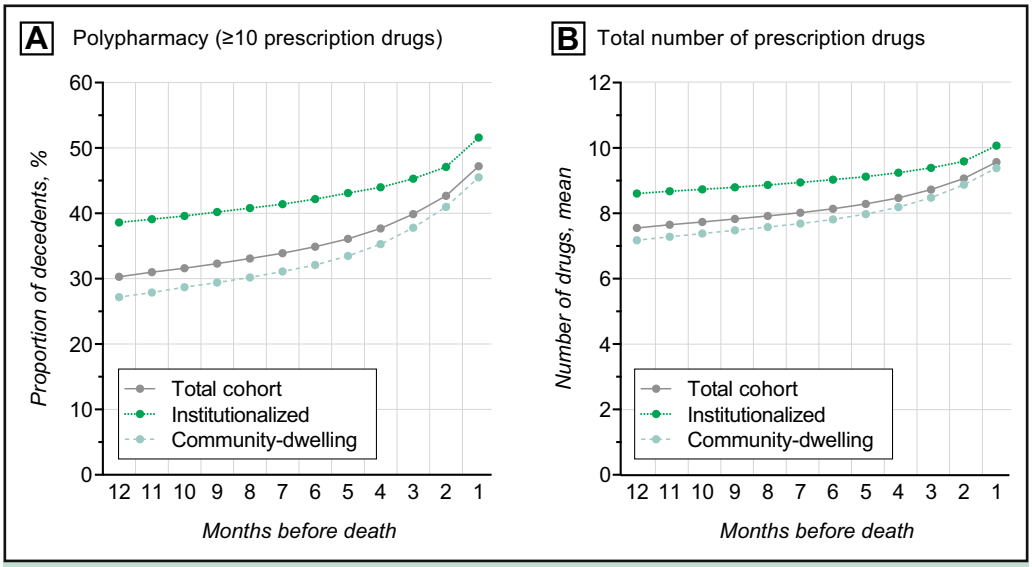

Figure (**A**) Polypharmacy and (**B**) number of prescription drugs over the course of the last 12 months of life of older people in Sweden, by living arrangement. Proportions and means are standardized for both sex and age, using the total population as reference. All trends statistically significant (P <.01).

Table 2 Change in the Likelihood of Being Exposed to Polypharmacy During the Last Year of Life of Older Adults in Sweden, 2007-2013

		Polypharmacy (≥10 Drugs), %		Last Month vs 12th Month Before Death	
Parameter	N Total	12th Month Before Death	Last Month Before Death	Variation Rate, % (95% CI)*	Odds Ratio (95% CI)†
Total cohort	511,843	30.3	47.2	55.9 (55.1-56.7)	2.06 (2.05-2.07)
Sex					
Men	234,023	27.5	46.4	68.6 (67.3-69.9)	2.28 (2.25-2.31)
Women	277,820	32.6	47.8	46.9 (45.9-47.8)	1.90 (1.88-1.92)
Age at time of death (y)					
66-74	75,749	26.8	47.1	75.7 (73.2-78.1)	2.43 (2.38-2.48)
75-84	163,355	31.6	49.8	57.7 (56.3-59.0)	2.15 (2.12-2.18)
85-94	227,391	31.4	47.3	50.6 (49.5-51.7)	1.96 (1.94-1.98)
≥95	45,348	25.7	37.6	46.2 (43.4-49.1)	1.74 (1.69-1.79)
Living arrangement					
Community-dwelling	350,977	27.1	45.9	69.4 (68.3-72.5)	2.28 (2.26-2.31)
Institutionalized	160,866	37.2	50.0	34.4 (33.4-35.5)	1.69 (1.66-1.71)
Level of education‡					
Primary education	267,319	31.2	48.3	55.0 (53.9-56.1)	2.06 (2.04-2.09)
Secondary education	175,083	30.0	47.0	56.8 (55.4-58.2)	2.07 (2.04-2.10)
Tertiary education	45,122	27.6	44.6	61.7 (58.8-64.7)	2.11 (2.05-2.17)
Illness trajectory§					
Cancer	144,878	24.3	51.8	112.8 (110.5-115.9)	3.34 (3.29-3.39)
Organ failure	198,598	37.0	50.5	36.3 (35.3-37.3)	1.73 (1.71-1.76)
Prolonged dwindling	128,757	28.4	40.9	43.8 (42.3-45.4)	1.74 (1.71-1.77)
Sudden death	39,610	23.9	34.3	43.2 (40.0-46.4)	1.66 (1.61-1.71)
No. of chronic diseases					
0	5544	8.3	12.8	54.7 (38.4-72.9)	1.63 (1.44-1.84)
1	34,136	8.9	18.6	109.8 (101.5-118.5)	2.35 (2.24-2.46)
2	60,498	13.3	26.2	97.1 (92.3-141.9)	2.32 (2.25-2.39)
3	74,172	18.0	33.6	86.9 (83.5-92.4)	2.31 (2.25-2.37)
4	76,265	22.8	41.3	81.1 (78.3-84.4)	2.38 (2.33-2.44)
≥5	261,228	43.1	62.1	44.0 (43.2-44.7)	2.16 (2.14-2.18)

CI = confidence interval.

*Variation rates indicate the relative change in prevalence of polypharmacy between the 12th month and the final month before death.

†Odds ratio calculated by means of logistic regression models including polypharmacy (≥10 prescription drugs) as a binary dependent variable and time (last month before death vs. 12th month before death) as sole independent variable. Clustered standard errors at the individual level were used to account for correlation of observations within groups.

‡Missing values for level of education: 24,319 (4.7% of the total cohort).

§Illness trajectories were constructed using all the diagnoses mentioned on the death certificates (ie, both underlying and contributing causes of death). When the different causes of death indicated more than 1 illness trajectory, we applied a previously described hierarchy (ie, from cancer to prolonged dwindling to organ failure to sudden death).[25]

1.71-1.77). As shown in **Table 3**, female sex, older age at time of death, and institutionalization were independently associated with a slower increase in the average number of medications over time. Older adults who died from cancer had the greatest increase in the number of prescription drugs (mean difference 3.37; 95% CI, 3.35-3.40). These associations were only partly attenuated when analgesics were excluded from the total count of prescribed drugs (Supplementary Tables 3 and 4, available online).

Most Commonly Used Drug Classes

Antithrombotic agents, diuretics, analgesics, psycholeptics, and β-blocking agents were found to be the 5 most common prescription drug classes during the last year of life (**Table 4**). Agents acting on the renin−angiotensin system, antianemic preparations, antidepressants, and drugs for acid-related disorders were also highly prevalent, with more than 30% of decedents exposed to these drugs during the final month before death. The pattern of prescription drug use changed over the course of the last 12 months of life, with a notable increase in the exposure to opioids (+120.7%), antimicrobials (+74.3%), anxiolytics (+59.5%), drugs for constipation (+57.8%), and antipsychotics (+47.3%). We found only a modest decrease in the use of preventive drugs. Hence, during their last month of life, a significant share of older adults used β-blockers (41.1%), angiotensin-converting enzyme inhibitors (21.4%), vasodilators (17.4%), lipid-lowering agents (16.3%),

Table 3 Factors Associated with Change in the Number of Prescription Drugs During the Last Year of Life of Older Adults in Sweden, 2007-2013

Factor	N Total	No. of Prescription Drugs, Mean (SD)		Mean Difference (95% CI)	Factor × Time, Adjusted β (95% CI)*
		12th Month Before Death	Last Month Before Death		
Total cohort	511 843	7.6 (4.4)	9.6 (4.7)	2.01 (2.00 to 2.02)	—
Sex					
Men	234 023	7.2 (4.3)	9.5 (4.7)	2.27 (2.25-2.29)	Ref
Women	277 820	7.9 (4.4)	9.6 (4.7)	1.80 (1.78-1.81)	−0.46 (−0.48 to −0.44)
Age at time of death (y)					
66-74	75 749	6.9 (5.0)	9.6 (5.3)	2.77 (2.74-2.80)	Ref
75-84	163 355	7.7 (4.6)	9.9 (4.9)	2.20 (2.18-2.22)	−0.57 (−0.61 to −0.54)
85-94	227 391	7.8 (4.1)	9.5 (4.4)	1.77 (1.75-1.78)	−1.00 (−1.03 to −0.96)
≥95	45 348	7.2 (3.8)	8.5 (4.0)	1.31 (1.29-1.34)	−1.44 (−1.49 to −1.39)
Living arrangement					
Community-dwelling	350 977	7.1 (4.4)	9.4 (4.8)	2.29 (2.28-2.31)	Ref
Institutionalized	160 866	8.5 (4.2)	9.9 (4.4)	1.40 (1.38-1.42)	−0.90 (−0.92 to −0.87)
Level of education†					
Primary education	267 319	7.7 (4.3)	9.7 (4.6)	2.01 (1.99-2.01)	Ref
Secondary education	175 083	7.5 (4.5)	9.6 (4.8)	2.05 (2.04-2.07)	0.05 (0.02-0.07)
Tertiary education	45 122	7.2 (4.4)	9.3 (4.8)	2.09 (2.05-2.13)	0.09 (0.05-0.12)
Illness trajectory‡					
Cancer	144 878	6.7 (4.4)	10.0 (4.9)	3.37 (3.35-3.40)	Ref
Organ failure	198 598	8.4 (4.5)	10.0 (4.8)	1.59 (1.57-1.61)	−1.79 (−1.82 to −1.77)
Prolonged dwindling	128 757	7.5 (3.9)	8.9 (4.1)	1.36 (1.34-1.38)	−2.01 (−2.04 to −1.98)
Sudden death	39 610	6.8 (4.2)	8.1 (4.4)	1.29 (1.26-1.31)	−2.09 (−2.14 to −2.05)
No. of chronic diseases					
0	5544	4.6 (3.2)	5.6 (3.3)	0.91 (0.85-0.97)	Ref
1	34 136	4.8 (3.4)	6.4 (3.6)	1.60 (1.57-1.64)	0.74 (0.61-0.86)
2	60 498	5.4 (3.6)	7.3 (3.8)	1.86 (1.83-1.89)	0.97 (0.86-1.09)
3	74 172	6.1 (3.7)	8.1 (4.0)	1.97 (1.94-1.99)	1.08 (0.96-1.20)
4	76 265	6.8 (3.8)	8.9 (4.1)	2.08 (2.06-2.11)	1.19 (1.07-1.30)
≥5	261 228	9.1 (4.4)	11.2 (4.7)	2.12 (2.10-2.14)	1.22 (1.10-1.33)

CI = confidence interval; SD = standard deviation.

*β-Coefficients computed by the mean of generalized estimating equation models with identity link functions at the individual level and unstructured correlations. The total number of distinct prescription drugs (5-digit Anatomical Therapeutic Chemical codes) was entered as continuous dependent variable with Gaussian distribution, while including all presented individual characteristics as independent variables. β-Coefficients for the interaction with time can be interpreted as the rate of change between the 12th month and the final month before death, compared with the reference category.

†Missing values for level of education: 24,319 (4.7% of the total cohort).

‡Illness trajectories were constructed using all the diagnoses mentioned on the death certificates (ie, both underlying and contributing causes of death). When the different causes of death indicated more than 1 illness trajectory, we applied a previously described hierarchy (ie, from cancer to prolonged dwindling to organ failure to sudden death).[25]

calcium channel blockers (15.4%), or potassium-sparing agents (12.1%). The prevalence of preventive medication was found to be higher among younger individuals (Supplementary Table 5, available online).

DISCUSSION

Our study has two main findings. First, the proportion of older adults exposed to ≥10 different prescription drugs increases over the course of the last year before death, and approximately half of individuals experience polypharmacy during their last month of life. Second, polypharmacy is fueled not only by an increased use of medications directed toward symptom management but also by the frequent continuation of long-term preventive treatments and disease-targeted drugs.

These results compare to earlier studies. McNeil et al[15] recently reported that patients with a life-limiting disease took on average 10.7 medications at time of death, with 69% of patients using 9 or more different drugs (excluding statins). In a retrospective cohort study of 100 patients who died from advanced cancer, researchers found a median of 11 prescribed medications 9 days before death.[27] Despite a considerable heterogeneity in study designs and populations, other studies investigating drug use near the end of life have reported comparable results.[6,28] These findings demonstrate the challenge of managing the accumulation of health problems in older adults with life-limiting illness.[29]

Table 4 Prevalence of the 20 Most Commonly Used Prescription Drug Classes During the Last Year of Life of Older People in Sweden, 2007-2013

Rank, Drug Class*	ATC Code	Prevalence, % (N = 511,843)			Variation Rate Between 12th Month and Last month Before Death, % (95% CI)†
		12th Month	6th Month	Last Month	
1. Antithrombotic agents	B01	52.5	53.5	53.8	2.6 (2.2-2.9)
Vitamin K antagonists	B01AA	7.9	7.7	6.7	−15.4 (−16.6 to −14.3)
Heparin group	B01AB	1.6	2.5	5.2	221.6 (213.8-229.6)
Platelet aggregation inhibitors	B01AC	44.3	44.9	44.9	1.4 (0.9-1.8)
2. Diuretics	C03	47.1	49.2	53.1	12.7 (12.3-13.2)
Low-ceiling diuretics	C03A-C03B	6.0	5.7	5.2	−12.5 (−13.9 to −11.1)
High-ceiling diuretics	C03C	37.2	40.1	45.6	22.7 (22.1-23.3)
Potassium-sparing agents	C03D	9.6	10.3	12.1	26.0 (24.6-27.4)
3. Analgesics	N02	40.2	45.9	60.8	51.2 (50.6-51.8)
Opioids	N02A	17.5	21.4	38.5	120.7 (119.1-122.2)
Other analgesics	N02B	35.0	39.6	49.2	40.6 (40.0-41.3)
4. Psycholeptics	N05	39.5	42.8	51.2	29.6 (29.0-31.1)
Antipsychotics	N05A	7.8	8.9	11.5	47.3 (45.6-49.1)
Anxiolytics	N05B	16.7	18.8	26.6	59.5 (58.3-61.7)
Hypnotics and sedatives	N05C	28.1	29.9	34.5	23.1 (22.4-23.8)
5. β-Blocking agents	C07	39.4	40.3	41.1	4.1 (3.6-4.6)
6. Drugs acting on the renin—angiotensin system	C09	31.8	31.9	30.6	−3.9 (−4.5 to −3.4)
ACE inhibitors	C09A-C09B	21.6	21.9	21.4	−1.0 (−1.7 to −0.2)
Angiotensin II receptor antagonists	C09C-C09D	10.9	10.7	9.8	−9.9 (−11.0 to −8.9)
7. Anti-anemic preparations	B03	30.6	32.9	34.6	12.9 (12.3-13.5)
Iron preparations	B03A	7.8	8.9	10.4	33.6 (32.0-35.3)
Vitamin B12 and folic acid	B03B	25.9	27.5	28.2	9.0 (8.3-9.7)
8. Psychoanaleptics	N06	27.4	29.5	32.6	18.9 (18.2-19.6)
Antidepressants	N06A	24.5	26.6	30.1	22.7 (21.9-23.5)
Anti-dementia drugs	N06D	5.4	5.4	5.0	−8.2 (−9.7 to −6.6)
9. Drugs for constipation	A06	25.3	30.1	39.9	57.8 (56.9-58.7)
10. Drugs for acid related disorders	A02	23.8	27.4	35.1	47.3 (46.4-48.2)
11. Cardiac therapy	C01	22.2	23.0	24.3	9.3 (8.4-19.4)
Cardiac glycosides	C01A	7.9	8.0	8.3	5.1 (3.7-6.5)
Vasodilators used in cardiac diseases	C01D	15.5	16.2	17.4	12.5 (11.6-13.5)
12. Emollients and protectives	D02	22.1	25.3	28.7	29.9 (29.0-35.8)
13. Lipid modifying agents	C10	18.7	18.1	16.3	−12.9 (−13.6 to −12.1)
Statins	C10AA	18.2	17.6	15.8	−13.3 (−14.1 to −12.6)
14. Calcium channel blockers	C08	17.8	17.1	15.4	−13.0 (−13.8 to −12.3)
15. Mineral supplements	A12	17.6	18.7	20.5	16.8 (15.9-17.8)
Calcium	A12A	12.6	13.0	12.9	2.8 (1.8-3.8)
Potassium	A12B	5.6	6.3	8.1	45.3 (43.2-47.4)
16. Drugs used in diabetes	A10	15.1	15.3	15.4	2.2 (1.3-3.1)
Insulin and analogues	A10A	8.8	9.4	10.3	16.5 (15.1-17.9)
Oral blood glucose lowering drugs	A10B	8.6	8.2	7.4	−14.0 (−15.1 to −12.8)
17. Ophthalmologicals	S01	14.7	15.2	15.3	3.8 (2.9-4.8)
18. Drugs for obstructive airway diseases	R03	12.5	13.3	14.9	19.5 (18.3-25.7)
19. Antibacterials for systemic use	J01	11.5	13.1	20.0	74.3 (72.6-75.9)
20. Thyroid therapy	H03	10.5	10.8	10.9	4.4 (3.3-5.6)

ACE = angiotensin-converting enzyme; ATC = Anatomical Therapeutic Chemical classification system; CI = confidence interval.

*Drug classes are ranked by descending order, using the second level of the ATC (therapeutic subgroups, eg, N02 Analgesics). For some classes, details are also provided for the pharmacological subgroups (eg, N02A Opioids).

†Variation rates calculated as the relative increase or decrease in prevalence of use between the 12th month and the final month before death, in with their 95 CI.

Polypharmacy near the end of life should, however, not be thought of as a homogeneous phenomenon. Data presented in our article suggest that polypharmacy does not stem from a unique drug class but is in fact propelled by 5 different types of prescriptions, each addressing specific goals of care. Medications to alleviate the burden of

symptoms (eg, analgesics, loop-diuretics, anxiolytics) compose the first of these 5 categories. This is expected, because the need for comfort care and symptom management increases sharply as death approaches.[19] The second category includes drug regimens used in the long-term prevention of chronic diseases that pose no immediate danger. Hence we found that statins were rarely discontinued and were still prescribed to 16% of older adults during their last month of life. Although this figure is consistent with previous reports,[8,30] it raises serious concern: the clinical benefit of treatments drugs aiming at preventing cardiovascular diseases during the final month of life is at the very least questionable.[31,32] Medications used to control the evolution of potentially life-threatening or disabling comorbidities form a third distinct group of prescriptions (eg, oral antidiabetics, platelet aggregation inhibitors, thyroid therapy, antidementia drugs, and cardiac stimulants). The fourth group is drugs prescribed in an attempt to cure or slow the progression of the main life-limiting illness (eg, chemotherapy, immunosuppressants). Finally, drugs administered to counteract the current or anticipated adverse effects of other medications constitute a fifth group of prescriptions. The widespread use of potassium supplementation, proton-pump inhibitors, and laxatives close to death may reflect a "prescribing cascade" (ie, prescriptions prompted by the onset of symptoms induced by other medications rather than by the disease itself).[33]

To help clinicians assess the value and the appropriateness of drug treatments in a context of limited life expectancy, Holmes et al[34] recommended that 2 key questions be taken into account. First, is the patient's life expectancy longer than the time needed for the medication to achieve its benefit? Second, are the objectives of the prescribed medication in keeping with the goals of care that the physician and the patient discussed and agreed upon? This prescribing model relies on the idea that drug treatments should be adapted to mirror the course of the disease as the remaining life expectancy diminishes. In other words, physicians should consider discontinuing drugs that may be effective and otherwise appropriate but whose potential harms outweigh the benefits that patients can reasonably expect before death occurs. The process of deprescribing (ie, withdrawing medications with the aim of improving health outcomes[35,36]) is now supported by a growing body of evidence.[37] In a recent randomized, controlled trial including patients with $\leq$12 months of estimated life expectancy, researchers found no significant survival difference according to statin continuation/discontinuation and showed that quality of life was significantly improved in the group of patients that discontinued statins.[38] Whether this conclusion is applicable to other drug classes remains uncertain, because data regarding the safety of discontinuing preventative medications in the context of end-of-life care remain scarce.[39] One should also balance the potential lack of benefit of a certain drug with the possible collateral effects of its discontinuation. For instance, although there is considerable uncertainty about the efficacy and safety of antidementia agents in older adults reaching the end of life,[40] the discontinuation of these medications may have indirect negative consequences, such as an increased risk of institutionalization.[41]

At the end of life, the challenge of deprescribing drug treatments is amplified by the uncertainty inherent to survival predictions[42] and by the natural tendency of healthcare professionals and patients to believe that medical interventions are more effective than they actually are (a phenomenon described as the "therapeutic illusion"[43]). The frequent continuation of potentially futile treatments may also be the consequence both of a lack of communication and of insufficient shared decision making between patients and prescribers, out of fear that discussing issues surrounding the end of life would be perceived as a failure or that it would amount to "giving up."[44,45] To overcome this predicament, the process of deprescribing requires timely patient−family−physician dialogue about the risk/benefit ratio of medications, and close monitoring of symptoms during the following weeks. As the situation worsens, the goals of care should be frequently reassessed to ensure that the treatment target remains concordant with the patient's preferences. It is also essential that patients and their relatives receive clear information about their options in terms of palliative care, to counter the feeling of abandonment that they may experience when disease-directed treatments are withdrawn.[29,46]

Our study should be interpreted with caution, considering the following limitations. First, the Swedish Prescribed Drug Register only records prescription drugs dispensed at pharmacies. Over-the-counter medications and medications administered in hospitals or from drug store rooms in nursing homes are not reported in the register, leading to a potential underestimation of the actual drug exposure. However, approximately 86% of defined daily doses dispensed to the Swedish population annually are prescription drugs delivered through pharmacies and are therefore covered by the Swedish Prescribed Drug Register. Second, we could only estimate drug exposure with the assumption that patients use the dispensed medications at the prescribed rate; we could therefore not account for nonadherence to treatment. Additionally, we did not investigate whether drugs that were continued until the final month of life were deintensified in terms of dosage, which could correspond to a shift toward a palliative approach. Notwithstanding these methodologic restrictions, it is the first study investigating the burden of medications near the end of life in an entire population (ie, irrespective of the underlying disease or care setting).

CONCLUSIONS

Polypharmacy increases sharply throughout the last year of life of older adults. To reduce the burden of medications of questionable benefit in older adults with life-limiting illness, robust evidence about the benefit and safety of deprescribing is needed. Following the example set by Kutner et al[38] with

the statin discontinuation trial, future clinical trials should be conducted to evaluate the effects of withdrawing preventive medications in people with advanced illness. These findings should then be embedded into clinical guidelines, in the same manner that new evidence regarding the benefit and safety of initiating drug therapy is incorporated into current practice guidelines. However, because end-of-life situations are shaped by different disease trajectories, symptoms, and personal preferences, the goals of care vary considerably from one person to another. Future clinical practice guidelines should thus foster personalized decision making rather than promote the systematic discontinuation of medications according to a one-size-fits-all set of criteria.

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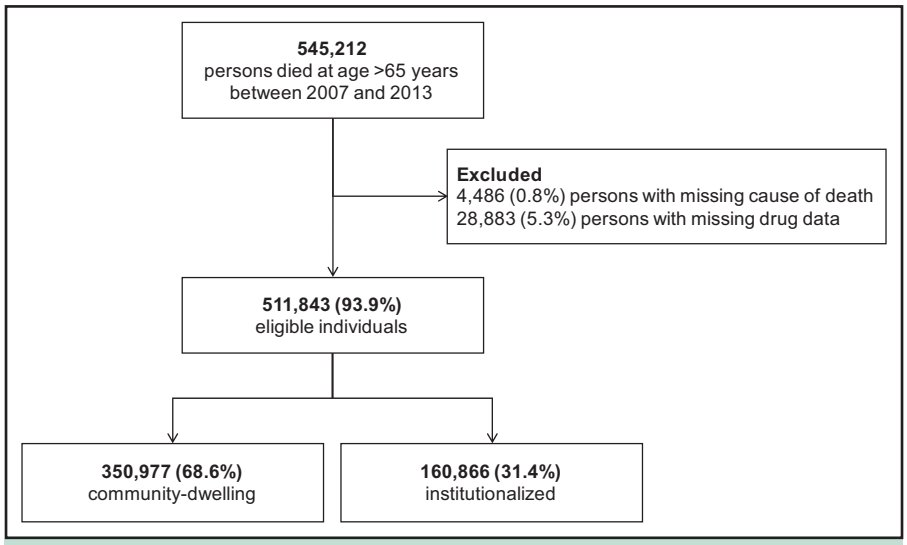
Authorship: LM conceived and designed the study, performed the statistical analysis, interpreted the data, drafted, and critically revised the manuscript. DLV, DR, and AC-L and interpreted the data and critically revised the manuscript. JF acquired, analyzed, and interpreted the data and critically revised the manuscript. KJ obtained funding, provided supervision, interpreted the data and, critically revised the manuscript. LM is the guarantors of the study and data integrity. All authors gave approval for the final version of the manuscript and agree to be accountable for all aspects of the work.

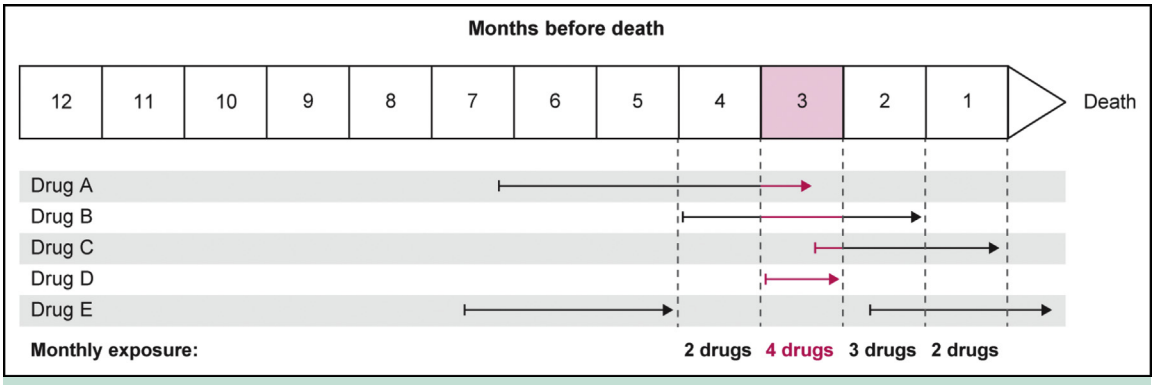
SUPPLEMENTARY DATA

Supplementary data accompanying this article can be found in the online version at http://dx.doi.org/10.1016/j.amjmed.2017.02.028.

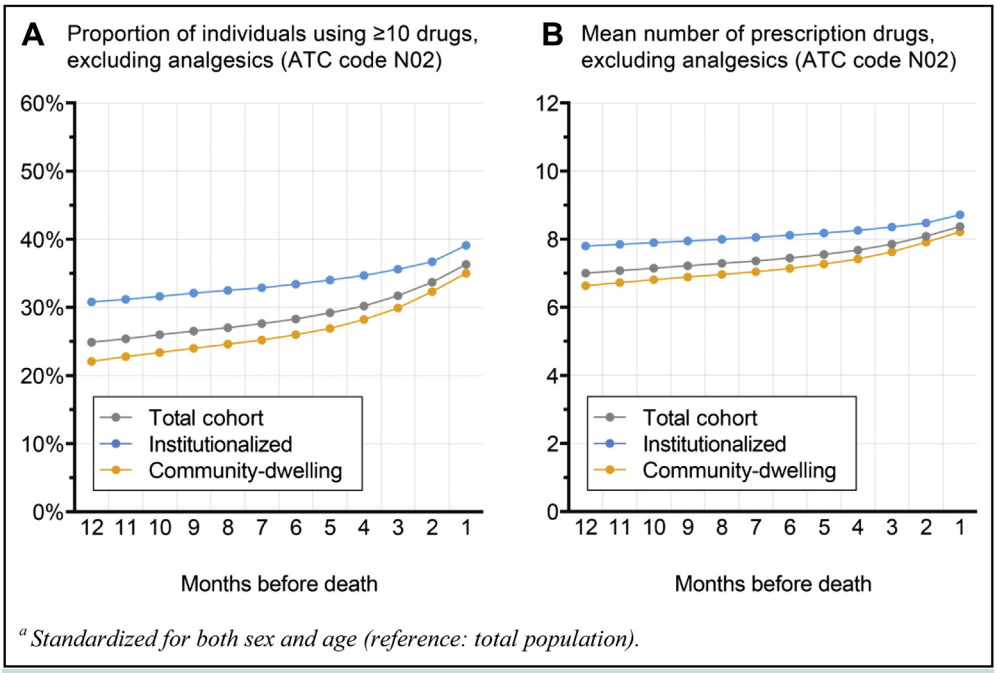
SUPPLEMENTARY DATA



Supplementary Figure 1 Study population flowchart.

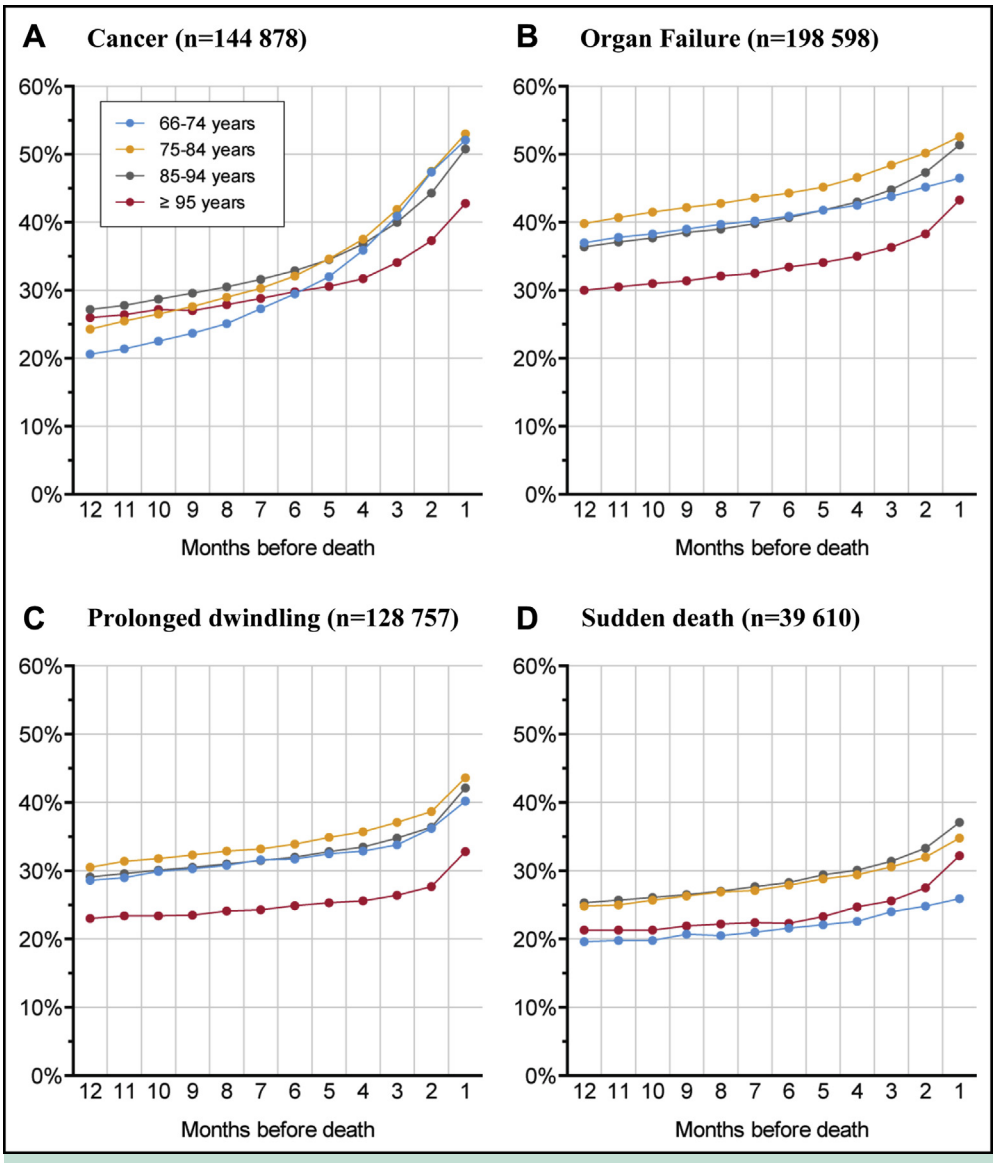


Supplementary Figure 2 Design of drug exposure calculation. Tick marks represent the date of drug dispensing ("start date"). Horizontal lines represent the estimated duration of drug exposure. Arrows represent the end of drug exposure ("end date").



[a] *Standardized for both sex and age (reference: total population).*

Supplementary Figure 3 Change in the number of nonanalgesic prescription drugs over the course of the last 12 months of life, by living arrangement. Standardized for both sex and age (reference: total population). ATC = Anatomical Therapeutic Chemical classification system.



Supplementary Figure 4 Polypharmacy (≥10 Drugs) over the course of the last 12 months of life of older people in Sweden, by illness trajectory and age at time of death.

Supplementary Table 1 Classification of Causes of Death into Illness Trajectories

Trajectory	ICD-10 Codes
1 — Cancer, leading to a short decline with evident terminal phase	
Neoplasm	C00-C26, C30-C34, C37-C41, C43-C58, C60-C85, C88, C90-C97, D00-D09, D32, D33, D37-D48
2 — Organ failure leading to long-term limitations with intermittent acute episodes	
Diabetes	E10-E14, G590, G632, H360, M142, N083
Other endocrinal diseases	E70-E72, E75-E77, E84-E85
Certain infectious and parasitic diseases	A520-A523, A527, A810, A812, B15-B19, B20-B24
Diseases of the blood	D60, D61, D69, D70, D752, D758, D86
Diseases of the cardiovascular system (including cerebrovascular diseases)	I231-I233, I238, I25, I50, I60-I64, I67, I688, I69, G46, I65, I66, I680-I682, I27, I42, I43, I51, I520, I70, I73, I74, I792, I970, I971, I978, I980, I981, I988
Diseases of the respiratory system (including abnormalities of breathing)	J40-J44, J47, J60-J62, J66, J701, J80, J841, J951-J953, J96, J980-J984, R060, R062-R065, R068
Diseases of the digestive system (including liver diseases)	K70-K77, K44, K50, K51, K55, K56, K85, K86, K871, K90
Diseases of the skin	L305, L40-L42, L44, L93, L945
Diseases of the musculoskeletal system	M360, M361, M05, M06, M13, M15, M21, M30-M35, M40-M43, M45-M51, M53, M54, M638, M80, M81, M820, M821, M843, M844, M86-M88, M907, M961
Diseases of the genitourinary system (including renal failure)	N02-N05, N11, N12, N136, N160, N18, N19, N25, N312, N318, N319, N82
Other (including congenital conditions)	Q01-Q06, Q078, Q079, Q20-Q28, Q31, Q33, Q40-Q45, Q60-Q68, Q714, Q75-Q79, Q850, Q86-87, Q89-Q93, Q95-Q97, Q99
3 — Prolonged dwindling, characterized by a progressive loss of both physical and cognitive capacities	
Alzheimer's disease	G30-G32
Mental and behavioral disorders	F00, F01, F02, F03, F05, F06, R54
Parkinson's disease	G20-G23
Multiple sclerosis	G35-G37
Other diseases of the nervous system	G10, G12, G70-G73, G03-G05, G07, G478, G518, G551, G608, G80-G83, G90-G99
4 — Sudden death	
None of the three trajectories above	

ICD-10 = International Classification of Diseases, 10th Revision.

Supplementary Table 2 Details of Diagnosis Codes and Drugs Used to Detect Chronic Conditions in the Last 2 Years of Life of Older People in Sweden

Chronic Disease	ICD-10 Codes	ATC Codes
Source(s) of data	National cause of death register (all contributing causes of death) National patient register (all inpatient and specialized outpatient diagnoses)	Swedish Prescribed Drugs Register
1. Allergy	J30.1-J30.4; J45.0; K52.2; L20; L23; L50.0; Z51.6	
2. Anemia	D50-D53; D55-D59 (excl. D56.3; D59.0; D59.2; D59.3; D59.6); D60-D64 (excl. D60.1; D61.1; D61.2; D62; D64.2)	B03A, B03XA
3. Asthma	J45	R03DC; R03BC
4. Atrial fibrillation	I48	
5. Autoimmune diseases	I73.1; L10 (excl. L10.5); L12; L40; L41; L93-L95; M30-M36 (excl. M32.0; M34.2; M35.7-M35.9; M36.0; M36.1; M36.2; M36.3)	D05
6. Blindness, visual loss	H54 (excl. H54.3); Z44.2; Z97.0	
7. Blood and blood forming organ diseases	D66-D69 (excl. D68.3; D68.4; D69.5); D71; D72.0; D73.0-D73.2; D74 (excl. D74.8); D75.0; D76.1; D76.3; D77; D80 (excl. D80.7); D81-D84; D86; D89 (excl. D89.1; D89.3)	
8. Bradycardias and conduction diseases	I44.1-I44.3; I45.3; I45.5; Z95.0	
9. Cardiac valve diseases	I05-I08; I09.1; I09.8; I34-I38; I39.0-I39.4; Q22; Q23; Z95.2-Z95.4	
10. Cataract and other lens diseases	H25-H28; Q12; Z96.1	
11. Cerebrovascular disease	G45; G46; I60-I64; I67; I69	
12. Chromosomal abnormalities	Q90-Q99	
13. Chronic infectious diseases	A15-A19; A30; A31; A50-A53 (excl. A51); A65-A67; A69.2; A81; B20-B24; B38.1; B39.1; B40.1; B57.2-B57.5; B65; B92; B94; J65; M86.3-M86.6	J04A, excl. J04AB01, J04AB02, J04AB03 and J04AC
14. Chronic kidney disease	I12.0; I13.0-I13.9; N01, N02, N04, N05; N07; N08; N11; N18.3-N18.9; Q60; Q61.1-Q61.9; Z90.5; Z94.0	
15. Chronic liver disease	B18; K70 (excl. K70.0; K70.1); K71.3-K71.5; K71.7; K72.1; K73; K74; K75.3-K75.8; K76.1; K76.6; K76.7; K77.8; Q44.6; Z94.4	
16. Chronic pancreas, biliary tract and gallbladder diseases	K80.0; K80.1; K80.2; K80.8; K81.1; K86 (excl. K86.2; K86.3; K86.9); Q44.0-Q44.5; Q45.0	A09AA02
17. Chronic ulcer of the skin	I83.0; I83.2; L89; L97; L98.4	
18. Colitis and related diseases	K52.0; K52.8; K55.1; K55.2; K57.2-K57.5; K57.8; K57.9; K58; K59.0; K59.2; K62 (excl. K62.0; K62.1; K62.5; K62.6); K63.4; K64 (excl. K64.5);	
19. COPD, emphysema, chronic bronchitis	J41-J44; J47	R03BB
20. Deafness, hearing loss	H80; H90; H91.1; H91.3; H91.9; Q16; Z45.3; Z46.1; Z96.2; Z97.4	
21. Dementia	F00-F03; F05.1; G30; G31	N06DA, N06DX01
22. Depression and mood diseases	F30-F34; F38; F39; F41.2	
23. Diabetes	E10; E11; E13; E14; E89.1	A10
24. Dorsopathies	M40-M43; M47-M53; Q67.5; Q76.4; Q76.1;	
25. Dyslipidemia	E78	
26. Ear, nose, throat diseases	H60.4; H66.1-H66.3; H70.1; H71; H73.1; H74.1; H81.0; H83.1; H83.2; H95; J30.0; J31-J33; J34.1-J34.3; J35; J37; J38.0; J38.6; K05.1; K05.3; K07; K11.0; K11.7; Q30-Q32; Q35-Q38	
27. Epilepsy	G40 (excl. G40.5)	
28. Esophagus, stomach and duodenum diseases	I85; I86.4; I98.2; I98.3; K21; K22.0; K22.2; K22.4; K22.5; K22.7; K23.0; K23.1; K25.4-K25.7; K26.4-K26.7; K27.4-K27.7; K28.4-K28.7; K29.3-K29.9; K31.1-K31.5; Q39; Q40; Z90.3	A02BX
29. Glaucoma	H40.1-H40.9	S01ED
30. Heart failure	I11.0; I13.0; I13.2; I27; I28.0; I42; I43; I50; I51.5; I51.7; I52.8; Z94.1; Z94.3	
31. Hematological neoplasms	C81-C96	
32. Hypertension	I10-I15	
33. Inflammatory arthropathies	M02.3; M05-M14; M45; M46.0; M46.1; M46.8; M46.9	M01CB

Supplementary Table 2 Continued

Chronic Disease	ICD-10 Codes	ATC Codes
34. Inflammatory bowel disease	K50; K51	A07E
35. Ischemic heart disease	I20-I22; I24; I25; Z95.1; Z95.5	C01DA, C01EB18
36. Migraine and facial pain syndromes	G43; G44.0-G44.3; G44.8; G50	N02C
37. Multiple sclerosis	G35	
38. Neurotic, stress-related and somatoform diseases	F40-F48 (excl. F43.0; F43.2)	
39. Obesity	E66	
40. Osteoarthritis and other degenerative joint diseases	M15-M19; M36.2; M36.3	
41. Osteoporosis	M80-M82	M05BA; M05BB; M05BX03; M05BX53
42. Other cardiovascular diseases	I09 (excl. I09.1; I09.8); I28.1; I31.0; I31.1; I45.6; I49.5; I49.8; I70-I72 (excl. I70.2); I79.0; I79.1; I95.0; I95.1; I95.8; Q20; Q21; Q24-Q28; Z95.8; Z95.9	
43. Other digestive diseases	K66.0; K90.0-K90.2; K91.1; K93; Q41-Q43; R15; Z90.4; Z98.0	
44. Other eye diseases	H02.2-H02.5; H04 (excl. H04.3); H05 (excl. H05.0); H10.4; H17; H18.4-H18.9; H19.3; H19.8; H20.1; H21; H31.0-H31.2; H31.8; H31.9; H33; H35.2-H35.5; H35.7-H35.9; H36; H47-H49 (excl. H47.0; H47.1; H48.1); H51; Q10-Q15 (excl. Q12); Z94.7	
45. Other genitourinary diseases	B90.1; N20.0; N20.2; N20.9; N21.0; N21.8; N21.9; N22; N30.1-N30.4; N31; N32.0; N32.3; N32.8; N32.9; N33; N35; N39.3; N39.4; N48.0; N48.4; N48.9; N70.1; N71.1; N73.1; N73.4; N73.6; N76.1; N76.3; N81; N88; N89.5; N90.5; N95.2; Q54; Q62.0-Q62.4; Q62.7; Q62.8; Q63.8; Q63.9; Q64.0; Q64.1; Q64.3-Q64.9; Z90.6; Z90.7; Z96.0	
46. Other metabolic diseases	E20-E31 (excl. E23.1; E24.2; E24.4; E27.3; E30); E34 (excl. E34.3; E34.4); E35 (excl. E35.0); E40-E46 (excl. E44.1); E64; E70-E72; E74-E77; E79 (excl. E79.0); E80 (excl. E80.4); E83-E89 (excl. E86; E87; E88.3; E89.0; E89.1); K90.3; K90.4; K90.8; K90.9; K91.2; M83; M88; N25	
47. Other musculoskeletal and joint diseases	B90.2; M21.2-M21.9; M22-M24; M25.2; M25.3; M35.7; M61; M65.2-M65.4; M70.0; M72.0; M72.2; M72.4; M75.0; M75.1; M75.3; M75.4; M79.7; M84.1; M89; M91; M93; M94; M96; M99; S38.2; S48; S58; S68; S78; S88; S98; T05; T09.6; T11.6; T13.6; T14.7; T90-T98; Q65; Q66; Q68; Q71-Q74; Q77; Q78; Q79.6; Q79.8; Q87; Z44.0; Z44.1; Z89.1-Z89.9; Z94.6; Z96.6; Z97.1	
48. Other neurological diseases	B90.0; D48.2; G04.1; G09-G14 (excl. G13.0; G13.1); G24-G26 (excl. G25.1; G25.4; G25.6); G32; G37; G51-G53 (excl. G51.0); G70; G71; G72.3-72.9; G73 (excl. G73.2-G73.4); G80-G83 (excl. G83.8); G90; G91; G93.8; G93.9; G95; G99; M47.1; Q00-Q07; Q76.0	
49. Other psychiatric and behavioral diseases	F04; F06; F07; F09; F10.2; F10.6; F10.7; F11.2; F11.6; F11.7; F12.2; F12.6; F12.7; F13.2; F13.6; F13.7; F14.2; F14.6; F14.7; F15.2; F15.6; F15.7; F16.2; F16.6; F16.7; F17.2; F17.6; F17.7; F18.2; F18.6; F18.7; F19.2; F19.6; F19.7; F50; F52; F60-F63; F68; F70-F89; F95; F99	N07BB
50. Other respiratory diseases	B90.9; E66.2; J60-J67; J68.4; J70.1; J70.3; J70.4; J84; J92; J94.1; J95.3; J95.5; J96.1; J98 (excl. J98.1); Q33; Q34; Z90.2; Z94.2; Z94.3; Z96.3	
51. Other skin diseases	L13; L28; L30.1; L43 (excl. L43.2); L50.8; L58.1; L85; Q80; Q81; Q82.1; Q82.2; Q82.9	
52. Parkinson and parkinsonism	G20-G23 (excl. G21.0)	N04BA; N04BX
53. Peripheral neuropathy	B91; G54-G60; G62.8; G62.9; G63 (excl. G63.1); M47.2; M53.1; M54.1	
54. Peripheral vascular disease	I70.2; I73 (excl. I73.1; I73.8); I79.2; I79.8	B01AC23
55. Prostate diseases	N40; N41.1; N41.8	G04C (excl. G04CB)
56. Schizophrenia and delusional diseases	F20; F22; F24; F25; F28	
57. Sleep disorders	G47; F51.0-F51.3	

Supplementary Table 2 Continued

Chronic Disease	ICD-10 Codes	ATC Codes
58. Solid neoplasms	All C (excl. C81-C96); D00-D09; D32.0; D32.1; D32.9; D33.0-D33.4; Q85	
59. Thyroid disease	E00-E03 (excl. E03.5); E05; E06.2; E06.3; E06.5; E07; E35.0; E89.0	H03AA; H03B
60. Venous and lymphatic diseases	I78.0; I83; I87; I89; I97.2; Q82.0	

ATC = Anatomical Therapeutic Chemical classification system; excl. = excluding; ICD-10 = International Classification of Diseases, 10th Revision.

Adapted with the authors' permission from Calderón-Larrañaga A, Vetrano DL, Onder G, et al. Assessing and measuring chronic multimorbidity in the older population: a proposal for its operationalization. *J Gerontol A Biol Sci Med Sci*. 2016 December 21.

Supplementary Table 3 Change in the Likelihood of Being Exposed to ≥10 Prescription Drugs (Excluding Analgesics) During the Last Year of Life of Older Adults in Sweden, 2007-2013

		Polypharmacy (Excluding Analgesics), %		Last Month vs 12th Month Before Death	
Parameter	N Total	12th Month Before Death	Last Month Before Death	Variation Rate, % (95% CI)*	Odds Ratio (95% CI)†
Total cohort	511,843	24.4	36.0	47.3 (46.5-48.2)	1.74 (1.72-1.75)
Sex					
Men	234,023	22.8	35.9	57.4 (56.0-58.9)	1.90 (1.87-1.92)
Women	277,820	25.8	36.0	39.9 (38.7-41.3)	1.62 (1.60-1.64)
Age at time of death (y)					
66-74	75,749	22.4	36.8	63.9 (61.3-66.6)	2.01 (1.97-2.06)
75-84	163,355	26.3	39.1	48.8 (47.3-52.3)	1.80 (1.78-1.83)
85-94	227,391	24.9	35.6	43.0 (41.7-44.3)	1.67 (1.65-1.69)
≥95	45,348	18.7	25.4	35.9 (32.5-39.3)	1.48 (1.43-1.53)
Living arrangement					
Community-dwelling	350,977	22.2	35.5	59.5 (58.3-63.8)	1.92 (1.90-1.94)
Institutionalized	160,866	29.2	37.1	27.1 (25.8-28.3)	1.43 (1.41-1.45)
Level of education‡					
Primary education	267,319	24.9	36.7	47.0 (45.8-48.2)	1.74 (1.72-1.76)
Secondary education	175,083	24.5	36.2	47.5 (45.9-49.8)	1.74 (1.72-1.77)
Tertiary education	45,122	22.7	34.5	52.0 (48.8-55.3)	1.79 (1.74-1.85)
Illness trajectory§					
Cancer	144,878	19.1	36.5	91.7 (89.3-94.2)	2.45 (2.40-2.49)
Organ failure	198,598	31.3	42.1	34.8 (33.6-35.9)	1.60 (1.58-1.62)
Prolonged dwindling	128,757	21.6	28.9	33.8 (32.0-35.6)	1.48 (1.45-1.50)
Sudden death	39,610	18.8	26.0	38.3 (34.7-42.3)	1.52 (1.47-1.57)
No. of chronic diseases					
0	5544	4.5	6.6	44.8 (23.9-69.3)	1.48 (1.25-1.75)
1	34,136	5.4	9.5	77.2 (67.7-87.3)	1.85 (1.75-1.97)
2	60,498	8.9	15.2	71.7 (66.3-77.2)	1.85 (1.78-1.91)
3	74,172	12.6	21.6	71.2 (67.2-75.2)	1.91 (1.86-1.96)
4	76,265	17.1	28.9	69.3 (66.1-72.6)	1.98 (1.93-2.02)
≥5	261,228	36.4	51.0	40.0 (39.1-46.9)	1.82 (1.80-1.84)

*Variation rates indicate the relative change in prevalence of polypharmacy (≥10 prescription drugs excluding analgesics) between the 12th month and the final month before death.

†Odds ratio computed by the mean of logistic regression models including polypharmacy (≥10 prescription drugs excluding analgesics) as a binary dependent variable and time (last month before death vs 12th month before death) as sole independent variable. Clustered standard errors at the individual level were used to account for correlation of observations within groups.

‡Missing values for level of education: 24,319 (4.7% of the total cohort).

§Illness trajectories were constructed using all the diagnoses mentioned on the death certificates (ie, both underlying and contributing causes of death).

Supplementary Table 4 Factors Associated with Change in the Number of Prescription Drugs (Excluding Analgesics) During the Last Year of Life of Older Adults in Sweden, 2007-2013

Factor	N Total	No. of Prescription Drugs, Mean (SD)		Mean Difference (95% CI)	Factor × Time, Adjusted β (95% CI)*
		12th Month Before Death	Last Month Before Death		
Total cohort	511,843	6.9 (4.1)	8.3 (4.2)	1.40 (1.40-1.41)	—
Sex					
Men	234,023	6.7 (4.0)	8.3 (4.2)	1.62 (1.61-1.63)	Ref
Women	277,820	7.1 (4.0)	8.4 (4.2)	1.22 (1.21-1.24)	−0.39 (−0.40 to −0.37)
Age at time of death (y)					
66-74	75,749	6.3 (4.6)	8.3 (4.7)	2.01 (1.98-2.04)	Ref
75-84	163,355	7.1 (4.2)	8.6 (4.4)	1.56 (1.54-1.58)	−0.45 (−0.48 to −0.42)
85-94	227,391	7.1 (3.8)	8.3 (4.0)	1.21 (1.20-1.22)	−0.80 (−0.83 to −0.77)
≥95	45,348	6.5 (3.5)	7.3 (3.6)	0.82 (0.79-0.84)	−1.19 (−1.23 to −1.15)
Living arrangement					
Community-dwelling	350,977	6.6 (4.1)	8.3 (4.3)	1.65 (1.64-1.66)	Ref
Institutionalized	160,866	7.6 (3.9)	8.5 (4.0)	0.86 (0.85-0.88)	−0.79 (−0.81 to −0.77)
Level of education†					
Primary education	267,319	7 (4.0)	8.4 (4.2)	1.40 (1.39-1.41)	Ref
Secondary education	175,083	6.9 (4.1)	8.3 (4.3)	1.43 (1.42-1.45)	0.03 (0.01 to 0.06)
Tertiary education	45,122	6.7 (4.1)	8.1 (4.3)	1.47 (1.43-1.50)	0.07 (0.03-0.10)
Illness trajectory‡					
Cancer	144,878	6.1 (4.0)	8.3 (4.3)	2.24 (2.22-2.26)	Ref
Organ failure	198,598	7.8 (4.2)	9.0 (4.4)	1.24 (1.22-1.25)	−1.01 (−1.03 to −0.99)
Prolonged dwindling	128,757	6.8 (3.6)	7.7 (3.8)	0.84 (0.83-0.86)	−1.39 (−1.42 to −1.37)
Sudden death	39,610	6.2 (3.9)	7.2 (4.0)	1.00 (0.97-1.02)	−1.25 (−1.29 to −1.21)
No. of chronic diseases					
0	5544	4.1 (2.9)	4.6 (2.9)	0.57 (0.52-0.63)	Ref
1	34,136	4.2 (3.0)	5.2 (3.1)	1.03 (1.00-1.05)	0.48 (0.37-0.59)
2	60,498	4.9 (3.2)	6.1 (3.3)	1.23 (1.21-1.26)	0.67 (0.57-0.78)
3	74,172	5.6 (3.4)	6.9 (3.5)	1.35 (1.32-1.37)	0.78 (0.68-0.89)
4	76,265	6.3 (3.5)	7.7 (3.6)	1.46 (1.44-1.48)	0.98 (0.78-0.99)
≥5	261,228	8.4 (4.1)	9.9 (4.2)	1.51 (1.50-1.53)	0.93 (0.83-1.04)

CI = confidence interval; SD = standard deviation.

*β-Coefficients computed by the mean of generalized estimating equation models with identity link functions at the individual level and unstructured correlations. The total number of distinct prescription drugs excluding analgesics was entered as continuous dependent variable with Gaussian distribution, while including all presented individual characteristics as independent variables. β-Coefficients for the interaction with time can be interpreted as the rate of change between the 12th month and the final month before death, compared with the reference category.

†Missing values for level of education: 24,319 (4.7% of the total cohort).

‡Illness trajectories were constructed using all the diagnoses mentioned on the death certificates (ie, both underlying and contributing causes of death).

Supplementary Table 5 Prevalence of the 20 Most Commonly Used Prescription Drug Classes During the Last Month of Life of Older People in Sweden, by Age (2007-2013)

Rank, Drug Class (ATC Code)*	Prevalence, %			
	66-74 y (N = 75,749)	75-84 y (N = 163,355)	85-94 y (N = 227,391)	≥95 y (N = 45,348)
1. Antithrombotic agents (B01)	44.2	54.9	57.5	48.0
Vitamin K antagonists (B01AA)	7.0	9.1	5.9	1.5
Heparin group (B01AB)	9.9	5.9	3.6	2.5
Platelet aggregation inhibitors (B01AC)	30.9	43.5	50.5	45.3
2. Diuretics (C03)	39.5	49.7	58.6	60.3
Low-ceiling diuretics (C03A-C03B)	4.9	5.8	5.2	3.9
High-ceiling diuretics (C03C)	31.5	41.8	51.4	54.1
Potassium-sparing agents (C03D)	11.9	12.2	12.3	11.5
3. Analgesics (N02)	55.7	58.4	63.0	66.9
Opioids (N02A)	42.7	38.8	37.2	37.0
Other analgesics (N02B)	38.9	46.0	53.2	57.7
4. Psycholeptics (N05)	48.4	49.7	52.6	54.7
Antipsychotics (N05A)	9.4	11.2	12.2	12.0
Anxiolytics (N05B)	26.5	25.6	26.8	29.2
Hypnotics and sedatives (N05C)	34.0	33.8	35.1	35.5
5. β-Blocking agents (C07)	37.7	43.5	42.5	30.4
6. Drugs acting on the renin-angiotensin system (C09)	31.9	34.5	29.8	17.8
ACE inhibitors (C09A-C09B)	20.8	23.5	21.6	13.6
Angiotensin II receptor antagonists (C09C-C09D)	12.2	11.8	8.6	4.3
7. Anti-anemic preparations (B03)	21.9	31.8	39.7	39.8
Iron preparations (B03A)	6.3	9.4	12.2	11.4
Vitamin B12 and folic acid (B03B)	16.9	25.5	32.9	33.8
8. Psychoanaleptics (N06)	25.4	32.9	35.7	28.5
Antidepressants (N06A)	24.3	29.8	32.7	27.2
Anti-dementia drugs (N06D)	2.1	6.0	5.8	2.3
9. Drugs for constipation (A06)	35.8	38.1	41.7	44.3
10. Drugs for acid related disorders (A02)	42.8	36.9	32.7	27.5
11. Cardiac therapy (C01)	15.2	23.0	27.9	26.2
Cardiac glycosides (C01A)	4.9	7.9	9.6	8.8
Vasodilators used in cardiac diseases (C01D)	10.4	16.2	20.2	19.3
12. Emollients and protectives (D02)	19.5	25.1	32.4	38.7
13. Lipid modifying agents (C10)	25.0	23.5	11.0	1.9
Statins (C10AA)	24.2	22.9	10.7	1.7
14. Calcium channel blockers (C08)	16.5	17.1	14.8	10.5
15. Mineral supplements (A12)	18.0	20.5	21.8	18.3
Calcium (A12A)	10.7	13.2	14.0	10.6
Potassium (A12B)	7.0	7.8	8.7	8.2
16. Drugs used in diabetes (A10)	20.8	19.0	12.7	6.8
Insulin and analogues (A10A)	14.6	12.8	8.2	4.2
Oral blood glucose lowering drugs (A10B)	10.2	9.1	6.0	3.2
17. Ophthalmologicals (S01)	7.2	12.3	18.6	23.5
18. Drugs for obstructive airway diseases (R03)	19.0	18.0	12.5	8.9
19. Antibacterials for systemic use (J01)	20.0	19.7	20.1	20.1
20. Thyroid therapy (H03)	7.9	10.4	12.1	11.8

ACE = angiotensin-converting enzyme; ATC = Anatomical Therapeutic Chemical classification system.

*Drug classes are ranked by descending order, using the second level of the ATC (therapeutic subgroups, eg, N02 Analgesics). For some classes, details are also provided for the pharmacologic subgroups (eg, N02A Opioids).