Received: 4 June 2021 | Revised: 14 December 2021 | Accepted: 17 December 2021

DOI: 10.1111/bcp.15211

SHORT COMMUNICATION

Is polypharmacy associated with mortality in the very old: Findings from the Newcastle 85+ Study

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Funding information
National Institute for Health Research School for Primary Care Research (NIHR SPCR), Grant/Award Number: SPCR-2014-10043

Polypharmacy is common in the very old (≥85 years), where little is known about its association with mortality. We aimed to investigate the association between polypharmacy and all-cause mortality in the very old, over an 11-year time period. Data were drawn from the Newcastle 85+ Study (741), a cohort of people who were born in 1921 and turned 85 in 2006. Survival analysis was performed using Cox proportional hazards models with time-varying covariates, wherein polypharmacy was operationalised continuously. Each additional medication prescribed was associated with a 3% increased risk of mortality (hazard ratio: 1.03, 95% confidence interval: 1.00–1.06). Amongst the very old, the risks and benefits of each additional medication prescribed should be carefully considered.

KEYWORDS
mortality, polypharmacy, very old

1 | INTRODUCTION

Polypharmacy—the use of multiple medications—is common in the very old (aged ≥85 years)[1] but whether it is associated with mortality in this fastest growing subpopulation[2] is seldom studied. Some researchers have found a positive association[3–7] and others a nonsignificant effect[8] across different populations, polypharmacy definitions, follow-up durations, covariate adjustments and periods in time.

Not forgetting the many benefits of medication, potential reasons for the association between polypharmacy and mortality in the very old include adverse drug reactions, nonadherence and inappropriate prescribing—be it through drug–drug interactions; improper doses, indications or durations; high-risk medicines or prescribing omissions.[9–12] Indeed the very old are likely to be sensitive to medication prescription due to age-related pharmacokinetic and pharmacodynamic changes, coupled with multimorbidity, cognitive impairment and/or frailty.[13–15] In other words, they have fewer physiological reserves to withstand potential adverse effects of multiple medications.

In addition to risk stratification for medication reviews, understanding the degree to which polypharmacy is associated with mortality in the very old could assist future care planning. In spite of life-limiting conditions such as frailty for example,[16] palliative care is not always optimised or provided in those aged 85 and over[17] and preventative medicines of questionable benefit are often sustained until the end-of-life[18]—increasing not only the patients' pill burden, awareness of morbidity and propensity for adverse drug reactions, but healthcare costs as well.[9,19,20]

The Newcastle 85+ Study is a population-based longitudinal study, detailing the health of an inception cohort of 85-year-olds through multidimensional health assessments and general practice medical records.[21] Linking this study with death registrations has allowed us to investigate the relationship between polypharmacy and all-cause mortality in the very old, over time, after accounting for multiple confounding factors.

2 | METHODS

2.1 | Recruitment and study protocol

Participants belonged to the Newcastle 85+ Study: a population-based longitudinal study of very old adults living in North East England who were born in 1921, aged 85 in 2006 and permanently registered with 1 of 53 participating general practices in Newcastle or North Tyneside.[21] When the study began (2006), the cohort was sociodemographically nationally representative but participants with end-stage terminal disease or the potential to endanger nurses were excluded ($n = 11$).[21] Data were collected in 2 ways: multidimensional health assessments at baseline (wave 1), 18 months (wave 2), 36 months (wave 3), 60 months (wave 4) and 120 months (wave 5), and general practice medical records at baseline, waves 3, 4 and 5.[22] Full details of the questions asked in the Newcastle 85+ Study are available at http://research.ncl.ac.uk/85plus/, whilst study retention can be found in Appendix A.

Both health assessment and general practice records data were available for 845 participants at study baseline, of whom 741 had complete data for confounding variables used in this analysis.

What is already known about this subject

- Polypharmacy is common in the very old (aged ≥85 years).
- Little is known about the association between polypharmacy and mortality in this fastest growing subpopulation.

What this study adds

- In a cohort of 85-year-olds followed over 11 years, each additional medication prescribed was associated with a 3% increased risk of mortality (hazard ratio: 1.03, 95% confidence interval: 1.00–1.06).
- Amongst the very old, the risks and benefits of each additional medication prescribed should be carefully considered.

2.2 | Ethics

The Newcastle 85+ Study was approved by the Newcastle and North Tyneside Local Research Committee One (Ref: 06/Q0905/2). Written informed consent was obtained from participants, and where people lacked capacity to consent—for example, because of dementia—an opinion was sought from a relative or carer (a *consultee*).[21]

2.3 | Mortality data

The exact date of death from all causes was reported to the study from the Health and Social Care Information Centre (now NHS digital). Survival time (in years) was calculated from the date of baseline health assessment to the date of death or censoring at 11.29 years.

2.4 | Polypharmacy status

A detailed discussion characterising polypharmacy in this cohort has previously been presented.[1] Data on prescribed medications were obtained from general practice medical records. Polypharmacy was operationalised as a time-varying covariate to address whether baseline polypharmacy status could be predictive of prospective mortality 11 years hence, and also reflect period effects in terms of prescribing prevalence typically increasing over time.[23] It was treated as a continuous variable to account for potential nonlinearity within categorical thresholds. Items such as vaccines, wound-management products and catheter/stoma products were excluded from the above definition (Appendix B).[24] Participant-reported over-the-counter medicines were also excluded to make our results directly applicable to prescribing practice in primary care. Medications were coded according to the British National Formulary (58th edition).[21]

2.5 | Confounders

Confounders were selected on their representation within the existing literature and log-rank results at $P < .05$. Those variables that were clinically or biologically important, but not statistically significant, were therefore retained. Sociodemographic factors included age, sex, housing status (standard/sheltered/institution), education (0–9/ 10–11/ ≥12 years) and socioeconomic position (<25th/25th–75th/>75th centile Index of Multiple Deprivation).[5,25–27] Lifestyle factors included smoking (current/former/never) and current alcohol intake (yes/no).[5] Health-related variables included arthritis, hypertension, eye disease, cardiovascular disease, respiratory disease, cerebrovascular disease, cognitive impairment, diabetes, osteoporosis, depression, cancer, renal impairment, self-rated health (excellent or very good/good/fair or poor), loneliness (always or often/sometimes/never) and disability ([instrumental] activities of daily living, none/1–6/7–12/13–17).[5,28–35] Disease groups were assessed individually (rather than through a simple disease count) to reduce the possibility of residual bias and reflect their heterogeneous effects. Indeed, being a crude measure, a simple disease count would lose valuable information, and disease groups that have a greater association with mortality than others would be treated equally under it. Full details of disease status construction and composition can be found in Appendix C.

2.6 | Statistical analysis

Cox proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI) for the risk of all-cause mortality associated with polypharmacy. Three models were explored:

i. Model 1 was unadjusted to benchmark the effect of confounders ($n = 845$)
ii. Model 2 was adjusted for sex due to the greater longevity of women ($n = 845$)
iii. Model 3 was adjusted for the 22 confounders detailed above ($n = 741$)

These models treated polypharmacy and all covariates as time-varying through updating their values at each study wave (excepting fixed variables such as sex, socioeconomic position and education, and those only available at baseline: smoking, current drinking and renal impairment).

The proportional hazards assumption for every cox regression model was checked by examining the Schoenfeld residuals, and variables that failed the proportionality test—eye disease, cerebrovascular disease, cardiac disease and cognitive impairment (model 3)—were adjusted for by stratification. No evidence of multicollinearity (checked through variance inflation) was detected. Efforts were made to reduce overfitting by: (i) avoiding stepwise selection; (ii) combing covariates into composites; (iii) excluding frailty due to overlap with disability ($r = 0.74$); and (iv) excluding Parkinson's disease ($n = 14$) and liver disease ($n = 12$) from the analysis to observe the 15:1 observations: covariate rule.[36–39] Marital status was also excluded as loneliness in widowhood may be transient,[40] and its inclusion (in place of loneliness) did not alter the figures in a sensitivity analysis. A full model fit of all hypothesised variables was therefore used as this technique is more discriminating and transparent.[38] Analyses were carried out using the *Survival* package in R.3.50.

3 | RESULTS

3.1 | Participant characteristics

Over this study period, there were 723 deaths (85.6%) and 122 (14.4%) right-censored observations (i.e. people who remained alive at the end of the analytical period). The median survival time was 5.39 years; 4.36 years for men and 6.17 years for women.

3.2 | Cox proportional hazards models

For every additional medication that was prescribed, a 3% corresponding increase in mortality was observed (HR: 1.03, 95% CI: 1.00–1.06; model 3, Table 1).

TABLE 1 Risk of all-cause mortality associated with each additional medication prescribed

Model	HR (95% CI)	*P*-value
Model 1 ($n = 845$)	1.08 (1.06–1.10)	<.001
Model 2 ($n = 845$)	1.08 (1.06–1.10)	<.001
Model 3 ($n = 741$)	1.03 (1.00–1.06)	.06

Note: Model 1 is not adjusted; Model 2 is adjusted for sex; Model 3 is adjusted for 22 health (diseases, self-rated health, loneliness, disability), sociodemographic (age, sex, housing status, education, socioeconomic position) and lifestyle factors (smoking status, current drinking), and treats all variables (excepting sex, education, socioeconomic position, renal impairment, smoking and drinking) as time-varying. CI = confidence interval; HR = hazard ratio.

4 | DISCUSSION

4.1 | Principal findings

In a cohort of 85-year-olds followed for approximately 11-years, each additional prescribed medication was associated with a 3% increased risk of mortality (HR: 1.03, 95% CI: 1.00–1.06).

4.2 | Comparison with existing literature

The suggestion of an increased risk of death associated with each additional prescribed medication might reflect the provision of symptom relief within a palliative context.[41] Alternatively, it may result from the increased potential for adverse drug reactions,[42] non-adherence[43] and inappropriate prescribing with rising medication counts,[44] as well as the law of diminishing returns[45] and greater sensitivity of older people to medication prescription.[46]

4.3 | Strengths and limitations

Our findings, over long-term follow up, extend the existing evidence[3–7] and support the recommendation that polypharmacy should be treated as a time-varying exposure in future observational studies.[47–49] Other strengths of this work include the comprehensive adjustment for mortality-related confounders, steps taken to avoid overfitting and use of data from general practice medical records rather than the less reliable method of self-report.[21]

The lower number of male participants ($n = 319$; in reflection of the "male–female health-survival paradox"),[27] meant that we were unable to reliably calculate hazard ratios separately by sex. Despite adjusting for a raft of mortality-related confounders including disability, residual and unmeasured confounding also cannot be excluded. It is therefore possible that medication prescription could be a marker of poor underlying health rather than an independent risk factor for mortality. *All-cause* mortality does not include COVID-19, as data analysis finished prior to the pandemic; diseases were grouped by body systems to increase power, 35 phase 5 participants with missing

GP records were assumed to have no diagnoses, and disease severity, delirium and gastrointestinal conditions could not be adjusted for, for example. Our results could also be distorted by a survivor effect—i.e. participants surviving to 95 years of age with polypharmacy could be more robust. There is potential for reverse causation in using time-varying polypharmacy because the number of prescribed medicines often increases prior to death,[41] although participants with end-stage terminal disease were excluded from the Newcastle 85+ Study, and the alternative of baseline polypharmacy status is unlikely to be predictive of mortality 11 years hence. It was beyond the scope of this work to make the distinction between chronic and acute medication prescription, and local and systemic effect. Furthermore, despite harnessing the longitudinal aspects of the data, we could not capture prescribing changes outside of data collection points, and to measure medication changes on an ideally monthly basis would require considerable computational power.[49] Finally, our multivariable results did not cross the threshold for statistical significance but are still clinically important—particularly given the pace of population aging[50] and likely rise in polypharmacy in tandem with multimorbidity projections.[51]

4.4 | Implications and conclusion

The suggestion of a 3% increased risk of death associated with each additional prescribed medication suggests the need for judicious prescribing in the very old. Prescribers could, for example, consider whether the time-to-benefit of certain medications outweighs patient potential life-expectancy and remain vigilant to prescribing cascades.

ACKNOWLEDGEMENTS

This paper presents independent research funded by the National Institute for Health Research School for Primary Care Research (NIHR SPCR; SPCR-2014-10043). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

The Newcastle 85+ Study has been funded by the Medical Research Council, Biotechnology and Biological Sciences Research Council, the Dunhill Medical Trust and the National Institute for Health Research School for Primary Care. Parts of the work have also been funded by the British Heart Foundation, Unilever Corporate Research, Newcastle University, NHS North of Tyne (Newcastle Primary Care Trust). Mortality data were obtained from NHS Digital. We acknowledge the operational support of the North of England Commissioning Support Unit, the National Institute for Health Research Clinical Research Network North East and North Cumbria, local general practitioners and their staff. We thank the research nurses, laboratory technicians, data management and clerical team for their work throughout, as well as many colleagues for their expert advice. Thanks are due especially to the study participants and, where appropriate, their families and carers.

COMPETING INTERESTS

All authors declare no conflict of interest.

CONTRIBUTORS

L.E.D.: conception and design, analysis and interpretation of the data, and drafting and editing the manuscript. A.K.: conception and design, analysis and interpretation of the data, and critique of the paper. A.T. and B.H.: conception and design, interpretation of the data and critique of the paper.

ETHICS APPROVAL

The Newcastle 85+ Study was approved by the Newcastle and North Tyneside Local Research Committee One (Ref: 06/Q0905/2).

DATA AVAILABILITY STATEMENT

Data cannot be shared publicly because of data governance, GDPR and contractual arrangements with outside organisations who provide individual level data to the study (NHS Digital). Data are available from the Newcastle 85+ Data Guardians (contact via https://research.ncl.ac.uk/85plus/datarequests/) for researchers who meet the criteria for access to confidential data.

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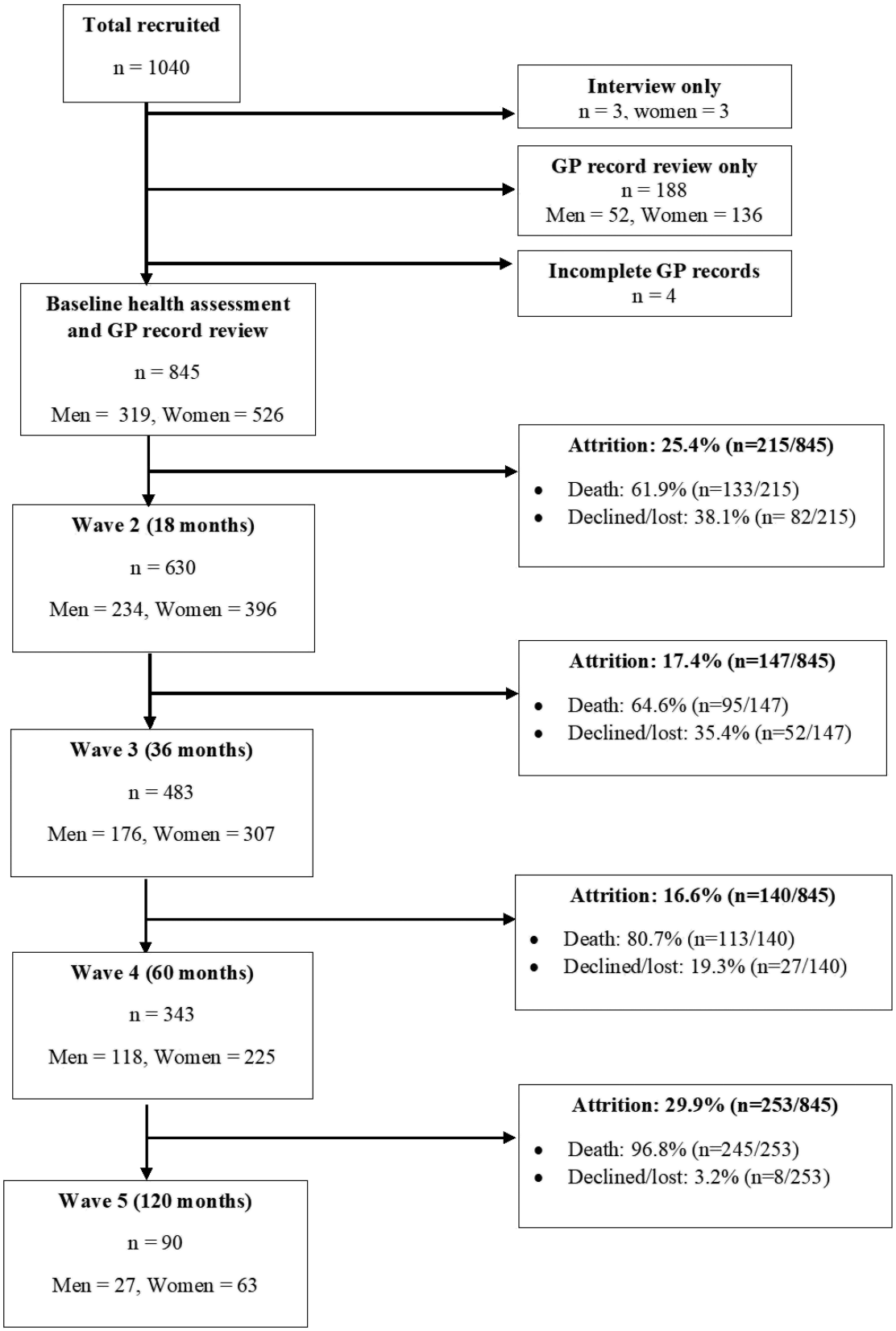
How to cite this article: Davies LE, Kingston A, Todd A, Hanratty B. Is polypharmacy associated with mortality in the very old: Findings from the Newcastle 85+ Study. *Br J Clin Pharmacol*. 2022;88(6):2988-2995. doi:10.1111/bcp.15211

APPENDIX A: Recruitment and retention in the Newcastle 85 + Study



APPENDIX B: Prescribed items excluded from polypharmacy definition

Prescribed item	BNF code
Stoma products	10800
Peak flow meters, inhaler devices and nebulisers	30150
Hypodermic equipment (excluding lancets)	60113
Diagnostic and monitoring agents for diabetes (including lancets)	60160
Ring/shelf pessary	70110
Electrolytes and water—water for injections	90221
Wound dressings	131300
Tubular bandages, compression hosiery and applicators	131310
Diphtheria vaccine	140404
Influenza vaccine	140410
Typhoid vaccine	140419
Pneumococcal vaccine	140420
Urinary catheter/sheath/leg bag	180500
Anal plug for bowel incontinence	180501
Truss—elastic band	180600
Borderline substances—food	180700
Syringe for injection	180800
KY jelly	180801
Sharps bin	180802
Gloves	180803

APPENDIX C: Definitions of disease groups

Disease group	Included diseases
Arthritis	Ankylosing spondylitis; cervical spondylosis; rheumatoid, degenerative, poly, gouty, septic, peri arthritis; generalised osteoarthritis; hand, hip or knee osteoarthritis; lumbar spondylosis or psoriatic arthropathy
Cancer	Any cancer within 5 years of diagnosis, excluding nonmelanoma skin cancer
Cardiovascular disease	Angina, coronary angioplasty, coronary artery bypass graft/stent, heart failure, myocardial infarction, atrial fibrillation or atrial flutter
Cerebrovascular disease	Carotid endarterectomy, stroke or transient ischaemic attack
Cognitive impairment	Standardised mini-mental state examination score ≤21, Alzheimer's disease or dementia
Depression	Presence of depression in the last 12 months
Diabetes	Type 1 diabetes, type 2 diabetes or unspecified diabetes
Eye disease	Cataracts, cataract surgery, age-related macular degeneration, glaucoma, diabetic eye disease, registered partially sighted or registered blind
Hypertension	Any recorded diagnosis of hypertension
Liver disease	Abnormal liver function tests (without diagnostic label), nonalcoholic fatty liver disease or autoimmune hepatitis
Osteoporosis	Osteoporosis
Parkinson's disease	Parkinson's disease
Renal impairment	Estimated glomerular filtration rate <30 mL/min/1.73 m^2
Respiratory disease	Fibrosing alveolitis, asbestosis, asthma, bronchiectasis, chronic bronchitis, chronic obstructive pulmonary disease, emphysema, pneumoconiosis or pulmonary fibrosis