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Polypharmacy's Association With Mortality: Confounding From Underlying Morbidity

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ABSTRACT

Background: Studies consistently associate use of multiple medications with increased mortality. However, such studies often lack adequate adjustment for confounding, particularly from underlying diseases.

Objective: To illustrate challenges in studying the association between polypharmacy and mortality by examining this relationship in two separate populations.

Methods: A register-based nationwide study utilizing a cohort of all Danish citizens admitted to nursing homes 2015–2021 ($n = 95{,}057$) and a community dwelling population cohort aged ≥65 years ($n = 1{,}005{,}963$). We examined the 1-year mortality using a Kaplan Meier plot from date of nursing home admission or index date and modeled the association between the number of medications used and death using restricted cubic splines with varying levels of adjustment. Further, we modeled the association between the 20 most used drugs and 1-year mortality.

Results: In the nursing home cohort, we found an approximately linear increase in mortality with the number of medications used. Adjusting for sex, age, and comorbidities markedly attenuated the association from an odds ratio of 4.70 (95% CI: 4.24–5.21) to 2.23 (95% CI: 1.99–2.49). Paradoxical associations were observed for individual drug classes, such as antidementia drugs showing a strong inverse association with mortality. When examining the stability of the number of drugs used over time, we found considerable fluctuations for individual residents. In the community dwelling population cohort, adjustment for covariates showed an even stronger impact on the association, reducing the odds ratio from 10.39 (95% CI: 9.79–11.03) to 1.34 (95% CI: 1.25–1.43). Further, the individual-level use of medication was found to be stable over time in the general population.

Conclusion: The association between levels of polypharmacy and mortality is strongly affected by confounding by indication. Basic adjustment for comorbidities attenuates but does not fully eliminate the association, with residual association possibly driven by residual confounding. This emphasizes the need for cautious interpretation of findings associating high use of medication with mortality.

Summary

- Key points
  - Polypharmacy is consistently associated with mortality; however, studies often inadequately adjust for underlying diseases.
  - The strong association between number of drugs and mortality within nursing home residents, was halved when adjusting for comorbidities, and largely removed upon adjusting within a community dwelling cohort of older adults.
  - Caution is necessary when interpreting studies of the association between medication use and mortality.
- Why does this matter?
  - This study illustrates the need for caution when interpreting studies on the association between mortality and number of medications used, in particular when data to adjust comorbidities and frailty are not available.
  - This is important as researchers risk affecting decision- and policymaking with potential faulty interpretations of this increasingly scrutinized association.

1 | Introduction

As the longevity among the general population increases, so does the prevalence of both acute and chronic disease, leading to an increase in medication use and polypharmacy prevalence among older adults [1–3]. Studies consistently associate polypharmacy, often defined as concurrent use of five or more medications [4, 5], to mortality [6–12]. However, most of these studies fail to adjust adequately for confounding, largely due to the complexity of exposure or lack of available data. As estimates of the association are highly prone to confounding from indication from the underlying disease(s) treated by the medications they use, existing findings must be interpreted with caution. Despite this, several such studies have concluded that polypharmacy is an independent risk factor for mortality and thus should be avoided [13–17]. In this study, we aim to provide an illustrative and cautionary example of the association between levels of polypharmacy and mortality to inform future studies. We do so by examining the association between the use of multiple medications and mortality in two separate populations to illustrate the inherent challenges in studying this association, by describing aspects of the association that point to a non-causal interpretation.

2 | Methods

2.1 | Data Sources

The data for the cohort were assembled, encrypted, and provided by the Danish Health Data Authority using data from the Danish National Prescription Registry [18] and the Danish National Patient Registry [19], linked via the personal identification number assigned to all Danish residents since 1968 [20]. Denmark is a welfare state with national, free, and easy access to healthcare services [21]. The personal identification number contains information such as sex and date of birth, death, and migration. The Prescription Registry holds individual-level data on all filled prescriptions at all community pharmacies in Denmark since 1995. This includes variables such as the type of drug, amount, and anatomic therapeutic chemical (ATC) classification [22]. The Patient Registry holds individual-level data on all admissions to Danish hospitals since 1994. This includes variables such as admission- and discharge diagnoses codes using the ICD-10. Comorbidities were scored using the Nordic Multimorbidity Index [23] which is a comorbidity score developed on register-based data in a cohort of Danish residents. The Nordic Multimorbidity Index is a validated score, which has been assessed using c-statistics against the Charlson Comorbidity Index and the Elixhauser Comorbidity Index [23]. The comorbidity score is comprised of 50 weighted ICD-10 diagnoses and ATC codes from filled prescriptions (Table S1).

2.2 | Study Cohorts

This was a register-based cohort study using, as a case example, a cohort of all Danish residents ≥65 years moving into a nursing home in the period 2015 to 2021. To contextualize findings outside of the nursing home setting, all analyses were repeated in a community dwelling population cohort comprising Danish residents aged ≥65 years per January 1st, 2016, in the period 2016–2019, that were assigned random index dates throughout the period 2016 to 2018 and followed up for one year. The cohorts were linked with individual-level registry data on prescriptions filled in community pharmacies in Denmark, and the comorbidity scores were calculated using all available look back up until nursing home admission or index date.

2.3 | Exposure and Outcomes

We obtained data on drug use from the Prescription Registry, that is, drugs filled in community pharmacies, while disregarding prescriptions for antibiotics (ATC: J), as these were assumed to correspond to shorter-term treatments. We used this information to identify our main exposure, that is, the number of unique drugs used, defined as filled prescriptions per full ATC level. The outcome of interest was all-cause death.

2.4 | Statistical Analyses

We examined the association between levels of polypharmacy and 1-year mortality using three different models: a Kaplan Meier plot, flexible modulation using splines, and logistic regression.

First, using a Kaplan Meier plot, we examined the 1-year mortality from the date of nursing home admission/index date, stratifying by number of drugs (0–1, 2–5, 6–10, 11–15, 16–19, ≥20) filled in the 120 days prior to nursing home admission/index date.

Second, we flexibly modeled the association between the number of drugs and 1-year mortality using restricted cubic splines (knots placed at the 5., 35., 65., and 95. percentiles), as well as modeled the association between the number of drugs and

1-year mortality, with increasing levels of adjustments for covariates: (i) sex and age, (ii) sex, age, and a full comorbidity score using the Nordic Multimorbidity Index [23]. We excluded individuals within the highest percentile of the number of different drugs used before modeling the association.

Third, we performed logistic regression associating the 20 most used individual medications (based on the proportion of users in the 120 days prior to nursing home admission) with odds of death within 1 year, in a crude model solely adjusted for age and sex as well as with adjustment for the Nordic Multimorbidity Index [23].

Last, we described the stability of the polypharmacy phenotype by cross-tabulating the number of individual medications filled in the 120 days prior to nursing home admission or index date and the number of medications filled in the 120 days following nursing home admission or index date, restricted to those surviving the first 120 days.

2.5 | Ethics and Approvals

This study did not require approval from an ethics review board, according to Danish law on studies based solely on register data [24]. In terms of data protection, the study was registered at the repository of University of Southern Denmark (11.277 and 10.113).

3 | Results

The nursing home cohort comprised 95,057 residents (62% female; median age 84 years) that used a median of eight different medications (interquartile range, IQR: 5–11) and had a 1-year mortality of 32%. The supplementary community dwelling population cohort of Danish residents, aged ≥65 years, comprised 1,005,963 people (54% female; median age 74 years), using a median of four different medications (IQR: 1–6) and with a 1-year mortality of 4.4%. Detailed characteristics of the nursing home cohort and the supplementary community dwelling population cohort are presented in Table S2.

When stratifying by number of different medications, the 1-year mortality more than doubled from around 20% among those taking 0–1 medications to just over 50% among those taking ≥20 medications (p value 0.0000) (Figure 1). The sex and age adjusted association between the 1-year mortality and number of medications presents an approximately linear trend increasing up to an odds ratio (OR) of 4.70 (95% CI: 4.24–5.21) with use of 20 medications compared to 0 medications (Figure 2b). The association between use of ≥20 medications and 1-year mortality dropped markedly with increasing adjustment. When additionally adjusting for the Nordic Multimorbidity Index, the OR dropped to 2.23 (95% CI: 1.99–2.49) among those taking ≥20 medications, while no excess risk was observed with low (1–5) use of medicines (Figure 2b).

When examining the use of medication 120 days prior to nursing home admission and 120 days following nursing home admission restricted to those surviving the first 120 days (n = 80,793), we found that among users of ≥16 medications, only 32% were still using ≥16 medications after nursing home admission (Table 1). Similarly, among those using only a few medications prior to admission, the use of medication also changed markedly. For example, among those using 2–3 medications prior to nursing home admission, only 37% stayed within this use category, while >20% used ≥6 medications in the subsequent 120-day window (Table 1).

The association between the 20 most used individual medication groups and 1-year mortality revealed several strong associations. Stronger associations were all markedly attenuated when adjusting for comorbidity, while adjusting for comorbidity

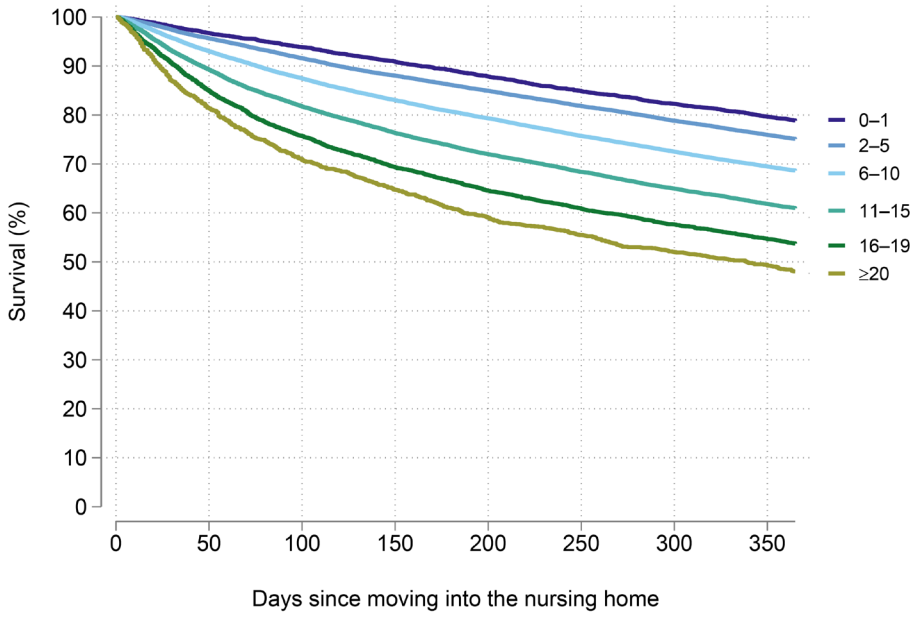

FIGURE 1 | Kaplan Meier plot showing the 1-year mortality from the date of nursing home admission adjusted for sex and age, stratifying by number of drugs (0–1, 2–5, 6–10, 11–15, 16–19, ≥20) filled in the 120 days prior to nursing home admission (p value 0.0000).

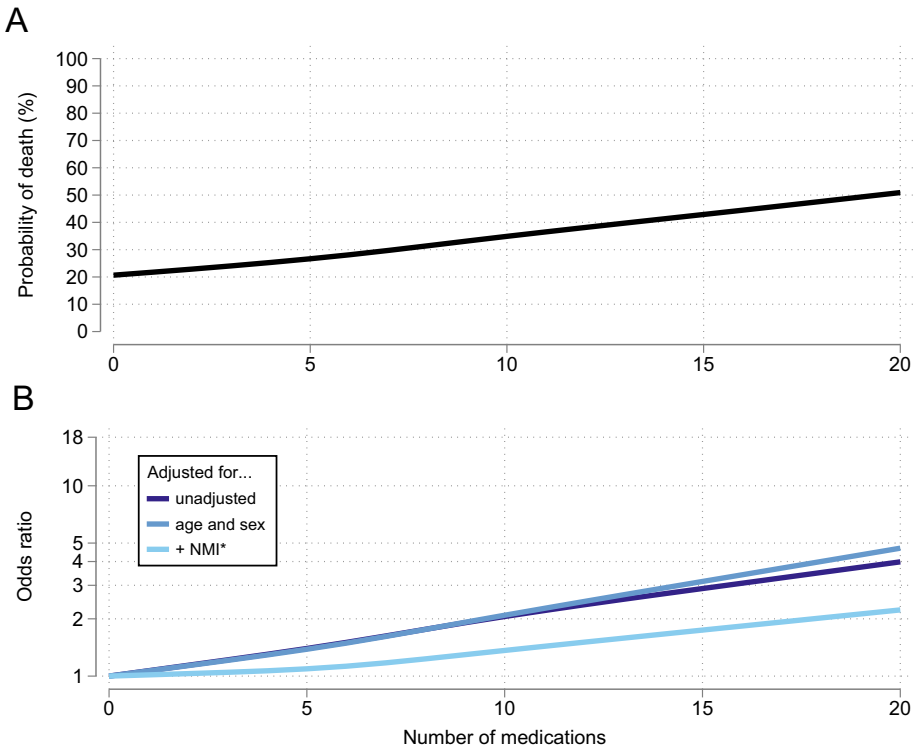

FIGURE 2 | (A) Crude flexible model of the association between number of drugs and odds of death within 1 year using restricted cubic splines (knots placed at the 5., 32., 59. and 95. percentiles) in the nursing home cohort. (B) The association between number of drugs and odds of death within 1 year, with increasing levels of adjustments for covariates: (i) unadjusted, (ii) sex and age, (iii) sex, age, and the Nordic Multimorbidity Index (NMI*) [23] in the nursing home cohort. The highest 1. percentile of number of different drugs was excluded before modeling the association in both A and B.

TABLE 1 | Table showing stability of polypharmacy phenotypes as proportion of nursing home residents 120 days prior to and 120 following nursing home admission, among those surviving 120 days following nursing home admission ($n = 80{,}793$).

120 days following nursing home admission: No. of medications	120 days prior to nursing home admission: 0	1	2-3	4-5	6-10	11-15	≥16
0	25%	7.0%	1.4%	0.41%	0.09%	0.06%	(n<5)
1	21%	22%	6.3%	1.6%	0.36%	0.08%	(n<5)
2-3	27%	38%	37%	14%	3.8%	0.70%	0.13%
4-5	13%	20%	32%	36%	14%	3.8%	1.1%
6-10	10%	12%	22%	44%	64%	42%	19%
11-15	2.4%	1.0%	1.5%	3.9%	16%	44%	47%
≥16	1.5%	0.25%	0.16%	0.23%	1.3%	8.6%	32%

had only a marginal effect on weaker associations (Table 2). However, several paradoxical associations remained, that is, the receipt of antidementia drugs or selective serotonin reuptake inhibitors (SSRIs) was strongly associated with reduced odds of death (OR 0.48; 95% CI: 0.47–0.49 for antidementia drugs; OR 0.79; 95% CI: 0.77–0.80 for SSRIs) (Tables 2 and S3).

In the supplementary community dwelling population cohort ($n = 1{,}005{,}963$), a similar approximately linear relationship between levels of polypharmacy and probability of death was seen (Figures S1 and 3a). However, in this cohort, the association between high levels of polypharmacy was, on the relative scale, appreciably stronger than in the nursing home cohort (OR 10.39; 95% CI: 9.79–11.03 with use of 15 medications), whereas adjusting for covariates had a more pronounced effect in attenuating this OR to 1.34 (95% CI: 1.25–1.43) (Figure 3b). When looking at the stability of the use of medication in the community dwelling population cohort, both low- and high-use of medication was found to be highly stable over time (Table S4). Similarly, as for the nursing home cohort, the 20 most used medications were strongly associated with mortality that was attenuated upon adjustment; however, here we also found paradoxical associations,

TABLE 2 | Table showing the unadjusted and adjusted odds ratios of the 20 most frequently used medications with risk of death within 1 year among both the nursing home cohort and the supplementary community dwelling population cohort. Medications are classified at the anatomic therapeutic chemical level 4.

		Nursing home cohort ($n = 95,057$)			Community dwelling population cohort (1,005,963)		
Anatomic therapeutic chemical (ATC)	**Drug class**	**Frequency, % (*n*)**	**Unadjusted OR, (95% CI)**	**Adjusted for NMI OR, (95% CI)**	**Frequency, % (*n*)**	**Unadjusted OR, (95% CI)**	**Adjusted for NMI OR, (95% CI)**
N02BE	Anilides (paracetamol)	61 (57,951)	0.98 (0.97–0.99)	0.99 (0.98–1.00)	26 (265,192)	1.17 (1.16–1.18)	1.10 (1.09–1.11)
B01AC	Platelet aggregation inhibitors[a]	33 (31,558)	0.79 (0.78–0.80)	0.86 (0.85–0.88)	22 (226,132)	0.83 (0.82–0.84)	0.95 (0.93–0.96)
A02BC	Proton pump inhibitors	31 (29,773)	1.10 (1.08–1.11)	1.09 (1.07–1.11)	18 (177,897)	1.09 (1.08–1.10)	1.03 (1.02–1.04)
A06AD	Osmotically acting laxatives	29 (27,312)	1.13 (1.11–1.15)	1.00 (0.98–1.02)	3.0 (30,142)	2.34 (2.29–2.39)	1.26 (1.23–1.29)
C10AA	HMG CoA reductase inhibitors (statins)	29 (27,113)	0.72 (0.71–0.73)	0.84 (0.83–0.86)	31 (314,194)	0.61 (0.60–0.62)	0.84 (0.83–0.85)
A12BA	Potassium	28 (26,819)	1.15 (1.13–1.17)	1.13 (1.11–1.15)	9.2 (92,266)	1.33 (1.32–1.35)	1.12 (1.11–1.14)
C03CA	Sulfonamides (furosemide)	26 (24,408)	1.34 (1.31–1.36)	1.21 (1.19–1.23)	9.0 (90,243)	1.46 (1.44–1.48)	1.06 (1.05–1.08)
C07AB	Selective beta blocking agents	24 (22,409)	0.99 (0.97–1.00)	1.05 (1.03–1.07)	18 (177,061)	0.79 (0.78–0.80)	0.95 (0.94–0.96)
N06AB	Selective serotonin reuptake inhibitors	20 (19,381)	0.77 (0.76–0.79)	0.79 (0.77–0.80)	6.2 (62,155)	1.39 (1.37–1.42)	1.10 (1.08–1.12)
C08CA	Dihydropyridine derivates (calcium channel blockers)	19 (18,246)	0.78 (0.76–0.80)	0.90 (0.88–0.92)	18 (182,765)	0.62 (0.61–0.63)	0.87 (0.85–0.88)
N02AA	Natural opium alkaloids (morphine)	19 (18,071)	1.42 (1.40–1.44)	1.25 (1.23–1.27)	3.5 (35,465)	2.35 (2.32–2.39)	1.47 (1.45–1.50)
N06AX	Other antidepressants	17 (16,223)	0.84 (0.82–0.86)	0.81 (0.79–0.83)	4.6 (46,348)	1.41 (1.38–1.43)	1.06 (1.05–1.08)
A06AB	Contact laxatives	17 (16,097)	1.19 (1.16–1.21)	1.06 (1.03–1.08)	1.6 (16,444)	2.33 (2.27–2.39)	1.22 (1.19–1.26)
B01AF	Direct factor Xa inhibitors	16 (15,543)	1.02 (1.00–1.05)	1.04 (1.01–1.06)	4.5 (45,719)	1.02 (1.00–1.04)	0.97 (0.95–1.00)
C09AA	ACE inhibitors	16 (14,932)	0.83 (0.82–0.85)	0.93 (0.91–0.95)	13 (134,009)	0.72 (0.71–0.73)	0.90 (0.88–0.91)
N06DA	Antidementia drugs (Anticholinesterases)	14 (13,774)	0.54 (0.52–0.55)	0.48 (0.47–0.49)	1.3 (13,054)	1.31 (1.27–1.35)	0.65 (0.63–0.67)

(Continues)

TABLE 2 | (Continued)

Anatomic therapeutic chemical (ATC)	Drug class	Nursing home cohort ($n = 95,057$)			Community dwelling population cohort (1,005,963)		
		Frequency, % (n)	Unadjusted OR, (95% CI)	Adjusted for NMI OR, (95% CI)	Frequency, % (n)	Unadjusted OR, (95% CI)	Adjusted for NMI OR, (95% CI)
N02AX	Other opioids	12 (11,766)	0.98 (0.96–1.01)	0.95 (0.93–0.98)	5.9 (59,434)	1.10 (1.08–1.12)	0.99 (0.97–1.01)
N05CF	Benzodiazepines related drugs	12 (11,475)	1.07 (1.04–1.09)	1.04 (1.01–1.06)	5.6 (56,672)	1.07 (1.05–1.09)	1.02 (1.00–1.04)
C09CA	Angiotensin II receptor blockers	12 (11,189)	0.78 (0.76–0.81)	0.92 (0.90–0.95)	12 (117,023)	0.58 (0.57–0.59)	0.85 (0.83–0.87)
B03BA	Vitamin B12	9.7 (9185)	0.81 (0.79–0.84)	0.86 (0.83–0.89)	3.5 (35,407)	1.04 (1.02–1.07)	1.04 (1.01–1.07)

Abbreviations: 95% CI, 95% Confidence Interval; NMI, Nordic Multimorbidity Index; OR, odds ratio.
[a]Excluding heparin.

that is, being treated with antidementia drugs having a strong protective effect against death (OR 0.65; 95% CI: 0.63–0.67) (Tables 2 and S3). However, the observed inverse association with SSRI use was not replicated (OR 1.10; 95% CI: 1.08–1.12) (Tables 2 and S3).

4 | Discussion

In this methodological case study, we report a strong association between the number of medications and 1-year mortality in both a cohort of nursing home residents and in the community dwelling population. However, this excess risk was greatly attenuated upon adjusting for sex, age, and comorbidities, in particular in analyses of the community dwelling population. Among the 20 most used drugs, several paradoxical associations were identified, for example, antidementia drugs being strongly protective against death.

This study replicates the association between the number of different medications used and mortality, reported in previous studies [6–12]. Similar to these studies, we found that the 1-year mortality and number of different medications presents as an approximately linear association. Likewise, previous studies also report an attenuated association when adjusting for covariates such as age and sex, and even further when adjusting for comorbidities. Despite this, a recent systematic review found that 30 out of 39 included studies did not adjust for comorbidities [6]. The marked attenuation of associations is possibly due to confounding from the underlying reason for drug treatment, that is, confounding by indication, which is notoriously difficult to adjust for, as also illustrated by the residual risks following adjustment in the present study. Generally, when a strong association is reduced to a weak association upon adjustment, this residual association should rarely be interpreted as a true effect. Any adjustment is imperfect, due to both minor inaccuracies in coding and use of proxy measures only in part capturing the true health status of the individual. Comparing community dwelling aged people with nursing home residents, might skew the confounding levels, as restricting to nursing home residents may innately account for some level of confounding, in terms of sickness and frailty [25]. Thus, when results are obtained that resemble those obtained in the present study for the community dwelling population cohort, that is, that a 10-fold increased risk is reduced to a 1.3-fold increased risk, we caution against simply interpreting the latter as a residual effect that should be attributed to the "true effect of polypharmacy." Nevertheless, one cannot rule out, using an observational design, that any residual effects will reflect harmful effects of polypharmacy. It is possible that adverse drug effects, including drug–drug interactions or drug-disease interactions, due to multiple medications may explain at least some of the residual effects.

Use patterns and selective prescribing in older frail people, such as nursing home residents, often affect the estimation of mortality risk associated with specific medications in this population, leading to seemingly paradoxical associations [26]. As an example, use of antidementia drugs and SSRIs showed strong protective "effects" against death in the nursing home cohort, even following adjustment. This might be explained by antidementia drugs being a marker of a need for care and thus a

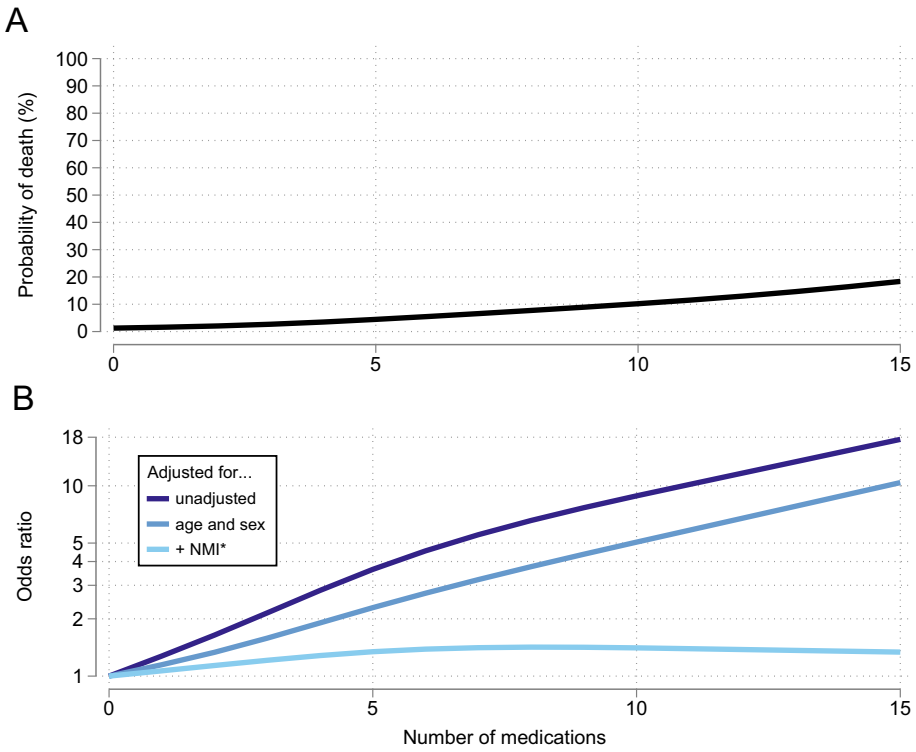

FIGURE 3 | (A) Crude flexible model of the association between number of drugs and odds of death within 1 year using restricted cubic splines (knots placed at the 5., 32., 59., and 95. percentiles) in the community dwelling population cohort. (B) The association between number of drugs and odds of death within 1 year, with increasing levels of adjustments for covariates: (i) unadjusted, (ii) sex and age, (iii) sex, age, and the Nordic Multimorbidity Index (NMI*) [23] in the community dwelling population cohort. The highest 1. percentile of number of different drugs was excluded before modeling the association in both A and B.

predictor for being admitting into a nursing home that carries lower mortality risk than other reasons for being admitted (e.g., frailty). In the community dwelling population cohort, antidementia drugs were found to have a strong association with death prior to comorbidity adjustment, which was then reversed into a strong protective effect against death following adjustments. Such paradoxical relationships have previously been described and attributed to selective under-prescribing of certain medications among older frail adults leading to artificially lower mortality risks [26].

We found that the use of medication is highly varying in a frail population, such as older adults living in nursing homes. Medication use is often considered at nursing home admission as baseline and analyzed using an "intention to treat" approach, which might not be without problems, as medication use fluctuates during follow-up as demonstrated. As such, this approach will infer considerable exposure misclassification. Of note, the magnitude of this misclassification is dependent on the patient population under scrutiny, as illustrated by the community dwelling population cohort where medication use was significantly more stable over time.

When reporting on studies on polypharmacy and mortality, there is a considerable need for transparency regarding the risk of estimates being confounded by both known and unknown confounders. Such confounders may affect populations in very different ways, which highlights the need for discussing the complex relationships in light of the individual patient population or setting. As an example, we showed that adjusting for comorbidity had a considerable impact on the association between SSRI use and mortality; however, this effect was very different in the nursing home cohort and in the community dwelling population cohort. Whether a given study will be able to provide trustworthy estimates of the causal association between the number of medications or levels of polypharmacy and mortality will depend on the data available for such adjustment and the methodological rigor applied. However, in most cases, and with usual register-based data available to the researcher, there is, as argued above, a considerable risk of residual confounding, and that interpretation of estimates should thus be done with caution.

4.1 | Strength and Limitations

The main strength of this study is the national cohorts of all Danes admitted to nursing homes in 2015 and onwards, and the full capture of the community dwelling population cohort, with complete and unambiguous linkage across the highly valid Danish Health registries [18–20]. However, this study has several limitations. First, the proxy used to identify medication use, that is, prescription fills, might not accurately capture the use of prescription medications specifically among nursing home residents, where treatment is often changed or uncertain, leading to a potential overestimation of medication use. Second, while we adjusted for a setting-specific comorbidity index [23], detailed clinical data on health status were not available. It is considered likely that the availability of data on for example, specific frailty measures [27, 28] might facilitate better adjusting for the

underlying health status and thus result in even stronger attenuation of the reported associations. Lastly, it is important to emphasize that the reported findings are highly dependent on the patient population and setting in question, as demonstrated by the differences in the analyses between the nursing home and community dwelling population cohorts.

5 | Conclusion

In this study we demonstrate that the association between the number of medications at the time of nursing home admission and mortality is highly affected by confounding by indication. Further, we demonstrated similar effects when examining community dwelling people aged ≥ 65 years. The risk was attenuated when adjusting for sex and age, but most significantly so when adjusting for comorbidities. However, a low persisting association possibly reflecting residual confounding illustrates the need for careful interpretation of reported associations between the number of medications and mortality risk.

Author Contributions

The initial study idea was proposed by Anton Pottegård, and the study was designed by Anton Pottegård and Emma Bjørk. The data analysis was performed by Jacob Harbo Andersen, and the initial draft was written by Emma Bjørk. All authors participated in writing and revising the article as well as read and approved the final version of the manuscript. All authors meet the criteria for authorship stated in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

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Conflicts of Interest

Anton Pottegård reports participation in research projects funded by Alcon, Almirall, Astellas, Astra-Zeneca, Boehringer-Ingelheim, Novo Nordisk, Servier, and LEO Pharma, all regulator-mandated phase IV studies, all with funds paid to the institution where he was employed (no personal fees) and with no relation to the work reported in this paper. Remaining authors declares no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.