

Research Article

# Is Who you Ask Important? Concordance Between Survey and Registry Data on Medication Use Among Self- and Proxy-Respondents in the Longitudinal Study of Aging Danish Twins and the Danish 1905-Cohort Study

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## Abstract

**Background:** This study investigates the accuracy of the reporting of medication use by proxy- and self-respondents, and it compares the prognostic value of the number of medications from survey and registry data for predicting mortality across self- and proxy-respondents.

**Methods:** The study is based on the linkage of the Longitudinal Study of Aging Danish Twins and the Danish 1905–Cohort Study with the Danish National Prescription Registry. We investigated the concordance between survey and registry data, and the prognostic value of medication use when assessed using survey and registry data, to predict mortality for self- and proxy-respondents at intake surveys.

**Results:** Among self-respondents, the agreement was moderate ( $\kappa = 0.52\text{--}0.58$ ) for most therapeutic groups, whereas among proxy-respondents, the agreement was low to moderate ( $\kappa = 0.36\text{--}0.60$ ). The magnitude of the relative differences was, generally, greater among proxies than among self-respondents. Each additional increase in the total number of medications was associated with 7%–8% mortality increase among self- and 4%–6% mortality increase among proxy-respondents in both the survey and registry data. The predictive value of the total number of medications estimated from either data source was lower among proxies (c-statistic = 0.56–0.58) than among self-respondents (c-statistic = 0.74).

**Conclusions:** The concordance between survey and registry data regarding medication use and the predictive value of the number of medications for mortality were lower among proxy- than among self-respondents.

**Keywords:** Proxy, Self-respondents, Medication use, Register study, Denmark

Most research on old-age populations is based on survey data. Typically, survey data are collected via interviews with selected respondents, or, when this is not possible, with proxy-respondents. The inclusion of proxy interviews overcomes some methodological problems: as it increases the sample size and helps researchers reach institutionalized populations and individuals with physical and cognitive impairments,

it can improve the representativeness of the study population. Previous research has shown that the exclusion of proxy interviews leads to the severe underestimation of the prevalence of activities of daily living disabilities, mobility limitations, and psychological problems (1). However, the inclusion of proxy-respondents may create another challenge, as the lower accuracy of proxy responses may lead to biased estimates.

Generally, the existing research suggests that compared to self-respondents, proxies provide fairly accurate evaluations of physical functioning, frailty, and cognitive status, but less accurate assessments of psychological measures (2,3). Proxy-respondents are less likely to give accurate responses to questions on more subjective matters, such as emotions and pain, but they are more likely to provide accurate response to questions on more easily observable indicators, such as measures of physical function, most chronic conditions, smoking history, and usual alcohol consumption and physical activity (2,4–6). The accuracy of reporting differs by the age of the index person, as proxies tend to overstate activities of daily living and instrumental activities of daily living disabilities for individuals aged 65-plus, and to understate disability levels for younger individuals (7).

Studies on medication use have generally found that the agreement between self-reported data and pharmacy records varies across medications: that is, it is higher for medicines that are taken regularly (eg, medicines for treating cardiovascular diseases, diabetes, and obstructive airway diseases), than for medicines that are taken as needed (eg, antimigraine, analgesics, hypnotics, and sedatives) (8–12). The lowest level of agreement is usually found for over-the-counter medicines, for which self-reports can be a more valid source of data than pharmacy records (9,11). Research evidence indicates that the agreement between proxy and index subjects is high for antihypertensive medications, oral contraceptive use, and hormone replacement therapy and is moderate for aspirin use (6). Previous works, however, have been conducted in small groups of specific patients, and, thus, have limited generalizability to population-based study settings.

Medication use has been shown to be a good measure of health status at older ages, and it has been used as a proxy measure for treatment-seeking behavior (13,14). Comorbidity scores created using pharmacy data have been found to predict 1-year mortality and future physician visits among individuals aged 65-plus (13). As medication use is the most common form of medical treatment among older adult, studying patterns of medication use is essential for monitoring health, improving the quality of health care, and projecting future health care costs for old-aged populations. Our previous work among Danish nonagenarians has indicated that the number of prescription medications reported was lower among proxy-respondents than among self-respondents (15). In another study, we found that the total number of medicines reported by survey participants was lower than the total number of dispensed medications in the registry data (16). To a similar extent in both men and women, this gap widened as the number of prescribed medications increased. However, the accuracy of reporting of medication use by respondent type has not been analyzed.

Since surveys are the main source of information on medication use, and many contemporary surveys of old-aged populations allow for proxy-respondents, it is important to evaluate the accuracy of the reporting of medication use by respondent type. Thus, the present study aims to compare medication use reported by self-respondents and proxies with medication use recorded in administrative registers in Denmark. It also examines the prognostic value of medication use, when assessed using survey and registry data, for predicting mortality across self- and proxy-respondents.

## Methods

### Study Population

The study is based on the linkage of two surveys, the Longitudinal Study of Aging Danish Twins (LSADT) and the Danish 1905–Cohort Study (1905-Cohort), with registers maintained by the Statistics

Denmark. The LSADT included Danish twins aged 75 years and older who were residing in Denmark in January 1995 (17). Follow-up assessments were conducted in 1997, 1999, and 2001, and included survivors from previous waves and newly added twins who were at least 70 years old at the time of the respective surveys (18).

The 1905–Cohort study included all Danes who were born in 1905 and were alive in 1998 (aged 92–93 years), with consecutive waves in 2000, 2003, and 2005 involving the survivors from the previous waves (19). In all surveys, individuals who were residing in nursing homes or sheltered accommodations were considered eligible to participate in the study. If individuals refused or were unable to participate in the face-to-face interview, a proxy-respondent—usually a close relative—was sought. The two studies are comparable with regard to their design, implementation, and data collection instruments; with only minor differences that are mainly related to the age distributions in the two surveys.

The Danish Civil Registration System (CRS) contains individual-level sociodemographic information on all residents of the country (20). Using a unique 10-digit Civil Personal Register (CPR) number, it is possible to link various thematically organized registers at the individual level. All LSADT and 1905-Cohort participants were linked to the Danish National Prescription Registry (DNPR), which contains the Anatomical Therapeutic Chemical (ATC) classification system codes of all dispensed medications, dates of purchase, and other drug-related information since 1995 (21).

### Medication Use

The reported information on medication use in the LSADT and the Danish 1905-Cohort study was obtained by asking the participants/proxy-respondents to list all medicines they take on a regular basis. To avoid recall bias, respondents were asked to present their drug storage or medication list. All prescribed medications reported by the participants were assigned an ATC code by a pharmacologist (22). Alternative medications and vitamins were excluded. Because the DNPR codes are available since 1995, the analyses of medication use in the LSADT data include the intake participants in 1997, 1999, and 2001.

Medication use in the registry data is assessed using a 4-month fixed-time window (8), because in Denmark patients receive a 3-month reserve of each medication, and another 30 days are added to account for minor noncompliance and irregular filling patterns (23). As the drugs administered in hospitals are reported on the ward level, they are not included in the present analysis.

### Statistical Analysis

Kappa statistics were estimated for self- and proxy-respondents separately to assess the agreement in medication use information in the survey and registry data at the ATC therapeutic subgroup level (ATC level 2). The most commonly used therapeutic groups were selected: A02—medicines for acid-related disorders, B01—antithrombotic agents, C01—cardiac therapy, C03—diuretics, N02—analgesics, N05—psycholeptics, and R03—medicines for obstructive airway disease. Psychotropic medications were selected to determine whether there was lower agreement due to the reluctance of survey participants to report these medications to the interviewers.

We compared the total numbers of reported and registered medications for each study participant. The number of medications for each individual in the data was estimated as a total count of unique medications at the chemical subgroup level (ATC level 4). To reveal potential systematic differences between the two data sources, the relative difference was calculated as the difference between the mean

number of medications in the survey and registry data as a percentage of the mean number of medications in the registry. The agreement between the survey and registry data was assessed for total drug use and for the most commonly used medicines at the ATC 1 level: cardiovascular (ATC-C), alimentary tract and metabolism I (ATC-A), blood and blood-forming organs (ATC-B), nervous (ATC-N), and respiratory (ATC-R) system medications. For each index person, the relative differences in total drug use were calculated by gender and 10-year age group. A similar analysis for system-specific medications by gender and age group was not feasible due to the small number of study participants in each group.

Cox proportional hazard regression models were used to examine the association between the numbers of medications from the survey and registry data and mortality for the self- and proxy-respondents. In all of the models, we defined the time scale as survival from the date of the interview to the date of death or the end of the follow-up, whichever came first. Adjustments were made for each index person's age, gender, education (<7 years, 7–8, 9–10, 11+, other), marital status (married, never married, divorced, widowed, unknown), and total number of hospitalizations in the three years prior to the interview (none, 1, 2, 3+). To account for within-twin-pair similarities, robust standard errors were estimated that allow for clustering within each twin pair, and that assume the independence of each pair (24). The proportional hazards assumption for each covariate was tested on the basis of Schoenfeld residuals after fitting a model. No crude violations of proportional hazards assumption were detected. All of the analyses were performed using STATA, version 14.0. Also, we estimated c-statistic (c) to compare the model performance in predicting mortality for self- and proxy-respondents and from survey and registry data (25). As the estimation procedure for c-statistic assumes that the individuals in the sample are independent and life spans of twins are known to be correlated (26), we dropped randomly one of the twins in a pair, if both twins participated in the LSADT. C-statistic was estimated in R, version 3.3.2, library survAUC.

## Results

The prevalence of different ATC medication groups in the survey and registry data and the kappa with 95% confidence intervals (CIs) for the self- ( $n = 4,098$ ) and proxy-respondents ( $n = 492$ ) at all baseline waves are presented in Table 1. Among the self- and proxy-respondents, the survey and registry data on medication use showed

that diuretics and analgesics were the most frequently used, while medicines for obstructive airway disease were the least frequently used. When registry data were considered, the prevalence of all medications, with the exception of medicines for obstructive airway disease, was consistently lower among self-respondents than among proxies; whereas there was no such clear pattern in the survey data.

Among self-respondents, the agreement was moderate ( $\kappa = 0.52$ – $0.58$ ) for most therapeutic groups: antithrombotic agents, analgesics, medicines for acid-related disorder, and psycholeptics (Table 1). High agreement was found for cardiac therapy (0.85, 95% CI: 0.82, 0.88) and diuretics (0.78, 95% CI: 0.75, 0.81). Among proxy-respondents, the agreement was low to moderate for all therapeutic groups ( $\kappa = 0.36$ – $0.60$ ) and was lower than among self-respondents, with the exception of medicines for obstructive airway disease (0.83, 95% CI: 0.75, 0.92).

Figure 1 shows that for more than half of self- and proxy-respondents, the absolute difference in the total numbers of medications between the two data sources varied between  $-1$  and  $1$ . The distribution was left-skewed, and the skewness was stronger among proxy-respondents than among self-respondents.

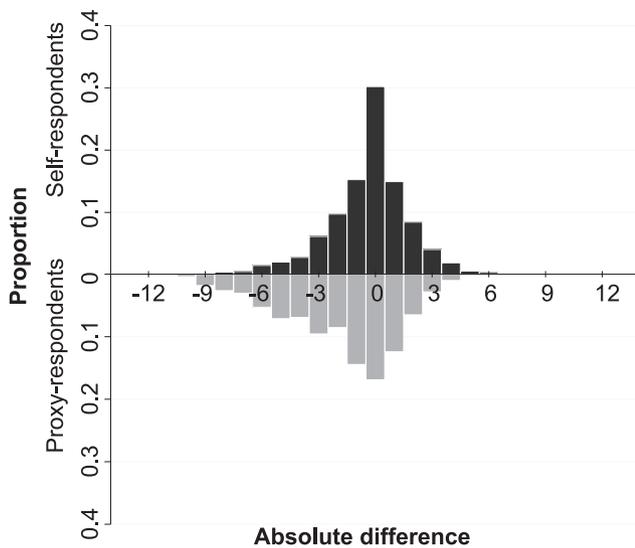
To examine potential systematic differences between the two data sources, we calculated the relative differences between the total number of reported medications and the total number of registered medications for all-cause and system-specific medications. A negative relative difference indicated that the number of medications was smaller in the survey data than in the registry data. Figure 2 shows that for both proxy- and self-respondents, the relative differences were negative for all-cause medications and for cardiovascular (ATC-C), nervous (ATC-N), and respiratory (ATC-R) system medications. The relative differences were greater among proxies than among self-respondents for these medicine groups; except for the ATC-R medications, for which the relative differences were similar. In contrast, the relative differences were positive for alimentary tract and metabolism medicines (ATC-A), and were almost zero for blood and blood-forming medicines (ATC-B) among self-respondents. Among proxy-respondents, the relative differences were negative for both medicine groups.

Finally, we assessed whether the prognostic value of medication use for predicting mortality varied between self- and proxy-respondents and between the two data sources. Among self-respondents, each additional medication was associated with a 7% (hazard ratio [HR] = 1.07, 95% CI: 1.06, 1.08) and an 8% (HR = 1.08, 95% CI: 1.06, 1.09) increase in mortality in the registry and survey data,

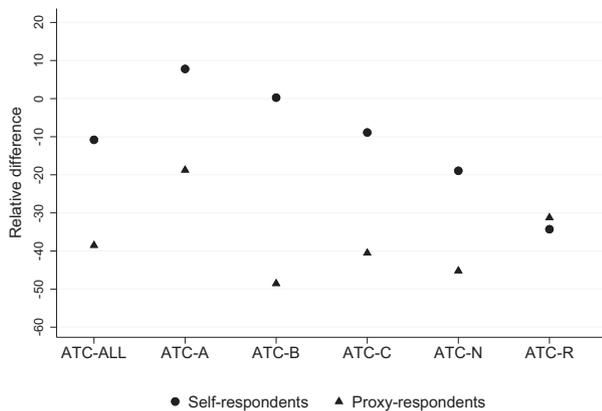
**Table 1.** Prevalence of Medication Use in and the Agreement Between the Survey and Registry Data by Response Type

Medication	Self-respondents ( $n = 4,098$ )				Proxy-respondents ( $n = 492$ )					
	Prevalence		$\kappa$	95% CI <sup>a</sup>	Prevalence		$\kappa$	95% CI		
	Survey	Registry			Survey	Registry				
A02 <sup>b</sup>	13.1	12.7	0.55	0.52	0.58	16.5	16.5	0.36	0.28	0.45
B01	20.9	21.8	0.52	0.49	0.55	11.8	24.6	0.41	0.33	0.49
C01	15.1	16.2	0.85	0.82	0.88	14.8	22.0	0.60	0.52	0.69
C03	33.1	33.9	0.78	0.75	0.81	28.7	47.8	0.43	0.35	0.51
N02	26.2	22.3	0.53	0.50	0.56	33.9	47.6	0.45	0.37	0.54
N05	16.6	27.9	0.58	0.55	0.61	20.3	44.1	0.42	0.34	0.49
R03	6.7	8.2	0.81	0.78	0.84	3.0	3.3	0.83	0.75	0.92

Note: <sup>a</sup>CI = Confidence interval. b: A02—medicines for acid-related disorders, B01—antithrombotic agents, C01—cardiac therapy, C03—diuretics, N02—analgesics, N05—psycholeptics, and R03—medicines for obstructive airway disease.



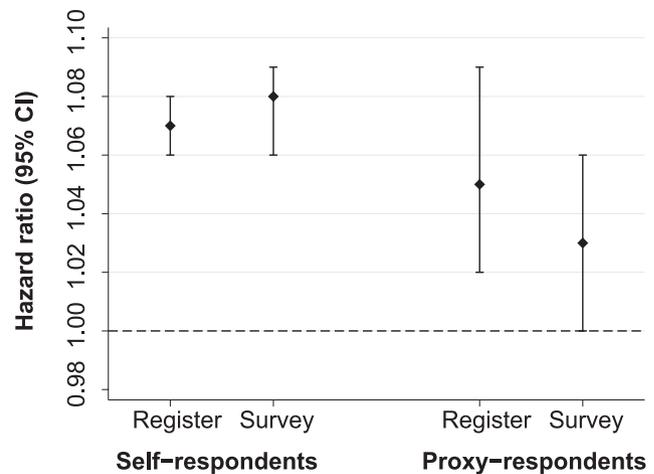
**Figure 1.** Distribution of the absolute differences in the total numbers of medications in the survey and registry data by response type.



**Figure 2.** Relative differences in the total numbers of medications in the survey and registry data by response type.

respectively, in the model adjusted for the total number of hospitalizations (Figure 3 and Supplementary Table 2). Among proxy-respondents, the levels of association between the total number of medications and mortality were lower for both the survey data (HR = 1.05, 95% CI: 1.02, 1.09) and the registry data (HR = 1.03, 95% CI: 1.00, 1.06) in the model adjusted for all selected covariates than among self-respondents (Figure 3 and Supplementary Table 2).

In the subsamples with no restriction of follow-up times, the number of medications performed similarly in predicting mortality among self- versus proxy-respondents and in registry versus survey data varying from 0.53 to 0.58 (c-100% in Supplementary Table 3). However, in the subsamples, where 10% of the individuals with the longest follow-up times were censored, the predictive ability of the number of medications for mortality remained unchanged among proxy respondents in survey and registry data: 0.58 and 0.56, respectively, while it improved among self-respondents: 0.74 in both survey and registry data (c-90% in Supplementary Table 3). These results suggest that the performance of the number of medications in predicting mortality is greater among self-respondents than among proxy-respondents.



**Figure 3.** Hazard ratios for mortality for the total number of medications by response type and data source. CI = Confidence interval.

### Discussion

The present study, which utilized data from large-scale longitudinal studies previously conducted in Denmark, has demonstrated that the concordance between survey and registry data with respect to medication use differed among self- and proxy-respondents. For most therapeutic groups, the agreement between survey and registry data was lower among proxies than among self-respondents, varying from moderate to high among self-respondents, and from low to moderate among proxy-respondents. In addition, the magnitude of the relative differences in the total numbers of medications in the survey and registry data was larger for proxies than for self-respondents for all but respiratory system medicines. The total numbers of reported medications were lower in the survey than in the registry data for all-cause and most system-specific medications among self- and proxy-respondents. Finally, we also found that the prognostic value of the total number of medications estimated from either data source was lower among proxies than among self-respondents. However, among both self-respondents and proxies, the prognostic value for mortality of the total number of medications was similar when assessed using survey versus registry data.

In line with other studies (8,9,11), we found that the agreement was higher for medicines that are taken regularly, such as cardiovascular system medications, than for medicines that are taken as needed. Our findings of high concordance between survey and registry data on medicines for obstructive airway disease among self- and proxy-respondents are not surprising because 78% of these medicines are inhalants, the use of which can be easily observed by family members/caregivers. Research evidence has shown that proxies are more likely to provide accurate responses to questions regarding more easily observable indicators than to questions of a more subjective nature (4,5). High agreement—albeit lower than in the present study—was found for obstructive airway disease medicines in previous studies that compared medication use based on self-reports and pharmacy records (8,9).

The present study utilized data from the DNPR, which enabled us to examine medication use at the individual level in a whole study population. The negative relative differences we found between the total numbers of reported and registered medications may point to the under-reporting of medication use among all respondents. Although registries are potentially more accurate sources of data on

dispensed medications, they may not reflect individuals' actual medicine use. In the present study, we were unable to assess whether the negative relative differences observed between the total numbers of reported and registered medications were due to the under-reporting of medication use by survey participants or to non-adherence to prescribed medical treatment. Although survey participants were asked to consult their drug storage or medication list to avoid recall bias, they might have forgotten about some of the medications in their drug storage, especially those that are not used regularly.

Previous research showed that characteristics of the proxy-respondents may influence the accuracy of the health assessment of the index subjects (6,27). Among all proxy-respondents, the most reliable responses on alcohol consumption and antihypertensive medication use were provided by wives, and that the most reliable responses on contraceptive use were provided by husbands but that the proximity of the proxy to the index subject had little influence on the reliability of responses on smoking status (6). Although the data collection instrument used in the Danish surveys included items on the relationships of proxy-respondents to the index persons and the frequency of the contact, it was not possible to investigate how these characteristics influenced the concordance between survey and registry data due to the small numbers in each proxy group. Another limitation of the present study is that because we utilized data conducted within approximately the same time period and in a single country, our findings may not be representative for other settings.

In conclusion, our analyses have shown that the concordance between survey and registry data regarding medication use differed between self- and proxy-respondents. We also have found that the predictive value of the number of medications for mortality is lower among proxy- than among self-respondents. These findings suggest that the levels of medication use and its ability to predict mortality may be underestimated when assessed through surveys, when proxy-respondents are involved. Thus, when studying medication use, it is desirable to supplement survey data with pharmacy records, if available.

## Supplementary Material

Supplementary data is available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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## Conflict of Interest

None reported.

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