PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2017; **26**: 152–161
Published online 28 October 2016 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.4120

ORIGINAL REPORT

Drug use among complete responders, partial responders and non-responders in a longitudinal survey of nonagenarians: analysis of prescription register data

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ABSTRACT

Purpose In observational studies, non-response can limit representativity and introduce bias. We aimed to investigate the longitudinal changes in the number of used drugs among complete responders, partial responders, and non-responders in a whole birth cohort of Danish nonagenarians participating in a longitudinal survey.

Methods We obtained prescription data on all individuals born in 1905 and living in Denmark when the Danish 1905 cohort study was initiated in 1998 ($n = 3600$) using the Danish National Prescription Registry. Drug use was assessed for complete responders, non-responders at baseline, and partial responders (i.e., dropouts) in the 4-month period preceding each wave of the study (1998, 2000, 2003, and 2005), that is, as the cohort aged from 92–93 to 99–100 years.

Results Complete responders, non-responders, and partial responders used a similar number of drugs at baseline, on average 4.4, increasing to 5.6 at the age of 99–100 years. In all groups, the number of used drugs increased over time; partial responders had the largest increase of 0.39 drugs per year (95% confidence interval (CI): 0.33–0.44) compared with 0.32 (95%CI: 0.27–0.37) and 0.30 (95%CI: 0.25–0.35) in the other groups. Furthermore, the most frequently used drug classes (e.g., loop diuretics and paracetamol) and the drug classes with the largest change (e.g., increase: laxatives and paracetamol; decrease: benzodiazepines) were similar across response groups.

Conclusions The number of used drugs increased in all response groups between the age of 92 and 100 years. In this study, drug use among complete responders was representative of the general drug use in the entire cohort.

KEY WORDS—aged; attrition; drug use; longitudinal; nonagenarians; pharmacoepidemiology

Received 18 March 2016; Revised 22 August 2016; Accepted 5 October 2016

INTRODUCTION

Longitudinal surveys are an important method to collect information on changes in drug use. However, non-response can limit representativity and introduce bias in these studies. This can be particularly challenging at higher ages, when surveys are affected by extensive loss to follow-up due to dropout and death. In the elderly population, both non-responders (at baseline) and partial responders (dropouts) tend to have poorer health[1–3] and higher healthcare consumption,[4,5] and they have also been reported to use more prescription drugs[6] than complete responders. These differences seem to be especially pronounced among the partial responders.[4,7]

The few longitudinal studies of the general pattern of drug use in the very old suggest an age-related increase in the number of used drugs.[8,9] In contrast, many cross-sectional studies find that the number of

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used drugs increases from middle age until 90–95 years of age, where it tends to plateau or decline.[10–12] It is unclear whether the increasing drug use among the responders in longitudinal studies is also found for partial responders and non-responders. Furthermore, little is known about the changes in the prescribing patterns of specific drug classes as individuals approach 100 years of age and whether this is related to response status.

By linking information from nationwide Danish registers, we are able to collect information on the drug use among the very elderly, irrespective of their response status in the Danish nationwide 1905 cohort study.[13] This allowed us to compare the drug use among complete responders, partial responders (dropouts), and non-responders (at baseline) in a cohort study of nonagenarians. The objective of this study was twofold: to add more knowledge about how drug use is related to response status in a longitudinal survey of the very old and to provide evidence on the general use of drugs among nonagenarians as they age to become centenarians.

METHOD

By linking the 1905 cohort study to Danish registers, we were able to collect information about drug use for complete responders, partial responders (dropouts), and non-responders (at baseline) in a longitudinal study of nonagenarians.

Study population

The complete cohort of all Danes born in 1905 and alive in 1998 was invited to participate in the Danish longitudinal 1905 cohort study. The 1905 cohort study is a multi-assessment study including interview, physical and psychological tests, and collection of biomaterial.[13] Persons were contacted regardless of housing, geography, and functional status. Additional waves were carried out in 2000, 2003, and 2005. Non-responders at baseline and dropouts were not allowed to participate at later waves in this study (i.e., monotonic attrition).

At baseline in 1998, 3738 eligible individuals were identified; 138 of these died before the first contact.[13] The remaining 3600 individuals were contacted, and 2262 (63%) agreed to participate and were interviewed during a 3-month period (1 August to 31 October) in 1998. Of the 2262 responders, 200 of the cohort members had been interviewed in the spring of 1998 as a part of a pilot study, prior to the baseline data collection conducted in the fall of 1998.[13]

At the first follow-up, performed in 2000, 1400 persons were still alive and 1086 (78%) agreed to participate. The interviews were performed from 4 September 2000 to 13 January 2001. When the second follow-up was performed in 2003, 564 persons were alive and 437 (77%) responded. The interviews took place from 6 February to 24 May. When the last follow-up was performed in 2005, 225 persons were alive and 166 (74%) were interviewed between 15 February and 13 June. Approximately 13% of the responders from the previous wave dropped out at each follow-up. The response pattern and mortality is depicted in more detail in Figure 1.

Response status

Eligible participants of the 1905 cohort study were classified based on their cumulative response status (Figure 1). Complete responders were those responding at baseline and completing each possible wave (until the last wave or death). Partial responders were those responding at least at baseline but failing to respond for other reasons than death or emigration at some of the later waves. Only two persons emigrated during the course of the study.[14] The non-responders at baseline were followed until the last wave or death. In the rare scenario where a person both declined to participate in a given follow-up and died before the first day of interviewing (6–14 individuals per wave), the person was considered dead rather than a partial responder.

Register linkage

Using the personal identification number (the CPR number), a unique identifier assigned to all Danish individuals since 1968,[15] it was possible to link individual-level information from Danish registers to the study population.[16] Data on mortality were available through the Danish Civil Registration System,[15] and use of medications was obtained from the Danish National Prescription Register.[17]

The Danish National Prescription Registry[17] contains data on all prescription drugs dispensed in Denmark since 1995. For each dispensing, information on the date of dispensing, the substance, brand name, and quantity is available from the register. The dosing information and the indication for prescribing are not recorded.[17] Drugs are classified according to the Anatomical Therapeutic Chemical (ATC) code, a hierarchical classification system developed by the World Health Organization.[18]

DOI: 10.1002/pds

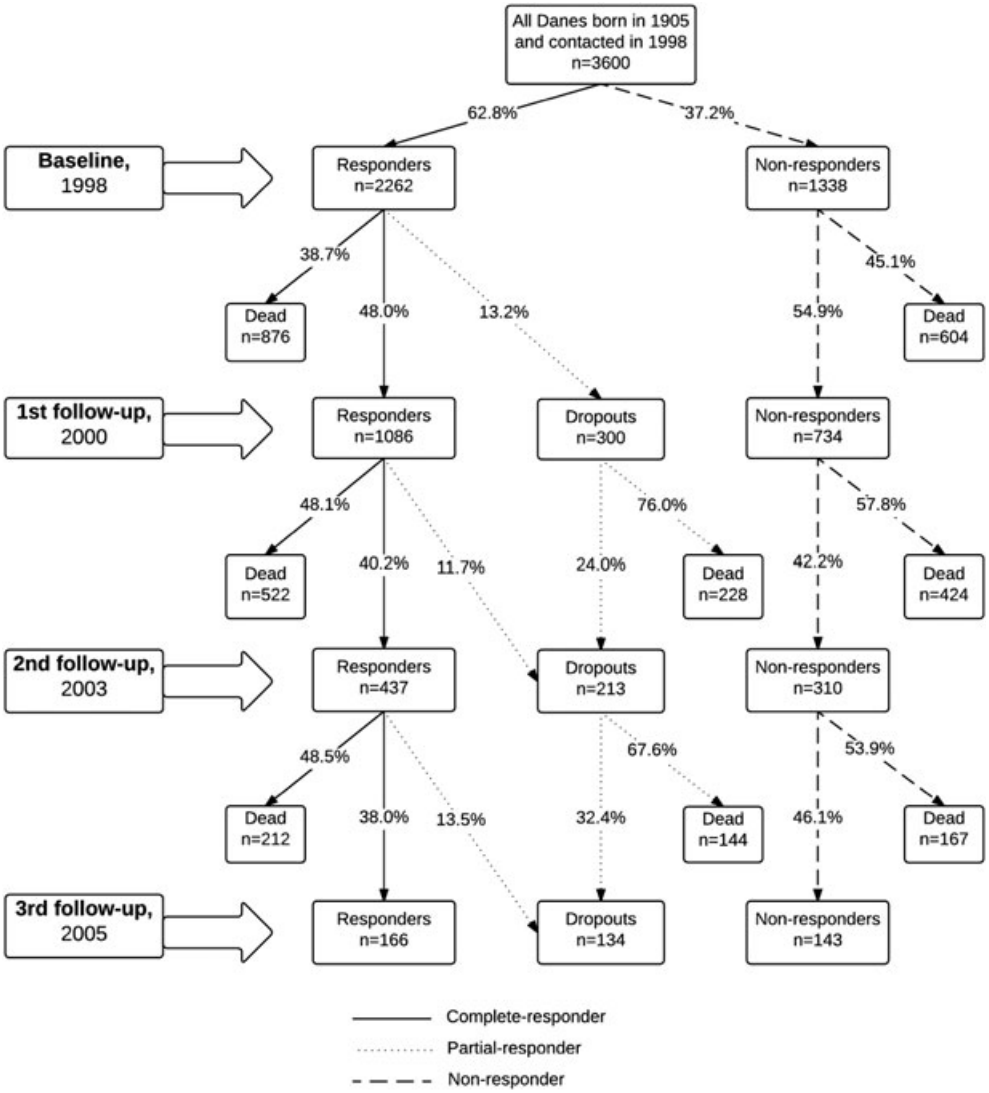

Figure 1. Flow chart of response pattern and mortality in the Danish 1905 cohort, 1998–2005

The register covers all drugs dispensed in the out-care setting including nursing homes, while drugs used during hospital admission are not included.

Number of drugs

The number of drugs used by each individual was determined as the number of unique chemical drug

Table 1. Characteristics and response status (from the Danish 1905 cohort survey) in the complete cohort of Danes born in 1905, alive at each wave, 1998–2005

	Baseline, 1998 ($n = 3600$) % (n)	Wave 1, 2000 ($n = 2120$) % (n)	Wave 2, 2003 ($n = 960$) % (n)	Wave 3, 2005 ($n = 443$) % (n)
Age	92/93	94/95	97/98	99/100
Women	76.4 (2751)	79.7 (1689)	81.6 (783)	84.0 (372)
Responder status				
Complete responders	48.9 (1762)	42.5 (900)	39.4 (378)	37.5 (166)
Partial responders	13.9 (500)	22.9 (486)	28.3 (272)	30.2 (134)
Non-responders	37.2 (1338)	34.6 (734)	32.3 (310)	32.3 (143)

DOI: 10.1002/pds

Table 2. Mean, median, and trend in number of drugs by responder status, 1998–2005

	All				Complete responders				Partial responders				Non-responders			
	Mean	95%CI	Median	IQR	Mean	95%CI	Median	IQR	Mean	95%CI	Median	IQR	Mean	95%CI	Median	IQR
All																
Age																
92/93	4.4	4.2–4.5	4	2–6	4.6	4.4–4.7	4	2–6	4.2	3.9–4.4	4	2–6	4.2	4.0–4.3	4	2–6
94/95	4.6	4.5–4.8	4	2–7	4.7	4.5–4.9	4	2–7	4.9	4.6–5.2	5	2–7	4.4	4.1–4.6	4	2–6
97/98	5.4	5.1–5.6	5	3–7	5.4	5.1–5.8	5	3–8	5.6	5.2–6.0	5	3–8	5.1	4.7–5.5	5	3–7
99/100	5.6	5.2–5.9	5	3–8	5.6	5.0–6.2	5	3–8	6.2	5.5–6.8	6	3–9	5.0	4.5–5.6	5	2–7
Yearly change,[1] no. of drugs (95%CI)	0.33	(0.30–0.36)			0.32	(0.27–0.37)			0.39	(0.33–0.44)			0.30	(0.25–0.35)		
Women																
Age																
92/93	4.5	4.4–4.6	4	2–6	4.7	4.6–4.9	4	2–7	4.3	4.0–4.6	4	2–6	4.3	4.1–4.4	4	2–6
94/95	4.7	4.6–4.9	4	2–7	4.9	4.7–5.1	5	3–7	4.9	4.6–5.2	5	3–7	4.4	4.2–4.7	4	2–6
97/98	5.5	5.2–5.7	5	3–8	5.5	5.1–5.9	5	3–8	5.7	5.2–6.2	5	3–8	5.1	4.7–5.5	5	3–7
99/100	5.6	5.2–6.0	5	3–8	5.8	5.1–6.4	5	3–8	6.1	5.4–6.8	6	3–9	5.0	4.4–5.6	5	2–7
Yearly change,[1] no. of drugs (95%CI)	0.32	(0.28–0.35)			0.31	(0.26–0.37)			0.36	(0.30–0.42)			0.28	(0.23–0.34)		
Men																
Age																
92/93	3.9	3.7–4.1	3	2–6	4.0	3.8–4.3	3	2–6	3.7	3.1–4.2	3	2–5	3.8	3.4–4.1	3	2–5
94/95	4.3	4.0–4.6	4	2–7	4.2	3.8–4.6	4	2–6	4.8	4.1–5.5	5	2–7	4.0	3.5–4.6	3	2–6
97/98	4.9	4.4–5.4	5	2–7	4.9	4.1–5.7	4	3–7	5.1	4.2–6.0	5	2–7	4.9	3.9–5.8	5	2–7
99/100	5.5	4.6–6.4	5	2–8	4.9	3.6–6.2	5	1–8	6.6	4.8–8.5	6	4–9	5.3	4.0–6.6	4.5	4–6
Yearly change,[1] no. of drugs (95%CI)	0.38	(0.31–0.45)			0.33	(0.22–0.44)			0.49	(0.33–0.65)			0.39	(0.27–0.51)		

[1]Estimated with mixed effects linear regression.

DOI: 10.1002/pds

classes (fourth ATC level, e.g., A02BC proton pump inhibitors) filled in the 4 months prior to the interview date. For partial responders and non-responders, drug use was assessed in the 4 months prior to the first day of interviewing among the complete responders. In Denmark, most drugs are supplied for 3 months at a time. Thereby, a 120-day window (4 months) corresponds to one full supply, when adding 30 days to account for minor non-compliance and irregular filling patterns.

Statistical analysis

Mean and median numbers of drugs used were compared between complete responders, partial responders, and non-responders at baseline and at each survey wave, overall and for women and men separately. The within-person change in number of used drugs (with 95% confidence intervals (CIs)) was estimated using mixed-effects linear regression, with the drug measurement at each wave (level 2) nested within individuals (level 1). Years since baseline were the independent variable in order to estimate annual change (Table 2). Higher-level polynomials were tested but only had a negligible effect on the fit of the model. The proportion of users of the 14 anatomical main groups (first-level ATC) was calculated (Table 3). We identified the 15 most frequently used drug classes (fourth-level ATC) at baseline (Table 4) and the drug classes (fourth-level ATC) with largest change in the absolute proportion of users between baseline and the last survey (Table 5). All analyses were performed for complete responders, partial responders, and non-responders separately. The analyses were performed with STATA 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

In order to be able to interpret the observed changes for specific drug classes within our study cohort, we accessed www.medstat.dk, a data source, holding publicly available aggregate drug use statistics for all Danish. For the 10 chemical classes with the largest increase or decrease among complete responders, we tabulated the prevalence proportion of use among all 92-year olds in 1999 (used as a proxy for 1998 as age-specific data prior to 1999 were not available) and 2005 (Table 6). Age 92 was chosen to reflect the age at first contact. As this shows the changes in drug use based on a dynamic cohort of 92-year olds, rather than a closed cohort as in the survey, it allowed us to disentangle the effect of aging from a pure secular trend in drug use by the elderly.

RESULTS

In 1998, 3600 persons aged 92–93 years were contacted to participate in the baseline survey. At the last wave in 2005, at age 99–100 years, 443 persons (12%) of those contacted were still alive. About three quarters of the cohort were women at baseline, increasing to 84% at the last wave (Table 1). Almost half of those contacted responded at each wave until last wave or death (complete responders). About 37% declined to respond at baseline (non-responders), and 14% dropped out at some point of the study (partial responders). Mortality was lowest among the complete responders, with 38% dying

Table 3. Proportion of users for each of the 14 main anatomical drug groups (Anatomical Therapeutic Chemical groups) at baseline in 1998[1]

		Complete responders ($n = 1762$) %	Partial responders ($n = 500$) %	Non-responders ($n = 1338$) %
C	Cardiovascular system	63.9	58.8	56.7
N	Nervous system	59.4	58.2	58.8
A	Alimentary tract and metabolism	44.3	41.8	43.6
B	Blood and blood forming organs	36.1	30.4	29.2
J	Anti-infectives for systemic use	22.7	19.4	20.9
S	Sensory organs	20.7	24.0	19.0
M	Musculoskeletal system	16.7	15.8	13.2
R	Respiratory system	14.3	14.4	14.2
D	Dermatologicals	13.5	11.2	13.8
H	Systemic hormonal preparations, excluding sex hormones, and insulins	8.3	7.6	7.2
G	Genitourinary system and sex hormones	5.8	5.2	5.3
P	Antiparasitic products, insecticides, and repellents	3.9	4.0	4.7
L	Antineoplastic and immunomodulating agents	0.7	0.2	0.3
V	Various	0.1	0.0	0.1

[1]Sorted by frequency in complete responders.

DOI: 10.1002/pds

Table 4. The 15 most frequently used drugs (fourth-level ATC) at baseline[1] by response status, 1998

		Complete responders ($n = 1762$) %	Partial responders ($n = 500$) %	Non-responders ($n = 1338$) %
C03CA	Loop diuretics	33.5	25.2	29.7
N02BE	Paracetamol	30.6	27.6	29.5
A12BA	Potassium	28.5	24.8	27.5
B01AC	Platelet aggregation inhibitors	27.6	23.0	22.6
C01AA	Digitalis glycosides	19.2	13.0	16.7
C03AB	Thiazides and potassium combination	15.7	16.6	13.9
N05CD	Benzodiazepine hypnotics	13.8	15.8	13.7
N05CF	Benzodiazepine-related hypnotics	11.6	11.0	10.3
N05BA	Benzodiazepine tranquilizers	11.3	12.8	14.3
C01DA	Organic nitrates	10.3	9.2	7.9
N06AB	Selective serotonin reuptake inhibitors	9.1	8.8	9.3
S01AA	Antibiotic eye drops	8.0	6.2	6.1
J01EB	Short-acting sulfonamide antibiotics	6.9	6.2	6.8
N02AX	Other opioids	6.6	7.6	5.7
M01AE	NSAIDs, propionic acid derivatives	6.4	8.6	7.4

[1]Sorted by frequency among complete responders.
ATC, Anatomical Therapeutic Chemical; NSAID, nonsteroidal anti-inflammatory drug.

before the first follow-up, and 48% dying before the second and third follow-up, compared with the non-responders who had a higher mortality (45%, 58%, and 54% at each wave, respectively). The partial responders had the highest mortality, at around 70% between the follow-ups (Figure 1).

The mean and median numbers of drugs used per individual at each wave are depicted in Table 2, specified by response status. In the total sample, the average number of used drugs at age 92/93 was 4.4 (median: 4) increasing to 5.6 (median: 5) drugs at age 99/100. The mean and median number of drugs increased with age for all response groups. Partial responders used slightly more drugs than complete responders and non-responders in the later waves of the survey. The annual within-person increase in the number of used drugs was 0.39 drugs (95%CI: 0.33–0.44) for the partial responders, 0.32 (95%CI: 0.27–0.37) for the complete responders, and 0.30 (95%CI: 0.25–0.35) for the non-responders. On average, women used more drugs than men (4.5 vs. 3.9 at baseline and 5.6 vs. 5.5 at last wave). Men and women had a similar increase in their drug use.

Cardiovascular drugs and drugs acting on the nervous system were the most frequently used drugs at baseline, used by more than 50% of the individuals in each response group (Table 3). The number of used drugs increased or remained stable in all main categories (data not shown).

The 15 most frequently used drugs according to chemical subgroup (fourth-level ATC) at baseline are depicted in Table 4. The list is dominated by cardiovascular drugs (e.g., loop diuretics, digitalis glycosides, and organic nitrates), pain relieving drugs (e.g., paracetamol), and psychotropic drugs (e.g., selective serotonin reuptake inhibitors and benzodiazepine hypnotics). The differences between the response groups were generally small, both regarding the proportion of users and the ranking of the most frequently used drugs.

Table 5 presents the drug classes with largest absolute changes in the proportion of users between the first and last wave of the study. The drugs with the largest changes were similar across the response groups: among the drugs with the largest increase were laxatives (A06AD; 12–26 percentage point increase), paracetamol (N02BE; 11–19 percentage point increase), and proton pump inhibitors (A02BC; 9–14 percentage point increase). The largest decrease was seen for drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs; M01AE; 3–5 percentage point decrease), benzodiazepine hypnotics (N05CD; 4–7 percentage point decrease), and thioxanthene antipsychotics (N05AF; 2–4 percentage point decrease).

Table 6 presents the prevalence of use among all Danish 92-year olds in 1999 and 2005 for the 10 chemical classes with the largest increase or decrease among complete responders. Among the drugs that showed particularly large increases were osmotic laxatives (increasing 464%), proton pump inhibitors (88%), beta-blocking agents (251%), and coxibs (1293%).

DOI: 10.1002/pds

Table 5. Drug classes (fourth-level ATC) with largest absolute change in proportion of users (10 positive and 10 negative) from baseline to last survey,[1] 1998–2005

Complete responders			Partial responders			Non-responders		
		%			%			%
Increase			**Increase**			**Increase**		
A06AD	Osmotically acting laxatives	11.8	A06AD	Osmotically acting laxatives	25.6	A06AD	Osmotically acting laxatives	15.4
N02BE	Paracetamol	10.9	N02BE	Paracetamol	19.4	N02BE	Paracetamol	13.1
A02BC	Proton pump inhibitors	10.7	C03CA	Loop diuretics, plain	15.8	A02BC	Proton pump inhibitors	8.6
S01XA	Other ophthalmologicals	7.6	A06AB	Contact laxatives	15.1	N05CF	Benzodiazepine-related hypnotics	7.9
C03CA	Loop diuretics	6.2	A02BC	Proton pump inhibitors	14.2	A02AA	Magnesium compounds	7.6
A06AB	Contact laxatives	5.7	J01CA	Penicillins with extended spectrum	10.8	N02AX	Tramadol	7.6
C07AB	Beta-blocking agents, selective	5.6	A06AG	Enemas	8.7	A06AB	Contact laxatives	7.1
B01AC	Platelet aggregation inhibitors	4.9	B01AC	Platelet aggregation inhibitors	7.6	C03CA	Loop diuretics	6.0
N02AX	Tramadol	4.8	C09AA	ACE inhibitors, plain	6.9	C07AB	Beta-blocking agents, selective	5.3
M01AH	Coxibs	4.2	C07AB	Beta-blocking agents, selective	6.5	A06AG	Enemas	5.1
Decrease			**Decrease**			**Decrease**		
M01AE	NSAIDs, propionic acid derivatives	−4.5	N05CD	Benzodiazepine hypnotics	−6.8	C01AA	Digitalis glycosides	−9.7
N05CD	Benzodiazepine hypnotics	−4.2	A02BA	H2-receptor antagonists	−4.3	N05CD	Benzodiazepine hypnotics	−6.0
J01EB	Short-acting sulfonamide antibiotics	−3.9	C03AB	Thiazides and potassium in combination	−3.2	N05AF	Thioxanthene antipsychotics	−4.2
C07AA	Beta-blocking agents, nonselective	−2.3	D07AB	Topical corticosteroids, moderately potent (group II)	−2.5	A02BA	H2-receptor antagonists	−2.6
N05AF	Thioxanthene antipsychotics	−1.9	S01GA	Sympathomimetics used as decongestants	−2.4	M01AE	NSAIDs, propionic acid derivatives	−2.5
C03EA	Low-ceiling diuretics and potassium-sparing agents	−1.8	S01ED	Beta-blocking agents, eye drops	−1.9	C01DA	Organic nitrates	−2.3
S01EC	Carbonic anhydrase inhibitor eye drop	−1.8	J01XX	Other antibacterials	−1.8	N05AB	Phenothiazine antipsychotics	−2.2
C01AA	Digitalis glycosides	−1.7	C08DA	Phenylalkylamine calcium blockers	−1.7	C08DA	Phenylalkylamine calcium blockers	−2.1
D07AB	Topical corticosteroids, moderately potent (group II)	−1.7	R06AX	Other antihistamines for systemic use	−1.7	M01AB	NSAIDs, acetic acid derivatives	−2.0
C08DB	Benzothiazepine calcium blockers	−1.6	N05BA	Benzodiazepine tranquilizers	−1.6	S01EB	Parasympathomimetic eye drops	−1.9

[1]Sorted by change in complete responders.
ATC, Anatomical Therapeutic Chemical; ACE, angiotensin-converting enzyme; NSAID, nonsteroidal anti-inflammatory drug.

DISCUSSION

This study provides unique data on drug use among complete responders, partial responders, and non-responders from a nationwide longitudinal survey of nonagenarians. In general, we found small differences in the drug use between the response groups. All three response groups used on average approximately four drugs at baseline (92–93 years) and increased their drug use to about five to six drugs at last follow-up (99–100 years). Furthermore, the use of specific drug classes was also similar across the response groups. All groups exhibited a within-person increase of about 0.3 drugs annually.

While previous studies have shown that non-responders and especially partial responders have worse health than complete responders,[1–7] we only found small differences in the use of drugs across the response groups. Partial responders had a slightly higher use of drugs than complete respondents and non-respondents in the later waves of the survey. Non-responders had a similar drug use as complete responders at all waves. For drug use, the number of drugs used by complete responders seemed to be fairly representative of the number of used drugs in the full cohort. In contrast, mortality was higher among partial responders than complete responders and non-responders. The small differences in the number of used drugs across the response groups, but larger differences in mortality, could be due to a number of reasons. Potentially, drug use shows less agreement with health status (and mortality risk) among people at the

DOI: 10.1002/pds

Table 6. Secular trend in drug use among all Danish residents aged 92 years in 1999 and 2005

Drug class (ATC-code)		Prevalence of use (pr. 100 individuals) 1999	2005	Absolute change
10 drugs with largest increase in study cohort[1]				
A06AD	Osmotically acting laxatives	3.7	20.7	+17.0
N02BE	Paracetamol	48.4	52.5	+4.1
A02BC	Proton pump inhibitors	11.2	21.0	+9.8
S01XA	Other ophthalmologicals	6.7	8.2	+1.5
C03CA	Loop diuretics	39.8	38.3	−1.5
A06AB	Contact laxatives	10.3	15.5	+5.2
C07AB	Beta-blocking agents, selective	3.7	13.0	+9.3
B01AC	Platelet aggregation inhibitors	32.8	44.6	+11.8
N02AX	Tramadol	14.5	18.7	+4.2
M01AH	Coxibs	0.1	1.2	+1.1
10 drugs with largest decrease in study cohort[1]				
M01AE	NSAIDs, propionic acid derivatives	11.7	9.8	−1.9
N05CD	Benzodiazepine hypnotics	16.1	9.3	−6.8
J01EB	Short-acting sulfonamide antibiotics	17.0	15.6	−1.4
C07AA	Beta-blocking agents, nonselective	2.5	2.0	−0.5
N05AF	Thioxanthene antipsychotics	5.9	2.1	−3.8
C03EA	Low-ceiling diuretics and potassium-sparing agents	4.0	2.7	−1.3
S01EC	Carbonic anhydrase inhibitor eye drop	1.6	2.1	+0.5
C01AA	Digitalis glycosides	20.7	16.2	−4.5
D07AB	Topical corticosteroids, moderately potent (group II)	5.7	5.1	−0.6
C08DB	Benzothiazepine calcium blockers	2.7	2.0	−0.7

[1]According to absolute change among complete responders in Table 5
Data from www.medstat.dk
ATC, Anatomical Therapeutic Chemical; NSAID, nonsteroidal anti-inflammatory drug.

end of life, as de-prescribing and cessation of treatments are sometimes implemented as palliative measures.[19] Drug treatment may also become increasingly homogeneous at older ages. Furthermore, the attrition and recruitment to this study might be less related to health than in other studies, as the 1905 cohort study includes proxy responders, individuals living in institutions with a fairly good response rate.[13] However, the higher mortality among the partial responders suggests the opposite. The finding that mortality was highest among the partial responders suggests that dropout from a study is more strongly linked to poor health than refusal to participate at baseline, as also reported by others.[4,7,20]

Non-response and attrition can also lead to biases in the estimation of longitudinal patterns of health factors.[2] Drug use has been found to plateau or decline at the very highest ages in cross-sectional studies.[10,11] However, the few longitudinal studies of drug use among persons older than 75 years have found an increase in the number of used drugs with age.[8,9] We found drug use to increase by 0.3 drugs per year in all response groups combined and comparable estimates across the response groups. In this study, the increase in number of drugs found among the complete responders was representative of the full cohort. Both women and men showed an increase in their drug use, and the results for the different response groups were similar in both sexes. There was a tendency for men to increase their drug use at a faster rate than women, but the difference was not significant. With a larger sample size, it may have been possible to detect decreasing gender differences in drug use at very old ages, in line with previous findings.[21]

Drugs for cardiovascular disorders, pain, and mental health problems were the most frequently used drugs in this cohort. This is in agreement with earlier studies among the very old.[21–23] Notably, laxatives and proton pump inhibitors were among the drugs with the largest increases in the proportion of users. A substantial part of this is explained by a secular trend in drug use in the elderly, that is, these drugs becoming more popular among the elderly, rather than an aging effect in our cohort (Table 6). Another part of the explanation could be a so-called prescribing cascade, that is, when an additional drug treatment is initiated to treat the adverse effect of another drug, for example, laxatives to treat constipation among opioid users.[24] The largest reduction in the proportion of users was found for NSAIDs and antipsychotics. Both these drugs are generally considered inappropriate for older patients: NSAIDs increase the risk of gastrointestinal bleeding,[25] and antipsychotics (often prescribed for behavioral problems in dementia) have a range of side effects that are especially pronounced among the elderly.[26] The reduced use of these drugs suggests that measures are taken to increase the appropriateness of prescribing for the older patient. In general, there were small differences in the most frequently used drugs, and the drugs with the largest changes, between the response groups.

Strengths and limitations

Register linkage provided an opportunity to study drug use among all persons contacted for the 1905 cohort study irrespective of response status. As all individuals living in Denmark born in 1905 (regardless of their health status and living situation) were contacted for the 1905 cohort study, this study follows a complete nationwide birth cohort. Drug use was available from the Danish National Prescription Registry, and

DOI: 10.1002/pds

register-based information on drug use is probably the preferred method for drug use assessment at these high ages, when cognitive and communicative problems are common. Generally, older people are difficult to recruit to surveys of drug utilization.[27]

Although register-based studies using the Danish health registries are highly effective, there are a number of potential drawbacks. Over-the-counter drugs and drugs used in hospitals are not recorded in the registers, which may lead to an underestimation of drug use. However, as the elderly spend a fairly small proportion of their time being hospitalized, this should not pose a major limitation. Furthermore, we do not know whether the dispensed drugs are consumed, and adherence can be specifically low among individuals with complex treatments and cognitive limitations.[28] Another limitation is that the drug use among the complete responders was assessed at the date of their interview (and 4 months in retrospect), while drug use among partial responders and non-responders was assessed at the date when the interviews started among the complete responders (and 4 months in retrospect). Thus, partial responders and non-responders have their drug use recorded at an earlier time point than the majority of the complete responders. However, the interviews were performed in a relatively short time window (3–4 months), and drug use changed at a fairly slow rate, so this should not have a major influence on the interpretation of the results. Furthermore, our results are not directly comparable with studies that describe the use of medication only among survivors in a cohort, whereas we included all responders irrespective of later death. However, we perceive this as a strength as we provide more realistic estimates for the cohort as a whole and for the difference between the response groups.

CONCLUSIONS

We found that drug use increases between the age of 92 and 100 years for complete responders, as well as for partial responders and non-responders. In general, the use of drugs was similar across the three response groups, which suggests that the drug use among the complete responders from this longitudinal cohort study is a good approximation of drug use in the complete cohort.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS

- The number of used drugs continues to increase as nonagenarians age to become centenarians.
- The drug use pattern is similar among complete responders, partial responders, and non-responders in this longitudinal survey of nonagenarians.

ETHICS STATEMENT

The study was approved by the Central Scientific Ethical Committee of Denmark.

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