Changes in Drug Use and Polypharmacy After the Age of 90

A Longitudinal Study of the Danish 1905 Cohort

Wastesson, Jonas W.; Oksuzyan, Anna; von Bornemann Hjelmborg, Jacob; Christensen, Kaare

Published in:
Journal of the American Geriatrics Society

DOI:
10.1111/jgs.14416

Publication date:
2017

Document version:
Accepted manuscript

Citation for pulished version (APA):
Wastesson, J. W., Oksuzyan, A., von Bornemann Hjelmborg, J., & Christensen, K. (2017). Changes in Drug Use and Polypharmacy After the Age of 90: A Longitudinal Study of the Danish 1905 Cohort. *Journal of the American Geriatrics Society*, *65*(1), 160-164. https://doi.org/10.1111/jgs.14416

HHS Public Access

Author manuscript

J Am Geriatr Soc. Author manuscript; available in PMC 2018 January 01.

Published in final edited form as:

J Am Geriatr Soc. 2017 January ; 65(1): 160–164. doi:10.1111/jgs.14416.

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

Jonas W. Wastesson, PhD[1], **Anna Oksuzyan, MD, PhD**[2], **Jacob von Bornemann Hjelmborg, PhD**[3], and **Kaare Christensen, MD, PhD**[1,3,4,5]

[1]Max-Planck Odense Center on the Biodemography of Aging, Unit of Epidemiology, Biostatistics and Biodemography. University of Southern Denmark

[2]Max Planck Institute for Demographic Research, Konrad-Zusse-Str. 1, 18057 Rostock, Germany

[3]Unit of Epidemiology, Biostatistics and Biodemography, Dept of Public Health. University of Southern Denmark

[4]Danish Aging Research Center, Unit of Epidemiology, Biostatistics and Biodemography. University of Southern Denmark

[5]Department of Clinical Biochemistry and Pharmacology and Department of Clinical Genetics, Odense University Hospital, Odense, Denmark

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

Corresponding author: Jonas Wilhelm Wastesson, Epidemiologi, Biostatistik og Biodemografi, J.B. Winsløws Vej 9B st tv. DENMARK, telephone: +45 24 25 21 73, fax +45 (0)8 690 59 54, jonas.wastesson@ki.se. Alt. corresponding author: Kaare Christensen, kchristensen@health.sdu.dk.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Author contributions: Wastesson, Christensen: study concept. Wastesson: data analysis. Wastesson: preparation of first draft. All authors: comments on first draft, critical input, interpretation of data and approval of final version of the manuscript

Sponsor's Role: The financial sponsors played no part in the design, execution, analysis and interpretation of data, or writing of the study.

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 then 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 Theraputical 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.

Acknowledgments

Funding: This work was supported by the US National Institutes of Health—National Institute on Aging [grant number P01 AG08761], the Danish National Research Foundation, and the VELUX Foundation.

References

1. Rochon PA, Gurwitz JH. Optimising drug treatment for elderly people: the prescribing cascade. BMJ. 1997; 315:1096–1099. [PubMed: 9366745]
2. Wastesson JW, Canudas-Romo V, Lindahl-Jacobsen R, Johnell K. Remaining life expectancy with and without polypharmacy: A register-based study of swedes aged 65 years and older. J Am Med Dir Assoc. 2016; 17:31–35. [PubMed: 26341036]
3. Landahl S. Drug Treatment in 70–82-year-old-persons. A longitudinal study. Acta Med Scand. 1987; 221:179–184. [PubMed: 3591455]
4. Jylhä M. Ten-year change in the use of medical drugs among the elderly—a longitudinal study and cohort comparison. J Clin Epidemiol. 1994; 47:69–79. [PubMed: 8283196]
5. Stewart RB, Moore MT, May FE, et al. A longitudinal evaluation of drug use in an ambulatory elderly population. J Clin Epidemiol. 1991; 44:1353–1359. [PubMed: 1753266]
6. Veehof L, Stewart R, Haaijer-Ruskamp F, et al. The development of polypharmacy. A longitudinal study. Fam Pract. 2000; 17:261–267. [PubMed: 10846147]
7. Jyrkkä J, Vartiainen L, Hartikainen S, et al. Increasing use of medicines in elderly persons: a five-year follow-up of the Kuopio 75+ Study. Eur J Clin Pharmacol. 2006; 62:151–158. [PubMed: 16408226]
8. Blumstein T, Shmotkin D, Eyal N, et al. A longitudinal evaluation of medication use among the old-old population in Israel. Res Aging. 2008; 30:55–73.
9. Lavikainen P, Leskinen E, Hartikainen S, et al. Impact of missing data mechanism on the estimate of change: a case study on cognitive function and polypharmacy among older persons. Clin Epidemiol. 2015; 7:169–180. [PubMed: 25678815]
10. Bjerrum L, Søgaard J, Hallas J, et al. Polypharmacy: correlations with sex, age and drug regimen A prescription database study. Eur J Clin Pharmcol. 1998; 54:197–202.

11. Hovstadius B, Åstrand B, Petersson G. Dispensed drugs and multiple medications in the Swedish population: an individual-based register study. BMC Pharmacol Toxicol. 2009; 9:11.doi: 10.1186/1472-6904-1189-1111
12. Simiand-Erdociain E, Lapeyre-Mestre M, Bagheri-Charabiani H, et al. Drug consumption in a very elderly community-dwelling population. Eur J Clin Pharmacol. 2001; 57:691–692. [PubMed: 11791901]
13. Nobili A, Franchi C, Pasina L, et al. Drug utilization and polypharmacy in an Italian elderly population: the EPIFARM-elderly project. Pharmacoepidemiol Drug Saf. 2011; 20:488–496. [PubMed: 21264988]
14. Wastesson JW, Parker MG, Fastbom J, et al. Drug use in centenarians compared with nonagenarians and octogenarians in Sweden: a nationwide register-based study. Age Ageing. 2012; 41:218–224. [PubMed: 22130561]
15. Johnell K, Weitoft G, Fastbom J. Sex differences in inappropriate drug use: a register-based study of over 600,000 older people. Ann Pharmacother. 2009; 43:1233–1238. [PubMed: 19584395]
16. O'Mahony D, O'Connor MN. Pharmacotherapy at the end-of-life. Age Ageing. 2011; 40:419–422. [PubMed: 21622981]
17. Christensen K, McGue M, Petersen I, et al. Exceptional longevity does not result in excessive levels of disability. Proc Natl Acad Sci. 2008; 105:13274–13279. [PubMed: 18711139]
18. Nybo H, Gaist D, Jeune B, et al. The Danish 1905 Cohort A Genetic-Epidemiological Nationwide Survey. J Aging Health. 2001; 13:32–46. [PubMed: 11503846]
19. Nybo H, Gaist D, Jeune B, et al. Functional Status and Self-Rated Health in 2,262 Nonagenarians: The Danish 1905 Cohort Survey. J Am Geriatr Soc. 2001; 49:601–609. [PubMed: 11380754]
20. World Health Organization. Collaborating Centre for Drug Statistics Methodology; Oslo, Norway: http://www.whocc.no/ [Accessed 2015-01-30]
21. Gnjidic D, Hilmer SN, Blyth FM, et al. Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol. 2012; 65:989–995. [PubMed: 22742913]
22. Dufouil C, Brayne C, Clayton D. Analysis of longitudinal studies with death and drop-out: a case study. Stat Med. 2004; 23:2215–2226. [PubMed: 15236426]
23. Thinggaard M, McGue M, Christensen K. Age trajectory of high cognitive functioning among the oldest old. Annu Rev Gerontol Geriatr. 2013; 33:35–48.
24. Kingston A, Davies K, Collerton J, et al. The enduring effect of education–socioeconomic differences in disability trajectories from age 85 years in the Newcastle 85+ study. Arch Gerontol Geriatr. 2015; 60:405–411. [PubMed: 25747850]
25. Zimmer Z, Martin LG, Nagin DS, et al. Modeling disability trajectories and mortality of the oldest-old in China. Demography. 2012; 49:291–314. [PubMed: 22246796]
26. Oksuzyan A, Petersen I, Stovring H, et al. The male–female health–survival paradox: A survey and register study of the impact of sex-specific selection and information bias. Ann Epidemiol. 2009; 19:504–511. [PubMed: 19457685]
27. Nelson LM, Longstreth W Jr, Checkoutay H, et al. Completeness and accuracy of interview data from proxy respondents: demographic, medical, and life-style factors. Epidemiology. 1994; 5:204–217. [PubMed: 8172996]
28. Hovstadius B, Hovstadius K, Åstrand B, et al. Increasing polypharmacy-an individual-based study of the Swedish population 2005–2008. BMC Pharmacol Toxicol. 2010; 10:16.doi: 10.1186/1472-6904-1110-1116
29. Charlesworth CJ, Smit E, Lee DS, et al. Polypharmacy among adults aged 65 years and older in the united states: 1988–2010. J Gerontol A Biol Sci Med Sci. 2015; 70:989–995. [PubMed: 25733718]

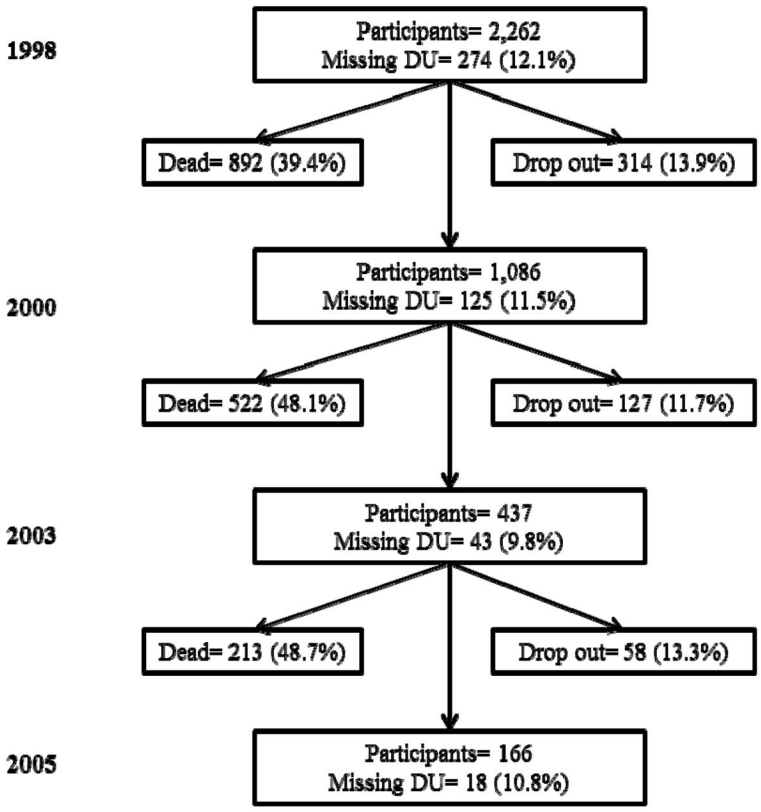

Figure 1.

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.

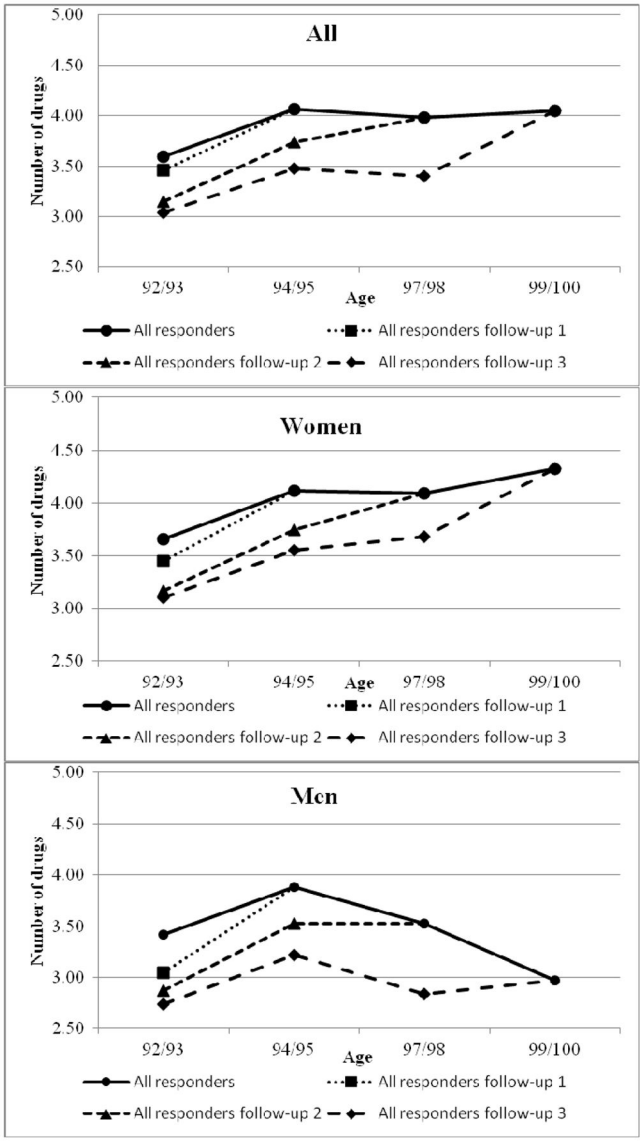

Figure 2.

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**
																		Within-person[b]	
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-level[c]	
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)				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**
																		Within-person[b]	
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-level[c]	
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)				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						

[a] The n changes between the waves due to missing information on drug use between the waves (Figure 1)

[b] Annual within-person change from growth curve models to estimate the intra-individual change

[c] Regression estimate from a standard linear regression to estimate the change

[d] Inverse probability weighting