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Changes in Drug Use and Polypharmacy After the Age of 90: A Longitudinal Study of the Danish 1905 Cohort

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Abstract

BACKGROUND—The number of drugs used after age 90 is often found to plateau or decrease in cross-sectional studies. However, little is known about the longitudinal development of drug use among very old people.

DESIGN—Longitudinal cohort study with waves in 1998, 2000, 2002, and 2005.

SETTING—Nationwide study in Denmark.

PARTICIPANTS—All living Danes born in 1905 were approached in 1998, 2262 individuals responded at baseline.

MEASUREMENTS—Self-reported use of regularly taken drugs. Mean and median number of drugs, and growth curve models were used to identify the change in number of drugs as the cohort aged from 92 to 100 years.

RESULTS—The within-person use of drugs increased with age for both women (0.19 per year; 95% CI: 0.15–0.24) and men (0.15 per year; 95% CI: 0.06–0.24). Persons leaving the study

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prematurely had higher baseline values, and a steeper increase in their annual use of drugs. The population-level mean number of drugs increased from baseline (3.6 drugs) to the first follow-up (4.1 drugs), but thereafter remained stable at about 4 drugs. Women used more drugs than men at all waves.

CONCLUSION—In this first longitudinal study of drug use among nonagenarians, we find that individuals use an increasing number of drugs as they age, also after the age of 90. This increase is difficult to detect in cross-sectional analyses of the population-level mean. More efforts to understand what is reasonable prescribing at these high ages are needed.

Keywords

Aged; drug use; longitudinal; nonagenarians; polypharmacy

INTRODUCTION

The prescription of drugs is the most common treatment for health problems at older ages [1], and after age 80 more than half of remaining life can be expected to be spent with polypharmacy [2]. However, little is known about the longitudinal development of drug use at these high ages.

Longitudinal studies of ‘younger old’ populations suggest that the number of used drugs increase with age, the increase has been estimated to be between 0.04 to 0.48 drugs annually [3–9]. Nonagenarians’ longitudinal pattern of drug use may be different from that of younger older adults, because cross-sectional data indicate that the number of used drugs increase from middle-age to old age, but tends to stagnate or decrease after approximately 90 years of age [10–14]. Further, women tend to use more drugs than men [7, 15], although the gender differences seems to decline at the very old ages [14].

Two hypotheses have been proposed to explain why nonagenarian’s drug use does not increase with age in cross-sectional studies. One suggestion is that prescribers deliberately avoid polypharmacy and are disinclined to start up new therapies as frailer individuals approaches death, since physiological changes make older people more sensitive to drugs [16]. Alternatively, it can be due to a healthy survivor effect. This would entail, individuals with poorer health using many drugs having a higher mortality, and will thus successively leave the cohort as they die, generating a sample of more robust individuals with a lower drug use.

Our hypothesis is that drug use continues to increase among nonagenarians. To address this we follow the Danish 1905 cohort, as they aged from 92/93 to 99/100 years. Population-level means of drug use are compared to the within-person change in drug use. Thus, we aim to investigate i) the population-level mean and median number of drugs used between ages 92 to 100 years ii) the within-person change in number of drugs used as individuals age from 92 to a 100 years.

METHODS

Study population

The Danish 1905 cohort was first contacted in 1998 and reassessed in 2000, 2003 and 2005 (age 92/93 to 99/100 years). All Danes born in 1905, irrespectively of living situation (institution or community-living) and health, were contacted for the study (n=3600). The response rate at the first contact in 1998 was 63% (n=2262) and in the latter surveys between 74% and 78% [17]. About 10% did not respond to the question about drug use at each wave (item non-response), we restricted the study population to the respondents with information on drug use at baseline (n=1,988). Proxy interviews, with a relative or caregiver, were performed if the respondent were unable to participate by themselves. A more comprehensive description of the cohort is available elsewhere [18, 19]. A flow chart of the 1905 cohort is depicted in Figure 1.

Drug use was assessed by self-reported information on regularly used drugs at each wave. Respondents were asked to present a list, or show their drug storage to avoid recall bias. We calculated the number of used drugs, including both prescription drugs and over-the-counter drugs, but excluding all alternative drugs and vitamins. All drugs were coded according to the Anatomical and Therapeutical Classification system as recommended by WHO [20].

Polypharmacy was classified as the concomitant use of five or more drugs [21].

Statistical analysis

Unweighted mean and median numbers of drugs are presented in Table 1. Multilevel growth curve models were performed to study the within-person changes in drug use over time (Table 1). Time was introduced as number of years from baseline to reflect annual change in drug use. Higher level polynomials were tested but only improved the fit of the model marginally. Models were performed separately for the attrition groups leaving the study at different waves. Ordinary linear regression was performed to estimate the general population-level change in number of used drugs. Number of used drugs is non-normally distributed variable why residual plots were used to assess that the normality assumption of the residuals was fulfilled.

Adjustment for drop-out (and item non-response) was implemented using inverse probability weighting for the within-person and population-level change. Weights were not applied for the loss to follow-up by death, because weighting for mortality will entail making inference about an “immortal population” [22]. Inverse probability weighting adjusts for drop-outs by weighting the person’s response at each wave by the inverse of the probability of participation for an individual having the same number of drugs as that person at the previous wave. The inverse probability weighting was only based on the number of used drugs and the procedure was done as described by Dufouil et al. [22]. All results are presented separately for women and men.

RESULTS

At baseline, 1,998 persons 92/93 year old had information about drug use, only 7% (n=146) of these were still participating in the last wave of the survey. The proportion of women in the study population increased from 75% (n=1483) at baseline to 84% (n=123) at last follow up.

About 18% (n=361) were interviewed via a proxy, and 27% (n=545) were living in an institution at baseline. Proxy respondents used fewer drugs than non-proxy respondents at baseline. Individuals living in institution used more drugs than persons living in the community. In the total sample 34% were on polypharmacy at baseline, compared to 40% at the last follow-up (not shown).

Figure 2 illustrates the mean number of used drugs at each wave (solid lines) and the dashed lines gives the previous means for all the responders in wave two, three and four respectively. In the complete sample, the mean number of drugs increased from baseline (3.6 drugs) to the first follow-up but remained stable at around 4 drugs thereafter. Women used more drugs than men at all waves of the survey. For women, the mean number of drugs increased from baseline (3.7 drugs) to 4.3 drugs at age 100 years. For men, the mean number of drugs also increased initially, and thereafter declined to be lower among 100 year olds (3.0 drugs) than at baseline (3.4 drugs). All responders from wave two, three and four (dashed lines) increased their use of drugs from baseline, albeit with a lower mean of drugs than the population mean at the previous waves. The only response group who did not show a clear increase in their use of drugs from baseline, was men responding up to the last follow-up of the survey. The medians presented in Table 1 show similar patterns.

The annual within-person change in mean drug use when all cohort members were included was 0.21 for women and 0.24 for men (Table 1). Women surviving to the last survey did also experience a within-person increase in the number of drugs (β : 0.18). For the surviving men the regression estimate was also positive, but the confidence intervals included zero. Earlier exit from the study seem to be associated with a steeper annual increase of drugs used, although confidence intervals are mostly overlapping.

Women increased their population-level drug use with 0.10 drugs annually, while drug use by men did not show a change over time. Applying inverse probability weighting for drop-outs, had a negligible effect on the population means and the change over time.

As a sensitivity analysis we reran the analyses without baseline proxy respondents. When excluding the proxy respondents the mean use of drugs was higher at baseline, but the within-persons estimate changed only slightly (second decimal for the regression estimates) (not shown).

DISCUSSION

This is to our knowledge the first longitudinal study of drug use among nonagenarians; we follow a nation-wide cohort of Danes as they age from 92/93 to 99/100 years. We found that both men and women experienced a within-person increase in their use of drugs also at these

very high ages. Participants exiting the study prematurely, due to drop out or death, used more drugs at baseline and tended to have a faster increase in their use of drugs. When only considering the population-level means at each wave, the increase was attenuated. Our results suggest that individual drug use continue to increase among nonagenarians and that this is difficult to capture in cross-sectional studies of drug use.

In line with our hypothesis that nonagenarians would use an increasing number of drugs as they aged, we found a within-person increase of 0.21 drugs annually for women and 0.24 for men. This confirms earlier longitudinal studies of drug use, in samples of younger older adults, suggesting an increase of 0.04 to 0.48 drugs annually [3–9]. Possibly, the stagnation or decrease in drug use among nonagenarians often found in cross-sectional studies [10–14] (similar to our results for the population-level mean) can likely be attributed to a healthy survivor effect: as the extensive drug users leave the cohort, the population means are kept down. At these very high ages, the decrease in drug use due to selective mortality and dropout among the extensive drug users is large enough to offset the individual level increase in drug use experienced by the less extensive drug users. Similar results have been found previously for independence, disability, depression, and physical and cognitive function in studies of nonagenarians [17, 23].

The groups leaving the study prematurely had a steeper annual increase in the use of drugs and higher baseline levels of drug use. This indicates that drug consumption is indeed increasing when people are approaching death. Thus, we find little support for a more palliative approach to prescribing taking place in this cohort, if this would entail the practice of de-prescribing and an inclination to reduce polypharmacy at end of life [16]. The only subgroup that did not experience an increased use of drugs, neither on the population-level or within-person, was men surviving to the last follow-up. The results of that specific subgroup should be regarded with caution because of the small sample size, but other longitudinal studies have also identified subgroups of men who do not seem to have an age-increase in the level of poor health at very high ages [24, 25].

We found that women used more drugs than men, which is in line with earlier research [14, 15]. However, less is known about the gender differences in the longitudinal development of drug use in older women and men. We found that both women and men experience an increase in the number of drugs used on an individual level.

The main strength of this study is that we follow a complete nation-wide cohort of nonagenarians, including people living in institutions and being cognitively impaired. As in all longitudinal studies of the older population many people are lost to follow-up because of drop-out and death. The main reason for loss to follow-up in this study was death. We applied inverse probability weighting to adjust for drop-out; this yielded only minor changes to the results.

A potential limitation with the study is the self-reported measure of drug use. For this cohort, it has been validated that self-reported drug use yield a slightly lower number of drugs than extracting the information from the Danish Prescription Medicine Registry [26]. However, it is unclear if the lower use of drugs from self-reports are due to underreporting or

secondary non-adherence. Some evidence suggest that proxy responders tend to underreport drug use [27], and proxy respondents had a lower drug use than self-responders at baseline in our study. Hence we performed a sensitivity analysis without the proxy responders at baseline, this did not lead to a substantial change in the results. Thus, we present our analysis including the proxy respondents in order to keep the nation-wide cohort intact. About 10% of the responders did not report their drug use at each wave. We do not know the reason for non-response for this item, and it is unclear how this might affect our results. Over time, people are using more drugs in most countries [28, 29], the increasing number of drugs used in this study can partly be due to period effects. Given that drug use patterns are time and country-specific; our results might not be directly generalizable to other countries with different health care systems and to different time periods.

In sum, we found that the nonagenarians use an increasing number of drugs as they age on an individual level. Whether it is good clinical practice to increase drug use also after 90 years of age can be debated. On one hand, it suggests that drug treatment is regularly updated. On the other hand, increased sensitivity to drugs leads to a higher risk of unwanted consequences with advancing age. Future studies should investigate which drugs are introduced, and what the mechanisms are leading to a higher use of drugs, also at very high ages.

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Figure 1.

Flow Chart of the Danish 1905 Cohort. Centered Boxes Gives the Number of Participants at Each Wave, and Number (%) of Missing Information on Drug Use (DU). The Number (%) of Dead and Drop out Between the Waves Are Reported in the Right and Left Boxes.

Figure 2.
Mean Number of Used Drugs. Solid Lines Depict the Mean Number of Drugs at Each Wave for All Responders. Dashed Lines Depict the “Historic” Mean for all Responders in Second, Third and Fourth Wave, Respectively.

Table 1

Longitudinal Assessment of Drug Use, Means with Standard Deviation (SD), Medians with Interquartile Range (IQR) and Regression Estimates With 95% Confidence Intervals (95% CI) of Annual Change in Number of Drugs in the Danish 1905 Cohort

Women	1998 (age 92/93)				2000 (age 94/95)				2003 (age 97/98)				2005 (age 99/100)				n ^a	Annual change ^d		
	Mean	95% CI	Median	IQR	Mean	95% CI	Median	IQR	Mean	95% CI	Median	IQR	Mean	95% CI	Median	IQR		β	95% CI	
Baseline only	3.9	(3.7–4.1)	4	(1–6)													726	-		
Baseline plus 1 follow-up	3.6	(3.4–3.9)	3	(2–5)	4.4	(4.1–4.6)	4	(2–6)									439	0.37	(0.25–0.50)	
Baseline plus 2 follow-ups	3.2	(2.9–3.5)	3	(1–5)	3.9	(3.5–4.3)	3	(2–5)	4.3	(4.0–4.7)	4	(2–6)					195	0.22	(0.15–0.30)	
Baseline plus 3 follow-ups	3.1	(2.7–3.5)	3	(2–4)	3.6	(3.1–4.0)	3	(2–5)	3.7	(3.2–4.2)	3	(2–5)	4.3	(3.8–4.8)	4	(2–6)	123	0.18	(0.10–0.25)	
All participants																	1483	0.21	(0.17–0.26)	
Population mean	3.7	(3.5–3.8)			4.1	(3.9–4.3)			4.1	(3.8–4.4)			4.3	(3.8–4.8)				Population-level ^c	0.10	(0.05–0.15)
Population mean, weighted ^d	3.7	(3.5–3.8)			4.1	(3.9–4.3)			4.1	(3.8–4.4)			4.4	(3.9–4.9)					0.10	(0.05–0.15)
Participants no.	1483				746				316				118							

Men	1998 (age 92/93)				2000 (age 94/95)				2003 (age 97/98)				2005 (age 99/100)				n ^a	Annual change		
	Mean	95% CI	Median	IQR	Mean	95% CI	Median	IQR	Mean	95% CI	Median	IQR	Mean	95% CI	Median	IQR		β	95% CI	
Baseline only	3.7	(3.4–4.0)	3	(1–5)													296	-		
Baseline plus 1 follow-up	3.1	(2.8–3.5)	3	(1–4)	4.0	(3.6–4.5)	4	(2–6)									138	0.52	(0.30–0.74)	
Baseline plus 2 follow-ups	2.9	(2.3–3.6)	2.5	(1–4)	3.7	(2.9–4.4)	3	(2–5)	4.0	(3.2–4.8)	3	(2–6)					48	0.19	(0.03–0.34)	
Baseline plus 3 follow-ups	2.7	(1.8–3.7)	2	(1–5)	3.2	(2.3–4.2)	2	(1–5)	2.8	(2.1–3.5)	2	(1–4)	3.0	(2.0–3.9)	2	(1–5)	23	0.05	(–0.09–0.19)	
All participants																	505	0.24	(0.13–0.35)	
Population mean	3.4	(3.2–3.6)			3.9	(3.5–4.3)			3.5	(3.0–4.1)			3.0	(2.0–3.9)				Population-level ^c	0.01	(–0.08–0.10)
Population mean, weighted ^d	3.4	(3.2–3.6)			3.9	(3.5–4.3)			3.6	(3.0–4.1)			3.1	(2.1–4.1)					0.01	(–0.08–0.10)
Participants no.	505				215				78				30							

^aThe n changes between the waves due to missing information on drug use between the waves (Figure 1)

^bAnnual within-person change from growth curve models to estimate the intra-individual change

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$\hat{p}_j$ inverse probability weighting
Regression estimate from a standard linear regression to estimate the change