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# Predicting poorer health outcomes in older community-dwelling patients with multimorbidity: prospective cohort study assessing the accuracy of different multimorbidity definitions



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# Predicting poorer health outcomes in older community-dwelling patients with multimorbidity: prospective cohort study assessing the accuracy of different multimorbidity definitions

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**Abstract:**

Purpose: The United Kingdom National Institute for Health Care Excellence (NICE) guidelines for multimorbidity suggest that a medication-orientated approach (≥10 regular medications) could be used to identify patients with complex multimorbidity in need of a tailored approach to management.

Objectives: To compare the accuracy of medication-based and diagnosis-based definitions in identifying older community-dwelling patients who are at risk of experiencing poorer health outcomes.

Design: A secondary analysis of a prospective cohort study with two year follow up (2010-12)

Setting: 15 general practices in Ireland

Participants: 904 older (≥70 years) community-dwelling patients.

Exposure: Baseline complex multimorbidity assessment based on medication count and chronic disease count were calculated.

Outcomes: Population characteristics for those defined as having complex multimorbidity using both definitions were compared. Outcomes examined were mortality, self-reported health related quality of life, mental health and physical functioning at follow-up.

Results: Of the 904 baseline participants, 53 died during follow-up and 673 patients completed the follow-up questionnaire. At baseline, 223 patients had 3 or more chronic conditions and 89 patients were prescribed 10 or more medications. For the mortality outcome, the medication count definition demonstrated low sensitivity (28.3%) but high specificity (89.1%) while the chronic disease count definition, had higher sensitivity (43.4%) and moderate specificity (70.3%). For poorer self-reported health outcomes at follow-up, the medication-based definition reported sensitivities ranging from 9.8% to 16.3 % and specificities from 88.8% to 91 % while the chronic disease count definition had sensitivities from 33% to 42.4% and specificities from 70.7% to 72%.

Conclusions: While neither classification had high sensitivity, using a definition of 10 or more regular medicines to define complex multimorbidity had higher specificity for predicting poorer health outcomes. This definition is simple to implement in practice and could be used for proactive identification of patients who may benefit from targeted clinical care.

Keywords: multimorbidity, accuracy, definition

Strengths and limitations of this study:

- To our knowledge, this is the first study comparing the UK NICE medication cut-point recommendation to define multimorbidity with the more traditional method of chronic disease counts. This approach could be used proactively in the clinical setting to identify higher risk people.
- Our study used a large dataset with robust data collection from electronic health records combined with linked national pharmacy claims data and a patient questionnaire for self-reported outcomes.
- This study only included older patients with multimorbidity, further research would be needed to validate these results in other populations.
- This study is a secondary analysis and as such is limited to the data collected from the recruited population in the primary cohort study.

**Introduction:**

A high proportion of patients consulting in primary healthcare present with multimorbidity, defined generally as the presence of at least two chronic medical conditions [1]. Multimorbidity has a significant impact across the age ranges but is more common in older patients and is associated with poorer quality of life [2, 3], psychological distress [4-6], loss of physical function [7], polypharmacy and adverse drugs events [8] and care duplication and inconsistencies [9, 10]. Within the broad multimorbidity population, outcomes are poorer in patients with more complex multimorbidity, which has been defined previously in terms of higher numbers of conditions or higher healthcare utilisation.

Even though associations with poorer health outcomes, are clear, identifying older patients with multimorbidity who will benefit from a community-based intervention is difficult due to the heterogeneity of definitions for multimorbidity, used in both public health and clinical interventions [11]. Existing trials have based inclusion on the number of conditions along with other markers of risk such as older age or high healthcare utilisation [12]. The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) 2016 Guidance on Multimorbidity recommends that health practitioners should proactively identify patients that could benefit from a multimorbidity approach to clinical care. The NICE Guidance suggests that the number of regular prescribed medicines can be used as a marker of risk with the advantage that this can be retrieved from the electronic health record. It suggests using a cut-off point of ≥10 medications with an additional risk of adverse event, such as unplanned hospital admission, or alternatively ≥15 medications [13]. Significant polypharmacy such as this is a marker of more complex multimorbidity. For condition count definitions, the suggestion is to use ≥3 chronic conditions as a marker for complexity [14, 15].

This study aimed to examine the accuracy of medication-based vs. condition count-based definitions of complex multimorbidity in predicting poorer health outcomes for older community-dwelling patients.

## Methods

The Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to guide the conduct and reporting of this study [16].

### Study design and population:

This is a secondary analysis of a two year, prospective cohort study that was established to examine potentially inappropriate prescribing and adverse health outcomes in older community-dwelling patients [17].

Ethical approval for this cohort study was granted by the Royal College of Surgeons in Ireland (RCSI) Human Research Ethics committee. The study population was recruited from 15 randomly selected general practices in Leinster, Ireland for a two year (2010-2012) prospective cohort study involving older community-dwelling patients. A proportionate stratified random sample of patients were recruited; of 3070 eligible patients, a total of 1764 were invited to participate. [17, 18]

*Study inclusion criteria:*

(1) age ≥70 years on 1 January 2010

(2) in receipt of a valid general medical services (GMS) card, which is means-tested and entitles the holder to free public medical services including GP care.

*Exclusion criteria:*

(1) receiving palliative care;

(2) cognitive impairment at the level that would affect their ability to complete the outcome measure (defined as Mini Mental State Examination ≤20);

(3) significant hearing/speech/ visual impairment;

(4) currently experiencing a psychotic episode;

(5) hospitalised long-term, in a nursing home, homeless or in sheltered accommodation;

(6) recent bereavement (within 4 weeks).

A total of 1487 were eligible and invited to participate at baseline (T0) and 904 (61%) agreed [17, 18]. A total of 673 patients completed a patient questionnaire and had their GP electronic record reviewed at two-year follow up (T1).

Two samples are presented in this study depending on the outcome of interest:

a. Patients who either completed T1 or died before T1 for mortality analysis (n = 726)
b. Patients who completed T1 questionnaires for patient reported health outcomes analysis (n= 673)

**Data collection**

**Exposure of interest: Multimorbidity definitions**

Two definitions of complex multimorbidity assessment definitions were selected based on current guidelines and literature [14, 15].

*Medication classes prescribed to the patient*

The number of regular prescribed medications was calculated by linkage to the national Health Services Executive (HSE)-Primary Care Reimbursement Scheme (PCRS) pharmacy claims database. The sample was divided using a cut-off definition of 10 or more prescribed medicines. The NICE guidelines indicate that a patient with 10 or more prescribed medicines and an additional risk factor would benefit from a multimorbidity approach [19]. As all cohort participants were 70 years or older, this population was considered as having an additional risk factor.

*Number of chronic diseases*

At baseline, chronic diseases were collected from the GP electronic medical record by eight trained medical students using standardised data collection forms. A disease count proposed by Barnett et al. which includes 40 chronic diseases on the basis of disease prevalence and severity was used to define complex multimorbidity [20]. A cut-off of ≥3 chronic diseases was considered to identify complex multimorbidity [14, 15].

## Primary Outcomes

Mortality and patient reported outcome measures (PROM) were selected to identify patients with poorer health at follow-up. The study examined poorer self-reported health between T0 (baseline) and T1 (24 months).

### *i. Mortality*

Mortality was assessed by examining each participant's GP electronic medical record.

### *ii. Health related quality of life*

The Euro-Qual 5 Dimensions (EQ-5D) is a generic instrument widely used to assess health related quality of life by using ordinal scaling to assess fives domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Poorer self-reported health was defined using the Paretian principles method described by Devlin et al [21]. A study participant who had deteriorated in more domains than had remained stable or improved between baseline and follow up were considered to have poorer health related quality of life [21].

### *iii. Mental health*

The Hospital Anxiety and Depression Scale (HADS) is a measure assessing independently levels of anxiety and depression which are then classified as normal, mild, moderate or severe [22]. Poorer self-reported mental health was defined as a higher score at follow up-compared to baseline [22].

### *iv. Physical functioning*

The Vulnerable Elders Survey (VES-13) is a patient-reported outcome measure used to identify older patients at risk of functional decline [23]. In development study for this tool, patients who scored ≥3 had four times the risk of death or functional decline over a two year period [23]. Accordingly, patients were classified as having poorer self-reported health if study participants who scored less than 3 at baseline (T0) scored ≥3 at follow up (T1).

*Descriptive statistics*

Sociodemographic variables collected included age, deprivation, gender, social class, education, marital status, living arrangements. Age and gender were collected from the GP electronic medical record. The deprivation score was obtained with the geocoded patients address based on the Small Area Health Research Unit (SAHRU) which uses electoral division [24]. Education levels were classified as; basic education (no formal education, primary education or lower secondary education only) or upper and post-secondary (all other higher levels of education). Social class was classified as unskilled (unskilled, gainfully occupied, unknown) or skilled (all other categories).

*Data analysis*

Conventional descriptive statistics were used to describe the cohort, with median and interquartile ranges (IQR) to summarise all continuous variables due to their skewed distributions. The sensitivity, specificity and positive and negative predictive values were calculated using an online tool [25] for each outcome and using all exposures of interest. For our analyses, sensitivity is the probability of a patient who experiences the health outcome of interest (i.e. death or decline in PROM at follow-up) having complex multimorbidity at baseline, specificity is the probability of a patient who does not experience the health outcome at follow-up not having complex multimorbidity at baseline, the positive predictive value is the probability of a patient with complex multimorbidity at baseline having the health outcome at follow-up and the negative predictive value is the probability of a patient without complex multimorbidity at baseline not having the health outcome at follow-up.

*Risk of Bias*

The risk of bias was assessed in the cohort study using the The Cochrane risk of bias tool for non-randomized studies [26].

*Patient and public involvement*

This study is a secondary analysis of a cohort study, no patient or member of the public were involved in its design phase.

## Results

*Participants*

A total of 223 participants (31%) met the criteria for the chronic disease count definition for multimorbidity, and 89 patients (12%) met the criteria for the medication count definition. The median age of the total sample was 76.4 years, 50% were males, 79% were classified as coming from the skilled social class and the majority (60%) reported a basic level of education. Descriptive characteristics of the patients identified by the disease count and the medication classes count cut-offs are presented in Table 1.

*Outcomes*

The proportions of patients defined as having complex multimorbidity using both definitions who died or reported poorer health outcomes is presented in Table 2. These are broadly similar but indicate that the medication count definition group had a higher proportion of patients who died or had a decline in HRQol, whereas, the condition count group had a higher proportion with declines in physical functioning and psychological well-being.

The sensitivity, specificity, positive predictive value and negative predictive value for both definitions of complex multimorbidity for each outcome is presented in Table 3. For mortality, the medication count definition demonstrated low sensitivity (28.3%), high specificity (89.1%) and a high negative predictive value (94%). The disease count definition, when used to predict mortality had low sensitivity (43.4%), moderate specificity (70.3%), and a high negative predictive value (94%).

In predicting poorer self-reported health over the two-year period, the medication count definition reported sensitivities ranging from 9.8% to 16.3 % and specificities from 88.8 % to 91.0 %. The disease count definition had low sensitivities ranging from 33.0% to 42.4% and moderate specificities (70.7% to 72.0%) at two-year follow-up.

A comparison of the sample of patients who died or had poorer health outcomes identified using each complex multimorbidity definition is presented in the appendix 1. The samples were similar in terms of socio-demographic characteristics, median scores of self-reported health status, self-esteem, self-efficacy and life satisfaction.

*Risk of Bias*

The risk of bias is reported fully in the primary cohort study [17]. Overall, the risk of bias was low regarding response rate. As this is a secondary analysis, exclusion of participants with cognitive impairment and the small sample of participants with 15 or more medication count could reduce generalizability [26].

## Discussion

*Main results*

In this population of community dwelling older patients, the medication count approach to defining complex multimorbidity demonstrated low sensitivity (9.8 % to 28.3%), but high specificity (88.8 to 91.0%) for identifying patients with a higher risk of mortality or poorer self-reported health over a two-year period. The disease count definition had a slightly higher sensitivity (28.4% to 43.4%) and lower specificity (70.3% to 72.0%) for these outcomes.

With high specificity, the medication count definition has better potential to proactively "rule-in" patients with complex multimorbidity who are more likely to have poorer health outcomes compared to the more widely used 3 or more chronic diseases definition. There are also fewer patients identified using the medication-count definition, which is more manageable from a clinical or organisational perspective. However, both definitions had insufficient sensitivity, showing a limited potential to accurately 'rule out' patient at risk of poorer health outcomes in this population. Ideally a definition with both high sensitivity and specificity could be used to target multimorbidity interventions but existing risk stratification models have similar limitations [27].

*Strengths and limitations*

This large dataset analysis is the first to describe the accuracy of using a medication cut-off definition to proactively identify patients with complex multimorbidity. In this cohort study, the medication classes count variable was obtained from linked national pharmacy claims data and the number of chronic diseases count was obtained via a medical record review by a GP, giving robustness to the main variables used in this analysis.

The first limitation of this study is inherent to the secondary analysis design, by using previously collected data it is not possible to align data collection directly with the goals of the current study, however we did have a wide range of patient reported and chart data available for analysis. The cohort study sample was limited to a community dwelling older population without cognitive, visual or hearing impairment, however other studies are highlighting that multimorbidity is not just a feature of ageing but is also prevalent in younger populations [1, 28, 29]. The main limitation of this study is that, the large primary study sample size was greatly reduced for sub-set analyses when considering only patients who had 10 or more prescribed medications and further research is needed to validate our findings in larger samples. As the UK NICE multimorbidity guidelines proposes a proactive identification of patients with 15 or more medications or 10 or more and an additional risk factor, only the second definition could be tested because of the lack of a sufficient sample of patients on 15 or more medicines within the cohort.

*Comparison with existing literature*

Previous studies have reported mixed results concerning the predictive power of multimorbidity definitions. Several studies have showed that the weighted diagnosis count, the Charlson index was an suitable measure to predict mortality [30-32] However, a large cohort study (n= 95 372) comparing six measure of multimorbidity identified that the number of prescribed medications was the most accurate multimorbidity measurement to predict future GP and practice nurses consultations and that it was also the second most accurate measure to predict mortality, just behind the Charlson index [33]. A previous analysis of the current cohort study data compared five continuous count-based definitions of multimorbidity and reported poor discrimination in predicting hospital admissions and self-reported functional decline for all multimorbidity measures, with the medication based definition performing marginally better than diagnosis based definitions [34]. The 10 or more medication cut-off performs similarly to another risk score, the X, used in clinical settings to predict cardiovascular disease risk at their high-risk cut-off, with low sensitivity and high specificity [27]. Our findings build on this previous research, by comparing the predictive power of a medication count definition against a dis-

ease count definition using pragmatic cut-off points, and also examining a range of self-reported health outcomes in addition to mortality.

*Implications for future research and clinical practice:*

Further research should assess the accuracy of multimorbidity definitions in a larger range of primary care populations, including middle aged patients with multimorbidity and older patients with cognitive decline. Larger sample sizes are needed to test the 15 or more medications-cut-off definition for multimorbidity also recommended as an alternative in the UK NICE Multimorbidity Guidelines [19]. The comparison between the two samples identified by both definitions offered shows a slight difference in age for both definitions, showing that the medication definition might better identify older people at higher risk. In the meantime, clinicians and researchers could use the medication definition to identify higher risk patients with multimorbidity as it is easy to use and offers a pragmatic approach and potential for identification of patients through prescribing or electronic health records.

**Conclusions**

This study shows that using a medication count cut-off definition of 10 or more medicines for complex multimorbidity had high specificity for predicting mortality and decline in health status, making it possible to rule-in a small sample of patients identified with a risk of poorer health outcomes with a low rate of false positives. However the low sensitivity means that some of those identified as low risk will also have poor outcomes. Within these limitations, our results support the UK NICE Multimorbidity Guidelines recommendations of utilising significant polypharmacy (10 or more medications) to proactively identify patients who could benefit from a multimorbidity-adapted approach to their healthcare.

**Author contributions.**

MS, SS and EW conceptualised the study, MS analysed the data and SS, EW and RM took part in the interpretation of results. MS wrote the original draft and SS, EW, RM, MF and LF contributed to the editing and reviewing of the draft.

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**Data sharing statement**

The database from the cohort study is available to Dr. Emma Wallace by local access only. Please contact corresponding author.

**Competing interests**

None declared

**Patient consent**

Not required.

## References

1. Fortin, M., et al., *Prevalence of multimorbidity among adults seen in family practice.* Annals of Family Medicine, 2005. **3**: p. 223 - 228.
2. Fortin, M., et al., *Relationship between multimorbidity and health-related quality of life of patients in primary care.* Quality of Life Research, 2006. **15**(1): p. 83-91.
3. Brettschneider, C., et al., *Relative impact of multimorbid chronic conditions on health-related quality of life–results from the MultiCare Cohort Study.* PLoS One, 2013. **8**(6): p. e66742.
4. Gunn, J.M., et al., *The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort.* Social psychiatry and psychiatric epidemiology, 2012. **47**(2): p. 175-184.
5. Fortin, M., et al., *Psychological distress and multimorbidity in primary care.* The Annals of Family Medicine, 2006. **4**(5): p. 417-422.
6. Read, J., et al., *Multimorbidity and Depression: A Systematic Review and Meta-analysis.* Journal of Affective Disorders, 2017.
7. Bayliss, E.A., et al., *Predicting declines in physical function in persons with multiple chronic medical conditions: what we can learn from the medical problem list.* Health and Quality of Life Outcomes, 2004. **2**(1): p. 47.
8. Guthrie, B., et al., *High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice.* Bmj, 2011. **342**: p. d3514.
9. Guthrie, B., et al., *Adapting clinical guidelines to take account of multimorbidity.* British Medical Journal, 2012. **345**.
10. Hughes, L.D., M.E.T. McMurdo, and B. Guthrie, *Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity.* Age And Ageing, 2013. **42**(1).
11. Almirall, J. and M. Fortin, *The coexistence of terms to describe the presence of multiple concurrent diseases.* Journal of Comorbidity, 2013. **3**(1): p. 4-9.
12. Smith, S.M., et al., *Interventions for improving outcomes in patients with multimorbidity in primary care and community settings.* The Cochrane Library, 2016.
13. Farmer, C., et al., *Clinical assessment and management of multimorbidity: summary of NICE guidance.* BMJ: British Medical Journal (Online), 2016. **354**.
14. Fortin, M., et al., *A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology.* The Annals of Family Medicine, 2012. **10**(2): p. 142-151.
15. Harrison, C., et al., *Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice.* BMJ Open, 2014. **4**(7).
16. Von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] statement: guidelines for reporting observational studies.* Gaceta Sanitaria, 2008. **22**(2): p. 144-150.

17. Wallace, E., et al., *Impact of potentially inappropriate prescribing on adverse drug events, health related quality of life and emergency hospital attendance in older people attending general practice: a prospective cohort study.* Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences, 2016. **72**(2): p. 271-277.
18. Cahir, C., et al., *Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients.* British journal of clinical pharmacology, 2014. **77**(1): p. 201-210.
19. National Guideline Centre UK, *Multimorbidity: Assessment, Prioritisation and Management of Care for People with Commonly Occurring Multimorbidity.* 2016.
20. Barnett, K., et al., *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study.* The Lancet, 2012. **380**(9836): p. 37-43.
21. Devlin, N., D. Parkin, and J. Browne, *Using the EQ-5D as a performance measurement tool in the NHS.* 2009.
22. Zigmond, A.S. and R.P. Snaith, *The Hospital Anxiety And Depression Scale.* Acta Psychiatr Scand, 1983. **67**.
23. Saliba, D., et al., *The Vulnerable Elders Survey: A Tool for Identifying Vulnerable Older People in the Community.* Journal of the American Geriatrics Society, 2001. **49**(12): p. 1691-1699.
24. Kelly, A. and C. Teljeur, *The national deprivation index for health & health services research.* Small Area Health Research Unit Technical Report. Small Area Health Research Unit, Trinity College Dublin, 2007.
25. Centre for Clinical Research and Biostatistics, *Confidence Intervals Calculator: Diagnostic Statistics* 2018.
26. Higgins, J.P. and S. Green, *Cochrane handbook for systematic reviews of interventions*. Vol. 4. 2011: John Wiley & Sons.
27. Chamnan, P., et al., *A simple risk score using routine data for predicting cardiovascular disease in primary care.* Br J Gen Pract, 2010. **60**(577): p. e327-e334.
28. Smith, S.M., A. Ferede, and T. O'Dowd, *Multimorbidity in younger deprived patients: An exploratory study of research and service implications in general practice.* BMC Family Practice, 2008. **9**: p. 6-6.
29. Yarnall, A.J., et al., *New horizons in multimorbidity in older adults.* Age and Ageing, 2017. **46**(6): p. 882-888.
30. Perkins, A.J., et al., *Common comorbidity scales were similar in their ability to predict health care costs and mortality.* Journal of clinical epidemiology, 2004. **57**(10): p. 1040-1048.
31. Quail, J.M., et al., *Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts.* BMC health services research, 2011. **11**(1): p. 146.
32. Schneeweiss, S., et al., *Consistency of performance ranking of comorbidity adjustment scores in Canadian and US utilization data.* Journal of general internal medicine, 2004. **19**(5p1): p. 444-450.

33. Brilleman, S.L. and C. Salisbury, *Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study.* Family Practice, 2013. **30**(2): p. 172-178.
34. Wallace, E., et al., *Comparison of count-based multimorbidity measures in predicting emergency admission and functional decline in older community-dwelling adults: a prospective cohort study.* BMJ open, 2016. **6**(9): p. e013089.

**Table 1: Patient characteristics at baseline (T0)**

| | All patients (n=726) | Patients with >=3 chronic diseases (n=223) | Patients with ≥ 10 prescribed drug classes (n=89) |
|---|---|---|---|
| **Sociodemographic variables** | | | |
| | **Median (IQR)** | **Median (IQR)** | **Median (IQR)** |
| Age (years) | 76.4 (72.9-80.3) | 77,6 (74.1-81.1) | 78.8 (73.8-83.4) |
| Deprivation score | 1.4 (-.6-2.9) | 1.7 (-0.4-3.0) | 1.7 (-0.1-3.2) |
| | **n (%)** | **n (%)** | **n (%)** |
| Gender | | | |
| Male | 348 (47.9%) | 112 (50.2%) | 33 (37.1%) |
| Female | 378 (52.1%) | 111 (48.8%) | 56 (62.9%) |
| Social class | | | |
| Unskilled | 161 (22.2%) | 55 (24.7%) | 29 (32.6%) |
| Skilled | 565 (77.8%) | 168 (75.3%) | 60 (67.4%) |
| Education | | | |
| Basic | 433 (59.6%) | 155 (69.5%) | 66 (74.2%) |
| Higher | 293 (40.4%) | 68 (30.5%) | 23 (25.8%) |
| Marital status* | | | |
| Married | 342 (47.1%) | 94 (41.3%) | 35 (39.3%) |
| Separated/divorced | 34 (4.7%) | 12 (5.4%) | 2 (2.2%) |
| Widowed | 224 (30.9%) | 81 (36.3%) | 39 (43.8%) |
| Single/never married | 125 (17.2%) | 35 (15.7%) | 13 (14.6%) |
| Living arrangement* | | | |
| Husband/wife/life partner | 333 (45.9%) | 92 (41.3%) | 33 (37.1%) |
| Family/relatives | 90 (12.4%) | 27 (12.1%) | 12 (13.5%) |
| Living alone | 266 (36.6%) | 91 (40.8%) | 37 (41.6%) |
| Other | 36 (5.0%) | 12 (5.4%) | 7 (7.9%) |

| **Multimorbidity measures** | | | |
|---|---|---|---|
| | **Median (IQR)** | **Median (IQR)** | **Median (IQR)** |
| Number Barnett conditions | 2.0 (1.0-3.0) | 3.0 (3.0-4.0) | 3.0 (2.0-4.0) |
| Total disease count | 2.0 (1.0-4.0) | 5.0 (4.0-6.0) | 4.0 (3.0-6.0) |
| Number of drug classes | 6.0 (3.0-8.0) | 8.0 (6.0-10.0) | 11.0 (10.0-13.0) |

IQR: Interquartile range; * missing for two persons

**Table 2:** Proportions of patients defined as having complex multimorbidity who died or reported poorer health outcomes

| | Multimorbidity criterion | |
|---|---|---|
| | **Patients with >=3 chronic diseases (n=223)** | **Patients with ≥ 10 prescribed drug classes (n=89)** |
| **Outcome** | | |
| | **n (%)** | **n (%)** |
| Death | 23 (10.3%) | 15 (16.9%) |
| Decline in health-related quality of life (EQ-5D) | 58 (23%) | 22 (29.7%) |
| Decline in physical functioning (VES-13) | 27 (13.5%) | 8 (10.8%) |
| Decline in psychological well-being (HADS) | 39 (19.5%) | 15 (20.3%) |

EQ5D : Euro-Qual 5 Dimensions; VES-13: Vulnerable Elders Survey; HADS: Hospital Anxiety and Depression Scale;

**Table 3: Sensitivity, specificity and predictive values of multimorbidity identification definitions**

| Multimorbidity criterion | Sample | Outcome | Sensitivity (%, 95% CI) | Specificity (%, 95% CI) | PPV (%, 95% CI) | NPV (%, 95% CI) |
|---|---|---|---|---|---|---|
| **Patients with ≥ 10 prescribed drug classes** | All patients (n=726) | Death | 28.3% (16.2%-40.4%) | 89.1% (86.8%-91.5%) | 17.1% (9.2%-24.9%) | 94.0% (92.2%-96.8%) |
| | Patients completing follow-up questionnaire (n=673) | Decline in health-related quality of life (EQ-5D) | 10.8% (6.5%-15.0%) | 91.0% (88.3% -93.7%) | 36.1% (24.0% – 48.1%) | 68.3% (64.5% -72.2% |
| | | Decline in physical functioning (VES-13) | 9.8% (3.3%–16.2%) | 88.8% (86.3%-91.4%) | 10.8% (3.7%-17.9%) | 87.7% (85.0%-90.4%) |
| | | Decline in psychological functioning (HADS) | 16.3% (8.8%-23.9%) | 90.0% (87.4%-92.4%) | 21.1% (11.6%-30.6%) | 86.7% (83.9%-89.4%) |
| **Patients with >=3 chronic diseases** | All patients (n=726) | Death | 43.4% (30.1%-56.7%) | 70.3% (66.9%-73.8%) | 10.4% (6.4%-14.4%) | 94.0% (92.0%-96.1%) |
| | Patients completing follow-up questionnaire (n=673) | Decline in health-related quality of life (EQ-5D) | 28.4% (22.2%-34.6%) | 71.8% (67.5%-76.0%) | 32.2% (25.4%-39.0%) | 68.0% (63.7%-72.3%) |
| | | Decline in physical functioning (VES-13) | 32.9% (22.8%-43.1%) | 70.7% (67.1%-74.4%) | 13.5% (8.8%-18.2%) | 88.4% (85.5%-91.3%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Decline in psychological functioning (HADS) | 42.4% (32.3%-52.5%) | 72.0% (68.3%-75.7%) | 20.0% (14.4%-25.6%) | 88.3% (85.3%-91.2%) |

EQ5D : Euro-Qual 5 Dimensions; VES-13: Vulnerable Elders Survey; HADS: Hospital Anxiety and Depression Scale; PPV: Positive Predictive Value; NPV: Negative Predictive Value

## Appendix 1.

**Table 4. Characteristics at baseline of patients identified as having poorer health outcomes at follow-up**

| | Poorer health outcomes at follow-up | | | |
|---|---|---|---|---|
| | Death | | Patients with at least one decline in health-related quality of life, physical functioning or psycho-logical functioning | |
| | Patients with >=3 chronic diseases (n=23) | Patients with ≥ 10 prescribed drug classes (n=15) | Patients with >=3 chronic diseases (n=86) | Patients with ≥ 10 prescribed drug classes (n=30) |
| **Sociodemographic variables** | | | | |
| | **Median (IQR)** | **Median (IQR)** | **Median (IQR)** | **Median (IQR)** |
| Age (years) | 81.0 (78.0-85.6) | 83.9 (78.0-87.7) | 77.8 (74.5-80.8) | 79.6 (75.2-83.1) |
| Deprivation score | 2.6 (0.01-3.4) | 2.7 (-0.6-6.3) | 1.7 (-0.2-2.9) | 1.3 (-0.3-3.0) |
| | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Gender | | | | |
| Male | 13 (56.5%) | 10 (66.7%) | 40 (46.5%) | 7 (23.3%) |
| Female | 10 (43.5%) | 5 (33.3%) | 46 (53.5%) | 23 (76.7%) |
| Social class | | | | |
| Unskilled | 5 (21.7%) | 3 (20.0%) | 22 (25.6%) | 10 (33.3%) |
| Skilled | 18 (78.3%) | 12 (80.0%) | 64 (74.4%) | 20 (66.7%) |
| Education | | | | |
| Basic | 15 (65.2%) | 12 (80.0%) | 63 (73.3%) | 24 (80.0%) |
| Higher | 8 (34.8%) | 3 (20.0%) | 23 (26.7%) | 6 (20.0%) |
| Marital status* | | | | |
| Married | 7 (30.4%) | 7 (46.7%) | 30 (34.9%) | 10 (33.3%) |
| Separated/divorced | 0 (0.0%) | 0 (0.0%) | 5 (5.8%) | 1 (3.3%) |

| | | | | |
|---|---|---|---|---|
| Widowed | 14 (60.9%) | 7 (47.7%) | 34 (39.5%) | 15 (50%) |
| Single/never married | 2 (8.7%) | 1 (6.7%) | 16 (18.6%) | 4 (13.3%) |
| Living arrangement** | | | | |
| Husband/wife/life partner | 7 (30.4%) | 7 (46.7%) | 30 (34.9%) | 8 (26.7%) |
| Family/relatives | 5 (21.7%) | 1 (6.7%) | 12 (14%) | 6 (20%) |
| Living alone | 10 (43.5%) | 6 (40%) | 38 (44.2%) | 14 (46.7%) |
| Other | 0 (0.0%) | 1 (6.7%) | 5 (5.8%) | 2 (6.7%) |

Interquartile range; * missing for one patient; ** missing for two patients

Interquartile range; EQ5D- VAS : Euro-Qual 5 Dimensions Visual Analogue Scale

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

| | | Reporting Item | Page Number |
|---|---|---|---|
| Title | #1a | Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| Abstract | #1b | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| Background / rationale | #2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | #3 | State specific objectives, including any prespecified hypotheses | 4 |
| Study design | #4 | Present key elements of study design early in the paper | 5 |
| Setting | #5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 |
| Eligibility criteria | #6a | Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. | 5 |

| | | | |
|---|---|---|---|
| | #6b | For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | #7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6-8 |
| Data sources / measurement | #8 | For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable. | 6-8 |
| Bias | #9 | Describe any efforts to address potential sources of bias | 8 |
| Study size | #10 | Explain how the study size was arrived at | 8 |
| Quantitative variables | #11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 8 |
| Statistical methods | #12a | Describe all statistical methods, including those used to control for confounding | 8 |
| | #12b | Describe any methods used to examine subgroups and interactions | NA |
| | #12c | Explain how missing data were addressed | NA |
| | #12d | If applicable, explain how loss to follow-up was addressed | NA |
| | #12e | Describe any sensitivity analyses | NA |
| Participants | #13a | Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. | 8 |
| | #13b | Give reasons for non-participation at each stage | 8 |
| | #13c | Consider use of a flow diagram | NA |
| Descriptive data | #14a | Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential | 17 |

| | | | |
|---|---|---|---|
| | | confounders. Give information separately for exposed and unexposed groups if applicable. | |
| | #14b | Indicate number of participants with missing data for each variable of interest | 17 |
| | #14c | Summarise follow-up time (eg, average and total amount) | 5 |
| Outcome data | #15 | Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable. | 19 |
| Main results | #16a | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 20-21 |
| | #16b | Report category boundaries when continuous variables were categorized | 20-21 |
| | #16c | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 20-21 |
| Other analyses | #17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | 22-23 |
| Key results | #18 | Summarise key results with reference to study objectives | 10 |
| Limitations | #19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | 10 |
| Interpretation | #20 | Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. | 11 |
| Generalisability | #21 | Discuss the generalisability (external validity) of the study results | 11 |
| Funding | #22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13 |

BMJ Open

# Predicting poorer health outcomes in older community-dwelling patients with multimorbidity: prospective cohort study assessing the accuracy of different multimorbidity definitions



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| Keywords: | multimorbidity, risk prediction, chronic diseases, medications |
| | |

# Predicting poorer health outcomes in older community-dwelling patients with multimorbidity: prospective cohort study assessing the accuracy of different multimorbidity definitions

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3 tables, 0 figures.

**Abstract:**

Purpose: Multimorbidity is commonly defined and measured using condition counts. the United Kingdom National Institute for Health Care Excellence Guidelines for Multimorbidity suggest that a medication-orientated approach could be used to identify those in need of a multimorbidity approach to management.

Objectives: To compare the accuracy of medication-based and diagnosis-based multimorbidity measures at higher cut-points to identify older community-dwelling patients who are at risk of poorer health outcomes.

Design: A secondary analysis of a prospective cohort study with two-year follow up (2010-12)

Setting: 15 general practices in Ireland

Participants: 904 older community-dwelling patients.

Exposure: Baseline multimorbidity measurements, based on both medication classes count (MCC) and chronic disease count (CDC).

Outcomes: Mortality, self-reported health related quality of life, mental health and physical functioning at follow-up.

Analysis: Sensitivity, specificity, positive predictive values and negative predictive values adjusting for clustering by practice for each outcome using both definitions.

Results: Of the 904 baseline participants, 53 died during follow-up and 673 patients completed the follow-up questionnaire. At baseline, 223 patients had 3 or more chronic conditions and 89 patients were prescribed 10 or more medication classes. Sensitivity was low for both MCC and CDC measures for all outcomes. For specificity, MCC was better for all outcomes with estimates varying from 88.8% (95% CI: 85.2 to 91.6%) for physical functioning to 90.9% (95% CI: 86.2 to 94.1%) for self-reported health related quality of life. There were no differences between MCC and CDC in terms of PPV and NPV for any outcomes.

Conclusions: Neither measure demonstrated high sensitivity. However, MCC using a definition of 10 or more regular medication classes to define multimorbidity had higher specificity for predicting poorer health outcomes. This definition is simple to implement in practice and could be used for proactive identification of patients who may benefit from targeted clinical care.

Keywords: multimorbidity, medications, risk prediction, chronic diseases

Strengths and limitations of this study:

- This study compares use of medication classes count with the more traditional method of chronic disease counts to define multimorbidity. This approach could be used proactively in the clinical setting to identify higher risk people.
- Our study used a large dataset with robust data collection from electronic health records combined with linked national pharmacy claims data and a patient questionnaire for self-reported outcomes.
- This study only included older patients with multimorbidity, further research would be needed to validate these results in other populations.
- This study is a secondary analysis and as such is limited to the data collected from the recruited population in the original cohort study.

## Introduction:

A high proportion of patients consulting in primary healthcare present with multimorbidity, defined generally as the presence of at least two chronic medical conditions [1]. Multimorbidity has a significant impact across the age ranges but is more common in older patients and is associated with poorer quality of life [2, 3], psychological distress [4-6], loss of physical function [7], polypharmacy and adverse drugs events [8] and care duplication and inconsistencies [9, 10]. Within the broad multimorbidity population, outcomes are poorer in patients with more complex multimorbidity, which has been defined previously in terms of higher numbers of conditions or higher healthcare utilisation.

Even though associations with poorer health outcomes are clear, identifying older patients with multimorbidity who will benefit from a community-based intervention is difficult due to the heterogeneity of multimorbidity definitions and measures, used in both public health and clinical interventions [11]. Existing trials have based inclusion on the number of conditions along with other markers of risk such as older age or high healthcare utilisation [12]. The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) 2016 Guidance on Multimorbidity recommends that health practitioners should proactively identify patients that could benefit from a multimorbidity approach to clinical care. The NICE Guidance suggests considering a multimorbidity approach to care for adults of any age who are prescribed ≥10 medications with the advantage that this information can be retrieved from the electronic health record [13]. This approach to care is patient-centred as it follows patient goals and preference of care, focusing on quality of life by reducing treatment burden, adverse events, and unplanned care and improving services coordination. Polypharmacy is a marker of multimorbidity and patients identified this way can be regarded as having multimorbidity and offered broad interventions beyond medicines management. For condition count multimorbidity measurement, the literature suggests using ≥3 chronic conditions to identify patients with higher needs. [14, 15].

This study aimed to examine the accuracy of medication-based versus condition count-based definitions of multimorbidity in predicting poorer health outcomes for older community-dwelling patients.

## Methods

The Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to guide the conduct and reporting of this study [16].

*Study design and population*

This is a secondary analysis of a two year, prospective cohort study that was established to examine potentially inappropriate prescribing and adverse health outcomes in older community-dwelling patients [17]. Ethical approval for this cohort study was granted by the Royal College of Surgeons in Ireland (RCSI) Human Research Ethics committee. The study population was recruited from 15 randomly selected general practices in Leinster, Ireland for a two year (2010-2012) prospective cohort study involving older community-dwelling patients. Proportionate stratified sampling was carried out based on the overall required sample size and the total number of eligible patients per practice assuming a 50% response rate and of 3070 eligible patients, a total of 1764 were invited to participate. [17, 18] Of this group, 152 were ineligible on invitation based on eligibility criteria and 125 were not contactable resulting in 1,487 patients eligible for participation.



Study inclusion criteria:

(1) age ≥70 years on 1 January 2010

(2) in receipt of a valid general medical services (GMS) card, which is means tested and entitles the holder to free public medical services including GP care.

Exclusion criteria:

(1) receiving palliative care;

(2) cognitive impairment at the level that would affect their ability to complete the outcome measure (defined as Mini Mental State Examination ≤20);

(3) significant hearing/speech/ visual impairment;

(4) currently experiencing a psychotic episode;

(5) hospitalised long-term, in a nursing home, homeless or in sheltered accommodation;

(6) recent bereavement (within 4 weeks).

Of 1487 eligible and invited to participate at baseline (T0) a total of 904 (61%) agreed [17, 18]. Two study populations are presented depending on the outcome of interest:

a. Patients who either completed two-year follow-up (T1) or died before T1 for mortality analysis (n = 726)
b. Patients who completed T1 self-reported questionnaires for patient reported health outcomes analysis (n= 673)

*Demographic data collected*

Sociodemographic variables collected included age, deprivation, gender, social class, education, marital status and living arrangements. Age and gender were collected from the GP electronic medical record. The deprivation score was obtained with the geocoded patients address based on the Small Area Health Research Unit (SAHRU) which uses electoral division [19]. Education levels were classified as basic education (no formal education, primary education or lower secondary education only) or upper and post-secondary (all other higher levels of education). Social class was classified as unskilled (unskilled, gainfully occupied, unknown) or skilled (all other categories). Marital status was classified as married, separated/divorced, widowed and single/never married. Living arrangements were classified as living with husband/wife/life partner, family/relatives, living alone and other.

*Exposure of interest: Multimorbidity measures*

Two measures of multimorbidity were selected based on current guidelines and literature [14, 15].

(i) Medication classes count (MCC)

The number of regular prescribed medication classes was calculated by linkage to the national Health Services Executive (HSE)-Primary Care Reimbursement Scheme (PCRS) pharmacy claims database. The number of medication classes prescribed to the patient

were classified using the first three characters of the WHO-ATC classification system and the sample was divided using a cut-off definition of 10 or more prescribed medication classes [20]. The NICE guidelines indicate that a patient with 10 or more prescribed medicines and an additional risk factor would benefit from a multimorbidity approach [21]. As all cohort participants were 70 years or older, this population was considered as having an additional risk factor.

(ii) Chronic disease count (CDC)

At baseline, chronic diseases were collected from the GP electronic medical record by eight trained medical students using standardised data collection forms. A disease count proposed by Barnett et al. which includes 40 chronic diseases on the basis of disease prevalence and severity was used to define multimorbidity [22]. A cut-off of ≥3 chronic diseases was used to identify multimorbidity [14, 15].

*Primary Outcomes*

Mortality and patient reported outcome measures (PROM) were selected to identify patients with poorer health at follow-up. The study examined poorer self-reported health between T0 (baseline) and T1 (2 years). The PROMs were dichotomized, as described below to identify changes in outcome over the 2 years.

(i) Mortality

Mortality was assessed by examining each participant's GP electronic medical record. Where there was any query regarding the date of death, it was double checked using a national repository of deaths in Ireland.

(ii) Health related quality of life

The Euro-Qual 5 Dimensions (EQ-5D) is a generic instrument widely used to assess health related quality of life by using ordinal scaling to assess fives domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Poorer self-reported health was defined using the Paretian principles method described by Devlin et al [23]. Following these principles, poorer health related quality of life was operationalised as a

decline in a greater number of domains scores compared to stable or improved domains scores [23].

(iii) Mental health

The Hospital Anxiety and Depression Scale (HADS) is a measure assessing levels of anxiety and depression independently, which are then classified as normal, mild, moderate or severe [24]. Poorer self-reported mental health was defined as a higher score at follow up-compared to baseline according to the HADS [24].

(iv) Physical functioning

The Vulnerable Elders Survey (VES-13) is a patient-reported outcome measure used to identify older patients at risk of functional decline [25]. In the derivation study for this tool, patients who scored ≥3 had four times the risk of death or functional decline over a two year period than patients who scored less than 3 [25]. Accordingly, patients were classified as having poorer self-reported health if study participants who scored less than 3 at baseline (T0) scored ≥3 at follow up (T1).

*Statistical Analysis*

Descriptive statistics are presented to describe patient characteristics. For categorical measures the number of patients and percentage was calculated, and for continuous measures the mean and standard deviation (SD). For continuous scales which showed evidence of, or were expected to show some skew, a median and inter-quartile range was presented. A Chi-squared test, t-test or Mann-Whitney test was used as appropriate, adjusting for clustering by practice, to examine possible associations between patient characteristics and multimorbidity measures (patients with ≥10 vs <10 prescribed medication classes and patients with ≥3 vs <3 chronic diseases).

The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), along with 95% confidence intervals, were calculated adjusting for clustering by practice using STATA version 15 (StataCorp. 2017. College Station, TX: StataCorp LLC) for each outcome and using both exposures of interest (MCC and CDC). For our

analyses, sensitivity is the probability of a patient who experiences the health outcome of interest (i.e. death or decline in PROM at follow-up) having multimorbidity at baseline, specificity is the probability of a patient who does not experience the health outcome at follow-up not having multimorbidity at baseline, the positive predictive value is the probability of a patient with multimorbidity at baseline having the health outcome at follow-up and the negative predictive value is the probability of a patient without multimorbidity at baseline not having the health outcome at follow-up.

*Risk of Bias*

The risk of bias was assessed in the cohort study using The Cochrane risk of bias tool for non-randomized studies [26].

*Patient and public involvement*

This study is a secondary analysis of a cohort study which started enrolment in 2010. No patients or members of the public were involved in its design phase.

## Results

*Participants*

A total of 223 participants (30.7%) met the criteria for the CDC definition for multimorbidity, and 89 patients (12.3%) met the criteria for the MCC definition. Overall, 61 patients met both criteria. The median age of the total sample was 76.4 years, a total of 348 (47.9%) participants were males, 565 (77.8%) were classified as coming from the skilled social class and 433 (59.6%) reported a basic level of education. Descriptive characteristics of the patients identified by the CDC and the MCC cut-offs are presented in Table 1. Patients with a disease count ≥3, compared to those with a disease count <3, were on average older and reported less formal education. Patients prescribed ≥10 medications classes were on average older, female and had less formal education compared to patients prescribed <10 medication classes.

*Outcomes*

The proportion of patients defined as having multimorbidity using both definitions who died or reported poorer health outcomes are presented in Table 2. Patients with ≥10 medication classes had a significantly higher mortality rate compared to patients with <10 medication classes (17% vs 6%, p <0.001). There was no difference in the other outcomes measured. Patients with a disease count of ≥3, compared to those with a disease count of <3, had a significantly higher decline in psychological well-being (19.5% vs 11.7%, p=0.017) but there was no difference in any of the other outcomes.

The sensitivity, specificity, PPV and NPV along with 95% confidence intervals adjusted for clustering by practice are presented in Table 3 for both definitions of multimorbidity for each outcome of interest. For mortality, specificity was higher for MCC (89.0%; 95% CI: 86.0%-91.5%) compared to the CDC (70.3%; 95% CI: 63.5%-76.3%). For decline in health-related quality of life, both CDC and MCC measures had low sensitivity, however, the CDC (28.5%; 95% CI: 22.1%-35.9%) was higher than the MCC (10.5%; 95% CI: 7.6%-14.4%). In terms of specificity, MCC (90.9%; CI: 86.2% -94.1%) was higher when compared to the CDC measure (71.9%; CI: 64.8%-78.1%).

Similar patterns were reported for decline in physical functioning and psychological functioning as were seen for decline in health-related quality of life. Specificity was moderate for the CDC measure for both decline in physical functioning (71.9%; 95% CI: 64.8%-78.1%) and decline in psychological functioning (71.1%; 95% CI: 64.6%-76.9%). The MCC demonstrated higher specificity (decline in physical functioning: 88.8%; 95% CI 85.2%-91.6% and decline in psychological functioning: 89.9%; 95% CI: 86.2%-92.7%).

*Risk of Bias*

The risk of bias is reported fully in the primary cohort study previously [17]. Overall, the risk of bias was low regarding losses to follow up. As this is a secondary analysis, exclusion of participants with cognitive impairment and the small sample of participants with 15 or more medication classes could reduce generalizability [26].

## Discussion

*Main results*

In this population of community dwelling older patients, sensitivity was low for both the MCC and CDC measures for all outcomes. However, for self-reported health related quality of life, psychological well-being and physical functioning at follow-up the CDC measure was more sensitive. There was no difference in sensitivity between measures for the outcome of death. In terms of specificity, the MCC approach was better for all outcomes with estimates varying from 88.8% (95% CI: 85.2 to 91.6%) for physical functioning to 90.9% (95% CI: 86.2 to 94.1%) for self-reported health related quality of life.

With high specificity, the MCC definition has better potential to proactively "rule-in" patients with multimorbidity who are more likely to have poorer health outcomes compared to the more widely used condition count approach. There are also fewer patients identified using the MCC definition, which is more manageable from a clinical or organisational perspective. However, both definitions had insufficient sensitivity, showing a limited potential to accurately 'rule out' patient at risk of poorer health outcomes in this population. Ideally a definition with both high sensitivity and specificity could be used to target multimorbidity interventions but existing risk stratification models have similar limitations [27].

*Strengths and limitations*

In this cohort study, the medication classes count variable was obtained from linked national pharmacy claims data and the number of chronic diseases count was obtained via review of the participants' electronic medical record, which adds to the robustness to the data used in this analysis. A main strength of the study is that the dataset includes a variety of outcomes including mortality and patient-reported outcomes.

The first limitation of this study is inherent to the secondary analysis design, by using previously collected data it is not possible to align data collection directly with the goals of the current study, however we did have a wide range of patient reported and chart data available for analysis. The cohort study sample was limited to a community-dwelling

older people without cognitive, visual or hearing impairment. However recent studies indicate that multimorbidity is not just a feature of ageing but is also prevalent in younger populations [1, 28, 29]. We limited the number of chronic conditions identified in the records to 40 pre-specified conditions. Another potential limitation is the collection of data from medical records as there may have been some variation in recording of conditions. Medication classes were used as the predictor of interest as per the WHO-ATC classification system rather than individual medications. Further research is needed to validate our findings in larger samples

*Comparison with existing literature*

Previous studies have reported mixed results concerning the predictive power of multimorbidity definitions for different outcomes. Several studies have showed that a weighted diagnosis count, the Charlson index was an suitable measure to predict mortality [30-32] However, a large cohort study (n= 95 372) comparing six measure of multimorbidity reported that the number of prescribed medications was the most accurate multimorbidity measurement to predict future GP and practice nurses consultations and that it was also the second most accurate measure to predict mortality, just behind the Charlson index [33]. A previous analysis of the current cohort study data compared five continuous count-based definitions of multimorbidity and reported poor discrimination in predicting hospital admissions and self-reported functional decline for all multimorbidity measures, with the medication class based definition performing marginally better than diagnosis based definitions [34]. A previous study reported that using a 10 or more medication class cut-off to measure multimorbidity performed similarly to another risk score with low sensitivity and high specificity, when applied in clinical settings to predict cardiovascular disease risk [27]. Our findings build on this previous research, by comparing the predictive power of a medication class count definition against a disease count definition using pragmatic cut-off points, and also examining a range of self-reported health outcomes in addition to mortality. Research to date has highlighted the limitations of multimorbidity measures in predicting adverse events and work in this area is now expanding to include biomarkers in an effort to address these limitations [35, 36].

*Implications for future research and clinical practice:*

Further research should assess the accuracy of multimorbidity measures in a larger range of primary care populations, including middle aged patients with multimorbidity and older patients with cognitive decline. Larger sample sizes are needed to test the 15 or more medications cut-off measure for multimorbidity also recommended as an alternative in the UK NICE Multimorbidity Guidance [21]. In our study, there was little difference in medication and condition count measures in identifying older people at higher risk of poor health outcomes but medication classes count demonstrated higher specificity shows a slight difference in age, suggesting that the medication definition might better identify older people at higher risk. In the meantime, clinicians and researchers could use the medication classes count measure to identify higher risk patients with multimorbidity as it is easy to use and offers a pragmatic approach and potential for identification of patients through prescribing or electronic health records.

## Conclusions

This study shows that using two measures of multimorbidity, a medication classes count cut-off of 10 or more and a chronic disease count of 3 or more chronic diseases had low sensitivity in relation to predicting mortality, self-reported health related quality of life, mental health and physical functioning, although the chronic disease count was slightly more sensitive for the majority of outcomes. The medication classes count approach demonstrated higher specificity for mortality and decline in health status, making it possible to rule-in a small sample of patients identified with a risk of poorer health outcomes with a low rate of false positives. However, the low sensitivity means that some of those identified as low risk will also have poor outcomes. Within these limitations, our results add support for the UK NICE Multimorbidity Guidance recommendations to use 10 or more regular medicines as a proxy for multimorbidity to proactively identify patients who could benefit from a multimorbidity-adapted approach to their healthcare.

**Author contributions.**

MS, SS and EW conceptualised the study, MS and FB analysed the data and SS, EW, FB and RM took part in the interpretation of results. MS wrote the original draft and SS, EW, FB, RM, MF and LF contributed to the editing and reviewing of the draft.

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**Data sharing statement**

The database from the cohort study is available from Dr. Emma Wallace by local access only. Please contact corresponding author.

**Competing interests**

None declared

**Patient consent**

Not required.

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## References

1. Fortin, M., et al., *Prevalence of multimorbidity among adults seen in family practice.* Annals of Family Medicine, 2005. **3**: p. 223 - 228.
2. Fortin, M., et al., *Relationship between multimorbidity and health-related quality of life of patients in primary care.* Quality of Life Research, 2006. **15**(1): p. 83-91.
3. Brettschneider, C., et al., *Relative impact of multimorbid chronic conditions on health-related quality of life–results from the MultiCare Cohort Study.* PLoS One, 2013. **8**(6): p. e66742.
4. Gunn, J.M., et al., *The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort.* Social psychiatry and psychiatric epidemiology, 2012. **47**(2): p. 175-184.
5. Fortin, M., et al., *Psychological distress and multimorbidity in primary care.* The Annals of Family Medicine, 2006. **4**(5): p. 417-422.
6. Read, J., et al., *Multimorbidity and Depression: A Systematic Review and Meta-analysis.* Journal of Affective Disorders, 2017.
7. Bayliss, E.A., et al., *Predicting declines in physical function in persons with multiple chronic medical conditions: what we can learn from the medical problem list.* Health and Quality of Life Outcomes, 2004. **2**(1): p. 47.
8. Guthrie, B., et al., *High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice.* Bmj, 2011. **342**: p. d3514.
9. Guthrie, B., et al., *Adapting clinical guidelines to take account of multimorbidity.* British Medical Journal, 2012. **345**.
10. Hughes, L.D., M.E.T. McMurdo, and B. Guthrie, *Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity.* Age And Ageing, 2013. **42**(1).
11. Almirall, J. and M. Fortin, *The coexistence of terms to describe the presence of multiple concurrent diseases.* Journal of Comorbidity, 2013. **3**(1): p. 4-9.
12. Smith, S., et al., *Interventions for improving outcomes in patients with multimorbidity in primary care and community settings.* The Cochrane Library, 2016.
13. Farmer, C., et al., *Clinical assessment and management of multimorbidity: summary of NICE guidance.* BMJ: British Medical Journal (Online), 2016. **354**.
14. Fortin, M., et al., *A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology.* The Annals of Family Medicine, 2012. **10**(2): p. 142-151.
15. Harrison, C., et al., *Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice.* BMJ Open, 2014. **4**(7).
16. Von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] statement: guidelines for reporting observational studies.* Gaceta Sanitaria, 2008. **22**(2): p. 144-150.
17. Wallace, E., et al., *Impact of potentially inappropriate prescribing on adverse drug events, health related quality of life and emergency hospital attendance in older people attending general practice: a prospective cohort study.* Journals of

Gerontology Series A: Biomedical Sciences and Medical Sciences, 2016. **72**(2): p. 271-277.
18. Cahir, C., et al., *Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients.* British journal of clinical pharmacology, 2014. **77**(1): p. 201-210.
19. Kelly, A. and C. Teljeur, *The national deprivation index for health & health services research.* Small Area Health Research Unit Technical Report. Small Area Health Research Unit, Trinity College Dublin, 2007.
20. World Health Organization, *WHO collaborating centre for drug statistics methodology. ATC/DDD index 2011.* World Health Organization2011WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index, 2011.
21. National Guideline Centre UK, *Multimorbidity: Assessment, Prioritisation and Management of Care for People with Commonly Occurring Multimorbidity.* 2016.
22. Barnett, K., et al., *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study.* The Lancet, 2012. **380**(9836): p. 37-43.
23. Devlin, N., D. Parkin, and J. Browne, *Using the EQ-5D as a performance measurement tool in the NHS.* 2009.
24. Zigmond, A.S. and R.P. Snaith, *The Hospital Anxiety And Depression Scale.* Acta Psychiatr Scand, 1983. **67**.
25. Saliba, D., et al., *The Vulnerable Elders Survey: A Tool for Identifying Vulnerable Older People in the Community.* Journal of the American Geriatrics Society, 2001. **49**(12): p. 1691-1699.
26. Higgins, J.P. and S. Green, *Cochrane handbook for systematic reviews of interventions*. Vol. 4. 2011: John Wiley & Sons.
27. Chamnan, P., et al., *A simple risk score using routine data for predicting cardiovascular disease in primary care.* Br J Gen Pract, 2010. **60**(577): p. e327-e334.
28. Smith, S.M., A. Ferede, and T. O'Dowd, *Multimorbidity in younger deprived patients: An exploratory study of research and service implications in general practice.* BMC Family Practice, 2008. **9**: p. 6-6.
29. Yarnall, A.J., et al., *New horizons in multimorbidity in older adults.* Age and Ageing, 2017. **46**(6): p. 882-888.
30. Perkins, A.J., et al., *Common comorbidity scales were similar in their ability to predict health care costs and mortality.* Journal of clinical epidemiology, 2004. **57**(10): p. 1040-1048.
31. Quail, J.M., et al., *Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts.* BMC health services research, 2011. **11**(1): p. 146.
32. Schneeweiss, S., et al., *Consistency of performance ranking of comorbidity adjustment scores in Canadian and US utilization data.* Journal of general internal medicine, 2004. **19**(5p1): p. 444-450.
33. Brilleman, S.L. and C. Salisbury, *Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study.* Family Practice, 2013. **30**(2): p. 172-178.

34. Wallace, E., et al., *Comparison of count-based multimorbidity measures in predicting emergency admission and functional decline in older community-dwelling adults: a prospective cohort study.* BMJ open, 2016. **6**(9): p. e013089.
35. Boeckxstaens, P., et al., *Multimorbidity measures were poor predictors of adverse events in patients aged≥ 80 years: a prospective cohort study.* Journal of clinical epidemiology, 2015. **68**(2): p. 220-227.
36. Boeckxstaens, P., et al., *Should we keep on measuring multimorbidity?* Journal of clinical epidemiology, 2016. **71**: p. 113-114.

**Table 1: Study population descriptive characteristics at baseline (T0)**

| Patient Characteristic | All patients | Patients with ≥ 10 prescribed medication classes | | | Patients with >=3 chronic diseases | | |
|---|---|---|---|---|---|---|---|
| | n (%)* | Yes n (%)* | No n (%)* | p-value** | Yes n (%)* | No n (%)* | p-value** |
| | | | | | | | |
| N | 726 (100%) | 89 (12.3%) | 637 (87.7%) | | 223 (30.7%) | 503 (69.3%) | |
| Median age (IQR), years | 76.4 (72.9 – 80.3) | 78.8 (73.8 – 83.2) | 76.1 (72.9 – 79.8) | 0.013 | 77.6 (74.1-81.1) | 76.0 (72.8 – 79.8) | 0.002 |
| Mean deprivation score (SD) | 1.4 (2.6) | 1.8 (2.3) | 1.4 (2.6) | 0.075 | 1.6 (2.4) | 1.3 (2.6) | 0.272 |
| Gender | | | | | | | |
| Male | 348 (47.9%) | 33 (37.1%) | 315 (49.5%) | 0.038 | 112 (50.2%) | 236 (46.9%) | 0.246 |
| Female | 378 (52.1%) | 56 (62.9%) | 322 (50.6%) | | 111 (48.8%) | 267 (53.1%) | |
| Social class | | | | | | | |
| Unskilled | 161 (22.2%) | 29 (32.6%) | 132 (20.7%) | 0.064 | 55 (24.7%) | 106 (21.1%) | 0.636 |
| Skilled | 565 (77.8%) | 60 (67.4%) | 505 (79.3%) | | 168 (75.3%) | 397 (78.9%) | |
| Education | | | | | | | |
| Basic | 433 (59.6%) | 66 (75%) | 367 (57.9%) | 0.014 | 155 (70.1%) | 278 (55.5%) | 0.006 |
| Higher | 293 (40.4%) | 22 (25.0%) | 267 (42.1%) | | 66 (29.9%) | 223 (44.5%) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Marital status*** | | | | | | | |
| Married | 342 (47.1%) | 35 (39.3%) | 307(42.3%) | 0.127 | 94 (42.3%) | 248 (49.3%) | 0.296 |
| Separated/divorced | 34 (4.7%) | 2 (2.3%) | 32 (5.0%) | | 12 (5.4%) | 22 (4.4%) | |
| Widowed | 224 (30.9%) | 39 (43.8%) | 185 (29.1%) | | 81 (36.5%) | 143 (28.4%) | |
| Single/never married | 125 (17.2%) | 13 (14.6%) | 112 (17.6%) | | 35 (15.8%) | 90 (17.9%) | |
| Living arrangement*** | | | | | | | |
| Husband/wife/life partner | 333 (45.9%) | 33 (37.1%) | 300 (47.2%) | 0.246 | 92 (41.4%) | 241 (47.9%) | 0.508 |
| Family/relatives | 90 (12.4%) | 12 (13.5%) | 78 (12.3%) | | 27 (12.2%) | 63 (12.5%) | |
| Living alone | 266 (36.6%) | 37 (41.6%) | 229 (36.0%) | | 91 (41.0%) | 175 (34.8%) | |
| Other | 36 (5.0%) | 7 (7.9%) | 29 (4.6%) | | 12 (5.4%) | 24 (4.8%) | |

IQR: Interquartile range; SD: Standard deviation
* Unless otherwise stated
** Cluster adjusted Mann-Whitney test (age), t-test (deprivation score) or chi-squared test for categorical variables.
*** Missing for two people

**Table 2: Patients with multimorbidity according to medication class count or chronic disease count and outcomes of death, decline in health-related quality of life, decline in physical functioning and decline in psychological well-being**

| | | Medication Classes Count (MCC) | | | Chronic Disease Count (CDC) | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | | **Patients with <10 medications** | **Patients with >=10 medications** | **Cluster adjusted chi-squared p-value** | **Patients with <3 chronic diseases** | **Patients with >=3 chronic diseases** | **Cluster adjusted chi-squared p-value** |
| Death (n=724) | No | 598 (94.0%) | 73 (83.0%) | <0.001 | 472 (94.0%) | 199 (89.6%) | 0.054 |
| | Yes | 38(6.0%) | 15 (17.0%) | | 30 (6.0%) | 23 (10.4%) | |
| Decline in health-related quality of life (EQ-5D) (n=636) | No | 393 (68.3%) | 39 (63.9%) | 0.443 | 310 (68.0%) | 122 (67.8%) | 0.820 |
| | Yes | 182 (31.7%) | 22 (36.0%) | | 146 (32.0%) | 58 (32.2%%) | |
| Decline in physical functioning (VES-13) (n=673) | No | 525 (87.7%) | 66 (89.2%) | 0.622 | 418 (88.4%) | 173 (86.5%) | 0.768 |
| | Yes | 74 (12.4%) | 8 (10.8%) | | 55 (11.6%) | 27 (13.5%) | |
| Decline in psychological well-being (HADS) (n=649) | No | 501 (86.7%) | 56 (78.9%) | 0.116 | 401 (88.3%) | 156 (80.0%) | 0.017 |
| | Yes | 77 (13.3%) | 15 (21.1%) | | 53 (11.7%) | 39 (19.5%) | |

EQ5D: Euro-Qual 5 Dimensions; VES-13: Vulnerable Elders Survey; HADS: Hospital Anxiety and Depression Scale;

**Table 3: Cluster-adjusted sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of multimorbidity measures**

| Multimorbidity measure | Sample | Outcome | Sensitivity (%, 95% CI) | Specificity (%, 95% CI) | PPV (%, 95% CI) | NPV (%, 95% CI) |
|---|---|---|---|---|---|---|
| **Patients with ≥ 10 prescribed medication classes** | All patients (n=726) | Death | 28.0% (18.7%-39.8%) | 89.0% (86.0%-91.5%) | 17.1% (9.9%-28.5%) | 94.1% (91.1%-96.2%) |
| | Patients who completed follow-up question-naire (n=673) | Decline in health-related quality of life (EQ-5D) (n=636) | 10.5% (7.6%-14.4%) | 90.9% (86.2% -94.1%) | 36.9% (24.4% – 51.5%) | 68.3% (65.1% -71.3%) |
| | | Decline in physical func-tioning (VES-13) | 8.9% (5.5%–14.3%) | 88.8% (85.2%-91.6%) | 10.1% (5.4%-18.0%) | 87.7% (84.6%-90.2%) |
| | | Decline in physical func-tioning (VES-13) (n=673) | 16.3% (10.4%-24.5%) | 89.9% (86.2%-92.7%) | 21.1% (13.0%-32.4%) | 87.3% (85.1%-89.2%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Patients with >=3 chronic diseases** | All patients (n=726) | Death | 41.6% (33.9%-49.7%) | 70.3% (63.5%-76.3%) | 10.5% (6.6%-16.1%) | 94.0% (91.8%-95.6%) |
| | Patients completing follow-up question-naire (n=673) | Decline in health-related quality of life (EQ-5D) (n=636) | 28.5% (22.1%-35.9%) | 71.9% (64.8%-78.1%) | 32.0% (28.8%-35.3%) | 67.9% (64.4%-71.2%) |
| | | Decline in physical func-tioning (VES-13) | 35.3% (22.9%-50.0%) | 71.1% (64.6%-76.9%) | 12.7% (9.9%-16.2%) | 88.8% (84,4%-92.0%) |
| | | Decline in physical func-tioning (VES-13) (n=673) | 42.8% (31.7%-54.6%) | 72.3% (66,0%-77.9%) | 19.9% (14.8%-26.1%) | 88.4% (85.6%-90.7%) |

EQ5D: Euro-Qual 5 Dimensions; VES-13: Vulnerable Elders Survey; HADS: Hospital Anxiety and Depression Scale; PPV: Positive Predictive Value; NPV: Negative Predictive Value

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

| | | Reporting Item | Page Number |
|---|---|---|---|
| Title | #1a | Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| Abstract | #1b | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| Background / rationale | #2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | #3 | State specific objectives, including any prespecified hypotheses | 4 |
| Study design | #4 | Present key elements of study design early in the paper | 5 |
| Setting | #5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 |
| Eligibility criteria | #6a | Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. | 5 |

| | | | |
|---|---|---|---|
| | #6b | For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | #7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6-8 |
| Data sources / measurement | #8 | For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable. | 6-8 |
| Bias | #9 | Describe any efforts to address potential sources of bias | 8 |
| Study size | #10 | Explain how the study size was arrived at | 8 |
| Quantitative variables | #11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 8 |
| Statistical methods | #12a | Describe all statistical methods, including those used to control for confounding | 8 |
| | #12b | Describe any methods used to examine subgroups and interactions | NA |
| | #12c | Explain how missing data were addressed | NA |
| | #12d | If applicable, explain how loss to follow-up was addressed | NA |
| | #12e | Describe any sensitivity analyses | NA |
| Participants | #13a | Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. | 8 |
| | #13b | Give reasons for non-participation at each stage | 8 |
| | #13c | Consider use of a flow diagram | NA |
| Descriptive data | #14a | Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential | 17 |

| | | | |
|---|---|---|---|
| | | confounders. Give information separately for exposed and unexposed groups if applicable. | |
| | #14b | Indicate number of participants with missing data for each variable of interest | 17 |
| | #14c | Summarise follow-up time (eg, average and total amount) | 5 |
| Outcome data | #15 | Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable. | 19 |
| Main results | #16a | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 20-21 |
| | #16b | Report category boundaries when continuous variables were categorized | 20-21 |
| | #16c | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 20-21 |
| Other analyses | #17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | 22-23 |
| Key results | #18 | Summarise key results with reference to study objectives | 10 |
| Limitations | #19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | 10 |
| Interpretation | #20 | Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. | 11 |
| Generalisability | #21 | Discuss the generalisability (external validity) of the study results | 11 |
| Funding | #22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13 |

BMJ Open

# Predicting poorer health outcomes in older community-dwelling patients with multimorbidity: prospective cohort study assessing the accuracy of different multimorbidity definitions

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| Keywords: | multimorbidity, risk prediction, chronic diseases, medications, polypharmacy |
| | |

# Predicting poorer health outcomes in older community-dwelling patients with multimorbidity: prospective cohort study assessing the accuracy of different multimorbidity definitions

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**Abstract:**

Purpose: Multimorbidity is commonly defined and measured using condition counts. the United Kingdom National Institute for Health Care Excellence Guidelines for Multimorbidity suggest that a medication-orientated approach could be used to identify those in need of a multimorbidity approach to management.

Objectives: To compare the accuracy of medication-based and diagnosis-based multimorbidity measures at higher cut-points to identify older community-dwelling patients who are at risk of poorer health outcomes.

Design: A secondary analysis of a prospective cohort study with two-year follow up (2010-12)

Setting: 15 general practices in Ireland

Participants: 904 older community-dwelling patients.

Exposure: Baseline multimorbidity measurements, based on both medication classes count (MCC) and chronic disease count (CDC).

Outcomes: Mortality, self-reported health related quality of life, mental health and physical functioning at follow-up.

Analysis: Sensitivity, specificity, positive predictive values and negative predictive values adjusting for clustering by practice for each outcome using both definitions.

Results: Of the 904 baseline participants, 53 died during follow-up and 673 patients completed the follow-up questionnaire. At baseline, 223 patients had 3 or more chronic conditions and 89 patients were prescribed 10 or more medication classes. Sensitivity was low for both MCC and CDC measures for all outcomes. For specificity, MCC was better for all outcomes with estimates varying from 88.8% (95% CI: 85.2 to 91.6%) for physical functioning to 90.9% (95% CI: 86.2 to 94.1%) for self-reported health related quality of life. There were no differences between MCC and CDC in terms of PPV and NPV for any outcomes.

Conclusions: Neither measure demonstrated high sensitivity. However, MCC using a definition of 10 or more regular medication classes to define multimorbidity had higher specificity for predicting poorer health outcomes. While having limitations, this definition could be used for proactive identification of patients who may benefit from targeted clinical care.

Keywords: multimorbidity, medications, risk prediction, chronic diseases

Strengths and limitations of this study:

- This study compares use of medication classes count with the more traditional method of chronic disease counts to define multimorbidity. This approach could be used proactively in the clinical setting to identify higher risk people.
- Our study used a large dataset with robust data collection from electronic health records combined with linked national pharmacy claims data and a patient questionnaire for self-reported outcomes.
- This study only included older patients with multimorbidity, further research would be needed to validate these results in other populations.
- This study is a secondary analysis and as such is limited to the data collected from the recruited population in the original cohort study.

## Introduction:

A high proportion of patients consulting in primary healthcare present with multimorbidity, defined generally as the presence of at least two chronic medical conditions [1]. Multimorbidity has a significant impact across the age ranges but is more common in older patients and is associated with poorer quality of life [2, 3], psychological distress [4-6], loss of physical function [7], polypharmacy and adverse drugs events [8] and care duplication and inconsistencies [9, 10]. Within the broad multimorbidity population, outcomes are poorer in patients with more complex multimorbidity, which has been defined previously in terms of higher numbers of conditions or higher healthcare utilisation.

Even though associations with poorer health outcomes are clear, identifying older patients with multimorbidity who will benefit from a community-based intervention is difficult due to the heterogeneity of multimorbidity definitions and measures, used in both public health and clinical interventions [11]. Existing trials have based inclusion on the number of conditions along with other markers of risk such as older age or high healthcare utilisation [12]. The United Kingdom (UK) National Institute for Health and Care Excellence (NICE) 2016 Guidance on Multimorbidity recommends that health practitioners should proactively identify patients that could benefit from a multimorbidity approach to clinical care. The NICE Guidance suggests considering a multimorbidity approach to care for adults of any age who are prescribed ≥10 medications with the advantage that this information can be retrieved from the electronic health record [13]. This approach to care is patient-centred as it follows patient goals and preference of care, focusing on quality of life by reducing treatment burden, adverse events, and unplanned care and improving services coordination. Polypharmacy is a marker of multimorbidity and patients identified this way can be regarded as having multimorbidity and offered broad interventions beyond medicines management. For condition count multimorbidity measurement, the literature suggests using ≥3 chronic conditions to identify patients with higher needs. [14, 15].

This study aimed to examine the accuracy of medication-based versus condition count-based definitions of multimorbidity in predicting poorer health outcomes for older community-dwelling patients.

## Methods

The Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used to guide the conduct and reporting of this study [16].

*Study design and population*

This is a secondary analysis of a two year, prospective cohort study that was established to examine potentially inappropriate prescribing and adverse health outcomes in older community-dwelling patients [17]. Ethical approval for this cohort study was granted by the Royal College of Surgeons in Ireland (RCSI) Human Research Ethics committee. The study population was recruited from 15 randomly selected general practices in Leinster, Ireland for a two year (2010-2012) prospective cohort study involving older community-dwelling patients. Proportionate stratified sampling was carried out based on the overall required sample size and the total number of eligible patients per practice assuming a 50% response rate and of 3070 eligible patients, a total of 1764 were invited to participate. [17, 18] Of this group, 152 were ineligible on invitation based on eligibility criteria and 125 were not contactable resulting in 1,487 patients eligible for participation.



Study inclusion criteria:

(1) age ≥70 years on 1 January 2010

(2) in receipt of a valid general medical services (GMS) card, which is means tested and entitles the holder to free public medical services including GP care.

Exclusion criteria:

(1) receiving palliative care;

(2) cognitive impairment at the level that would affect their ability to complete the outcome measure (defined as Mini Mental State Examination ≤20);

(3) significant hearing/speech/ visual impairment;

(4) currently experiencing a psychotic episode;

(5) hospitalised long-term, in a nursing home, homeless or in sheltered accommodation;

(6) recent bereavement (within 4 weeks).

Of 1487 eligible and invited to participate at baseline (T0) a total of 904 (61%) agreed [17, 18]. Two study populations are presented depending on the outcome of interest:

a. Patients who either completed two-year follow-up (T1) or died before T1 for mortality analysis (n = 726)
b. Patients who completed T1 self-reported questionnaires for patient reported health outcomes analysis (n= 673)

*Demographic data collected*

Sociodemographic variables collected included age, deprivation, gender, social class, education, marital status and living arrangements. Age and gender were collected from the GP electronic medical record. The deprivation score was obtained with the geocoded patients address based on the Small Area Health Research Unit (SAHRU) which uses electoral division [19]. Education levels were classified as basic education (no formal education, primary education or lower secondary education only) or upper and post-secondary (all other higher levels of education). Social class was classified as unskilled (unskilled, gainfully occupied, unknown) or skilled (all other categories). Marital status was classified as married, separated/divorced, widowed and single/never married. Living arrangements were classified as living with husband/wife/life partner, family/relatives, living alone and other.

*Exposure of interest: Multimorbidity measures*

Two measures of multimorbidity were selected based on current guidelines and literature [14, 15].

(i) Medication classes count (MCC)

The number of regular prescribed medication classes was calculated by linkage to the national Health Services Executive (HSE)-Primary Care Reimbursement Scheme (PCRS) pharmacy claims database. The number of medication classes prescribed to the patient

were classified using the first three characters of the WHO-ATC classification system and the sample was divided using a cut-off definition of 10 or more prescribed medication classes [20]. The NICE guidelines indicate that a patient with 10 or more prescribed medicines and an additional risk factor would benefit from a multimorbidity approach [21]. As all cohort participants were 70 years or older, this population was considered as having an additional risk factor.

(ii) Chronic disease count (CDC)

At baseline, chronic diseases were collected from the GP electronic medical record by eight trained medical students using standardised data collection forms. A disease count proposed by Barnett et al. which includes 40 chronic diseases on the basis of disease prevalence and severity was used to define multimorbidity [22]. A cut-off of ≥3 chronic diseases was used to identify multimorbidity [14, 15].

*Primary Outcomes*

Mortality and patient reported outcome measures (PROM) were selected to identify patients with poorer health at follow-up. The study examined poorer self-reported health between T0 (baseline) and T1 (2 years). The PROMs were dichotomized, as described below to identify changes in outcome over the 2 years.

(i) Mortality

Mortality was assessed by examining each participant's GP electronic medical record. Where there was any query regarding the date of death, it was double checked using a national repository of deaths in Ireland.

(ii) Health related quality of life

The Euro-Qual 5 Dimensions (EQ-5D) is a generic instrument widely used to assess health related quality of life by using ordinal scaling to assess fives domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Poorer self-reported health was defined using the Paretian principles method described by Devlin et al [23]. Following these principles, poorer health related quality of life was operationalised as a

decline in a greater number of domains scores compared to stable or improved domains scores [23].

(iii) Mental health

The Hospital Anxiety and Depression Scale (HADS) is a measure assessing levels of anxiety and depression independently, which are then classified as normal, mild, moderate or severe [24]. Poorer self-reported mental health was defined as a higher score at follow up-compared to baseline according to the HADS [24].

(iv) Physical functioning

The Vulnerable Elders Survey (VES-13) is a patient-reported outcome measure used to identify older patients at risk of functional decline [25]. In the derivation study for this tool, patients who scored ≥3 had four times the risk of death or functional decline over a two year period than patients who scored less than 3 [25]. Accordingly, patients were classified as having poorer self-reported health if study participants who scored less than 3 at baseline (T0) scored ≥3 at follow up (T1).

*Statistical Analysis*

Descriptive statistics are presented to describe patient characteristics. For categorical measures the number of patients and percentage was calculated, and for continuous measures the mean and standard deviation (SD). For continuous scales which showed evidence of, or were expected to show some skew, a median and inter-quartile range was presented. A Chi-squared test, t-test or Mann-Whitney test was used as appropriate, adjusting for clustering by practice, to examine possible associations between patient characteristics and multimorbidity measures (patients with ≥10 vs <10 prescribed medication classes and patients with ≥3 vs <3 chronic diseases).

The sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV), along with 95% confidence intervals, were calculated adjusting for clustering by practice using STATA version 15 (StataCorp. 2017. College Station, TX: StataCorp LLC) for each outcome and using both exposures of interest (MCC and CDC). For our

analyses, sensitivity is the probability of a patient who experiences the health outcome of interest (i.e. death or decline in PROM at follow-up) having multimorbidity at baseline, specificity is the probability of a patient who does not experience the health outcome at follow-up not having multimorbidity at baseline, the positive predictive value is the probability of a patient with multimorbidity at baseline having the health outcome at follow-up and the negative predictive value is the probability of a patient without multimorbidity at baseline not having the health outcome at follow-up.

*Risk of Bias*

The risk of bias was assessed in the cohort study using The Cochrane risk of bias tool for non-randomized studies [26].

*Patient and public involvement*

This study is a secondary analysis of a cohort study which started enrolment in 2010. No patients or members of the public were involved in its design phase.

## Results

*Participants*

A total of 223 participants (30.7%) met the criteria for the CDC definition for multimorbidity, and 89 patients (12.3%) met the criteria for the MCC definition. Overall, 61 patients met both criteria. The median age of the total sample was 76.4 years, a total of 348 (47.9%) participants were males, 565 (77.8%) were classified as coming from the skilled social class and 433 (59.6%) reported a basic level of education. Descriptive characteristics of the patients identified by the CDC and the MCC cut-offs are presented in Table 1. Patients with a disease count ≥3, compared to those with a disease count <3, were on average older and reported less formal education. Patients prescribed ≥10 medications classes were on average older, female and had less formal education compared to patients prescribed <10 medication classes.

*Outcomes*

The proportion of patients defined as having multimorbidity using both definitions who died or reported poorer health outcomes are presented in Table 2. Patients with ≥10 medication classes had a significantly higher mortality rate compared to patients with <10 medication classes (17% vs 6%, p <0.001). There was no difference in the other outcomes measured. Patients with a disease count of ≥3, compared to those with a disease count of <3, had a significantly higher decline in psychological well-being (19.5% vs 11.7%, p=0.017) but there was no difference in any of the other outcomes.

The sensitivity, specificity, PPV and NPV along with 95% confidence intervals adjusted for clustering by practice are presented in Table 3 for both definitions of multimorbidity for each outcome of interest. For mortality, specificity was higher for MCC (89.0%; 95% CI: 86.0%-91.5%) compared to the CDC (70.3%; 95% CI: 63.5%-76.3%). For decline in health-related quality of life, both CDC and MCC measures had low sensitivity, however, the CDC (28.5%; 95% CI: 22.1%-35.9%) was higher than the MCC (10.5%; 95% CI: 7.6%-14.4%). In terms of specificity, MCC (90.9%; CI: 86.2% -94.1%) was higher when compared to the CDC measure (71.9%; CI: 64.8%-78.1%).

Similar patterns were reported for decline in physical functioning and psychological functioning as were seen for decline in health-related quality of life. Specificity was moderate for the CDC measure for both decline in physical functioning (71.9%; 95% CI: 64.8%-78.1%) and decline in psychological functioning (71.1%; 95% CI: 64.6%-76.9%). The MCC demonstrated higher specificity (decline in physical functioning: 88.8%; 95% CI 85.2%-91.6% and decline in psychological functioning: 89.9%; 95% CI: 86.2%-92.7%).

*Risk of Bias*

The risk of bias is reported fully in the primary cohort study previously [17]. Overall, the risk of bias was low regarding losses to follow up. As this is a secondary analysis, exclusion of participants with cognitive impairment and the small sample of participants with 15 or more medication classes could reduce generalizability [26].

## Discussion

*Main results*

In this population of community dwelling older patients, sensitivity was low for both the MCC and CDC measures for all outcomes. However, for self-reported health related quality of life, psychological well-being and physical functioning at follow-up the CDC measure was more sensitive. There was no difference in sensitivity between measures for the outcome of death. In terms of specificity, the MCC approach was better for all outcomes with estimates varying from 88.8% (95% CI: 85.2 to 91.6%) for physical functioning to 90.9% (95% CI: 86.2 to 94.1%) for self-reported health related quality of life.

With high specificity, the MCC definition has better potential to proactively "rule-in" patients with multimorbidity who are more likely to have poorer health outcomes compared to the more widely used condition count approach. There are also fewer patients identified using the MCC definition, which is more manageable from a clinical or organisational perspective. However, both definitions had insufficient sensitivity, showing a limited potential to accurately 'rule out' patient at risk of poorer health outcomes in this population. Ideally a definition with both high sensitivity and specificity could be used to target multimorbidity interventions but existing risk stratification models have similar limitations [27].

*Strengths and limitations*

In this cohort study, the medication classes count variable was obtained from linked national pharmacy claims data and the number of chronic diseases count was obtained via review of the participants' electronic medical record, which adds to the robustness to the data used in this analysis. A main strength of the study is that the dataset includes a variety of outcomes including mortality and patient-reported outcomes.

The first limitation of this study is inherent to the secondary analysis design, by using previously collected data it is not possible to align data collection directly with the goals of the current study, however we did have a wide range of patient reported and chart data available for analysis. The cohort study sample was limited to a community-dwelling

older people without cognitive, visual or hearing impairment. However recent studies indicate that multimorbidity is not just a feature of ageing but is also prevalent in younger populations [1, 28, 29]. We limited the number of chronic conditions identified in the records to 40 pre-specified conditions. Another potential limitation is the collection of data from medical records as there may have been some variation in recording of conditions. Medication classes were used as the predictor of interest as per the WHO-ATC classification system rather than individual medications. Further research is needed to validate our findings in larger samples

*Comparison with existing literature*

Previous studies have reported mixed results concerning the predictive power of multimorbidity definitions for different outcomes. Several studies have showed that a weighted diagnosis count, the Charlson index was an suitable measure to predict mortality [30-32] However, a large cohort study (n= 95 372) comparing six measure of multimorbidity reported that the number of prescribed medications was the most accurate multimorbidity measurement to predict future GP and practice nurses consultations and that it was also the second most accurate measure to predict mortality, just behind the Charlson index [33]. A previous analysis of the current cohort study data compared five continuous count-based definitions of multimorbidity and reported poor discrimination in predicting hospital admissions and self-reported functional decline for all multimorbidity measures, with the medication class based definition performing marginally better than diagnosis based definitions [34]. A previous study reported that using a 10 or more medication class cut-off to measure multimorbidity performed similarly to another risk score with low sensitivity and high specificity, when applied in clinical settings to predict cardiovascular disease risk [27]. Our findings build on this previous research, by comparing the predictive power of a medication class count definition against a disease count definition using pragmatic cut-off points, and also examining a range of self-reported health outcomes in addition to mortality. Research to date has highlighted the limitations of multimorbidity measures in predicting adverse events and work in this area is now expanding to include biomarkers in an effort to address these limitations [35, 36].

*Implications for future research and clinical practice:*

Further research should assess the accuracy of multimorbidity measures in a larger range of primary care populations, including middle aged patients with multimorbidity and older patients with cognitive decline. Larger sample sizes are needed to test the 15 or more medications cut-off measure for multimorbidity also recommended as an alternative in the UK NICE Multimorbidity Guidance [21]. In our study, there was little difference in medication and condition count measures in identifying older people at higher risk of poor health outcomes but medication classes count demonstrated higher specificity shows a slight difference in age, suggesting that the medication definition might better identify older people at higher risk. While it shares some limitations with other multimorbidity measures, clinicians and researchers can follow the expert consensus in the UK NICE Multimorbidity Guidance recommendations by using medication classes count to identify higher risk patients with multimorbidity as it is easy to use and offers a pragmatic approach and potential for identification of patients through prescribing or electronic health records.

## Conclusions

This study shows that using two measures of multimorbidity, a medication classes count cut-off of 10 or more and a chronic disease count of 3 or more chronic diseases had low sensitivity in relation to predicting mortality, self-reported health related quality of life, mental health and physical functioning, although the chronic disease count was slightly more sensitive for the majority of outcomes. The medication classes count approach demonstrated higher specificity for mortality and decline in health status, making it possible to rule-in a small sample of patients identified with a risk of poorer health outcomes with a low rate of false positives. However, the low sensitivity means that some of those identified as low risk may also experience poorer health outcomes.

## Author contributions.

MS, SS and EW conceptualised the study, MS and FB analysed the data and SS, EW, FB and RM took part in the interpretation of results. MS wrote the original draft and SS, EW, FB, RM, MF and LF contributed to the editing and reviewing of the paper.

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**Data sharing statement**

The database from the cohort study is available from Dr. Emma Wallace by local access only. Please contact corresponding author.

**Competing interests**

None declared

**Patient consent**

Not required.

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## References

1. Fortin, M., et al., *Prevalence of multimorbidity among adults seen in family practice.* Annals of Family Medicine, 2005. **3**: p. 223 - 228.
2. Fortin, M., et al., *Relationship between multimorbidity and health-related quality of life of patients in primary care.* Quality of Life Research, 2006. **15**(1): p. 83-91.
3. Brettschneider, C., et al., *Relative impact of multimorbid chronic conditions on health-related quality of life–results from the MultiCare Cohort Study.* PLoS One, 2013. **8**(6): p. e66742.
4. Gunn, J.M., et al., *The association between chronic illness, multimorbidity and depressive symptoms in an Australian primary care cohort.* Social psychiatry and psychiatric epidemiology, 2012. **47**(2): p. 175-184.
5. Fortin, M., et al., *Psychological distress and multimorbidity in primary care.* The Annals of Family Medicine, 2006. **4**(5): p. 417-422.
6. Read, J., et al., *Multimorbidity and Depression: A Systematic Review and Meta-analysis.* Journal of Affective Disorders, 2017.
7. Bayliss, E.A., et al., *Predicting declines in physical function in persons with multiple chronic medical conditions: what we can learn from the medical problem list.* Health and Quality of Life Outcomes, 2004. **2**(1): p. 47.
8. Guthrie, B., et al., *High risk prescribing in primary care patients particularly vulnerable to adverse drug events: cross sectional population database analysis in Scottish general practice.* Bmj, 2011. **342**: p. d3514.
9. Guthrie, B., et al., *Adapting clinical guidelines to take account of multimorbidity.* British Medical Journal, 2012. **345**.
10. Hughes, L.D., M.E.T. McMurdo, and B. Guthrie, *Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity.* Age And Ageing, 2013. **42**(1).
11. Almirall, J. and M. Fortin, *The coexistence of terms to describe the presence of multiple concurrent diseases.* Journal of Comorbidity, 2013. **3**(1): p. 4-9.
12. Smith, S., et al., *Interventions for improving outcomes in patients with multimorbidity in primary care and community settings.* The Cochrane Library, 2016.
13. Farmer, C., et al., *Clinical assessment and management of multimorbidity: summary of NICE guidance.* BMJ: British Medical Journal (Online), 2016. **354**.
14. Fortin, M., et al., *A systematic review of prevalence studies on multimorbidity: toward a more uniform methodology.* The Annals of Family Medicine, 2012. **10**(2): p. 142-151.
15. Harrison, C., et al., *Examining different measures of multimorbidity, using a large prospective cross-sectional study in Australian general practice.* BMJ Open, 2014. **4**(7).
16. Von Elm, E., et al., *The Strengthening the Reporting of Observational Studies in Epidemiology [STROBE] statement: guidelines for reporting observational studies.* Gaceta Sanitaria, 2008. **22**(2): p. 144-150.
17. Wallace, E., et al., *Impact of potentially inappropriate prescribing on adverse drug events, health related quality of life and emergency hospital attendance in older people attending general practice: a prospective cohort study.* Journals of

Gerontology Series A: Biomedical Sciences and Medical Sciences, 2016. **72**(2): p. 271-277.
18. Cahir, C., et al., *Potentially inappropriate prescribing and adverse health outcomes in community dwelling older patients.* British journal of clinical pharmacology, 2014. **77**(1): p. 201-210.
19. Kelly, A. and C. Teljeur, *The national deprivation index for health & health services research.* Small Area Health Research Unit Technical Report. Small Area Health Research Unit, Trinity College Dublin, 2007.
20. World Health Organization, *WHO collaborating centre for drug statistics methodology. ATC/DDD index 2011.* World Health Organization2011WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index, 2011.
21. National Guideline Centre UK, *Multimorbidity: Assessment, Prioritisation and Management of Care for People with Commonly Occurring Multimorbidity.* 2016.
22. Barnett, K., et al., *Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study.* The Lancet, 2012. **380**(9836): p. 37-43.
23. Devlin, N., D. Parkin, and J. Browne, *Using the EQ-5D as a performance measurement tool in the NHS.* 2009.
24. Zigmond, A.S. and R.P. Snaith, *The Hospital Anxiety And Depression Scale.* Acta Psychiatr Scand, 1983. **67**.
25. Saliba, D., et al., *The Vulnerable Elders Survey: A Tool for Identifying Vulnerable Older People in the Community.* Journal of the American Geriatrics Society, 2001. **49**(12): p. 1691-1699.
26. Higgins, J.P. and S. Green, *Cochrane handbook for systematic reviews of interventions*. Vol. 4. 2011: John Wiley & Sons.
27. Chamnan, P., et al., *A simple risk score using routine data for predicting cardiovascular disease in primary care.* Br J Gen Pract, 2010. **60**(577): p. e327-e334.
28. Smith, S.M., A. Ferede, and T. O'Dowd, *Multimorbidity in younger deprived patients: An exploratory study of research and service implications in general practice.* BMC Family Practice, 2008. **9**: p. 6-6.
29. Yarnall, A.J., et al., *New horizons in multimorbidity in older adults.* Age and Ageing, 2017. **46**(6): p. 882-888.
30. Perkins, A.J., et al., *Common comorbidity scales were similar in their ability to predict health care costs and mortality.* Journal of clinical epidemiology, 2004. **57**(10): p. 1040-1048.
31. Quail, J.M., et al., *Comparing comorbidity measures for predicting mortality and hospitalization in three population-based cohorts.* BMC health services research, 2011. **11**(1): p. 146.
32. Schneeweiss, S., et al., *Consistency of performance ranking of comorbidity adjustment scores in Canadian and US utilization data.* Journal of general internal medicine, 2004. **19**(5p1): p. 444-450.
33. Brilleman, S.L. and C. Salisbury, *Comparing measures of multimorbidity to predict outcomes in primary care: a cross sectional study.* Family Practice, 2013. **30**(2): p. 172-178.

34. Wallace, E., et al., *Comparison of count-based multimorbidity measures in predicting emergency admission and functional decline in older community-dwelling adults: a prospective cohort study.* BMJ open, 2016. **6**(9): p. e013089.
35. Boeckxstaens, P., et al., *Multimorbidity measures were poor predictors of adverse events in patients aged≥ 80 years: a prospective cohort study.* Journal of clinical epidemiology, 2015. **68**(2): p. 220-227.
36. Boeckxstaens, P., et al., *Should we keep on measuring multimorbidity?* Journal of clinical epidemiology, 2016. **71**: p. 113-114.

**Table 1: Study population descriptive characteristics at baseline (T0)**

| Patient Characteristic | All patients | Patients with ≥ 10 prescribed medication classes | | | Patients with >=3 chronic diseases | | |
|---|---|---|---|---|---|---|---|
| | n (%)* | Yes n (%)* | No n (%)* | p-value** | Yes n (%)* | No n (%)* | p-value** |
| | | | | | | | |
| N | 726 (100%) | 89 (12.3%) | 637 (87.7%) | | 223 (30.7%) | 503 (69.3%) | |
| Median age (IQR), years | 76.4 (72.9 – 80.3) | 78.8 (73.8 – 83.2) | 76.1 (72.9 – 79.8) | 0.013 | 77.6 (74.1-81.1) | 76.0 (72.8 – 79.8) | 0.002 |
| Mean deprivation score (SD) | 1.4 (2.6) | 1.8 (2.3) | 1.4 (2.6) | 0.075 | 1.6 (2.4) | 1.3 (2.6) | 0.272 |
| Gender | | | | | | | |
| Male | 348 (47.9%) | 33 (37.1%) | 315 (49.5%) | 0.038 | 112 (50.2%) | 236 (46.9%) | 0.246 |
| Female | 378 (52.1%) | 56 (62.9%) | 322 (50.6%) | | 111 (48.8%) | 267 (53.1%) | |
| Social class | | | | | | | |
| Unskilled | 161 (22.2%) | 29 (32.6%) | 132 (20.7%) | 0.064 | 55 (24.7%) | 106 (21.1%) | 0.636 |
| Skilled | 565 (77.8%) | 60 (67.4%) | 505 (79.3%) | | 168 (75.3%) | 397 (78.9%) | |
| Education | | | | | | | |
| Basic | 433 (59.6%) | 66 (75%) | 367 (57.9%) | 0.014 | 155 (70.1%) | 278 (55.5%) | 0.006 |
| Higher | 293 (40.4%) | 22 (25.0%) | 267 (42.1%) | | 66 (29.9%) | 223 (44.5%) | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Marital status*** | | | | | | | |
| Married | 342 (47.1%) | 35 (39.3%) | 307(42.3%) | 0.127 | 94 (42.3%) | 248 (49.3%) | 0.296 |
| Separated/divorced | 34 (4.7%) | 2 (2.3%) | 32 (5.0%) | | 12 (5.4%) | 22 (4.4%) | |
| Widowed | 224 (30.9%) | 39 (43.8%) | 185 (29.1%) | | 81 (36.5%) | 143 (28.4%) | |
| Single/never married | 125 (17.2%) | 13 (14.6%) | 112 (17.6%) | | 35 (15.8%) | 90 (17.9%) | |
| Living arrangement*** | | | | | | | |
| Husband/wife/life partner | 333 (45.9%) | 33 (37.1%) | 300 (47.2%) | 0.246 | 92 (41.4%) | 241 (47.9%) | 0.508 |
| Family/relatives | 90 (12.4%) | 12 (13.5%) | 78 (12.3%) | | 27 (12.2%) | 63 (12.5%) | |
| Living alone | 266 (36.6%) | 37 (41.6%) | 229 (36.0%) | | 91 (41.0%) | 175 (34.8%) | |
| Other | 36 (5.0%) | 7 (7.9%) | 29 (4.6%) | | 12 (5.4%) | 24 (4.8%) | |

IQR: Interquartile range; SD: Standard deviation
* Unless otherwise stated
** Cluster adjusted Mann-Whitney test (age), t-test (deprivation score) or chi-squared test for categorical variables.
*** Missing for two people

**Table 2: Patients with multimorbidity according to medication class count or chronic disease count and outcomes of death, decline in health-related quality of life, decline in physical functioning and decline in psychological well-being**

| | | Medication Classes Count (MCC) | | | Chronic Disease Count (CDC) | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | | **Patients with <10 medications** | **Patients with >=10 medications** | **Cluster adjusted chi-squared p-value** | **Patients with <3 chronic diseases** | **Patients with >=3 chronic diseases** | **Cluster adjusted chi-squared p-value** |
| Death (n=724) | No | 598 (94.0%) | 73 (83.0%) | <0.001 | 472 (94.0%) | 199 (89.6%) | 0.054 |
| | Yes | 38(6.0%) | 15 (17.0%) | | 30 (6.0%) | 23 (10.4%) | |
| Decline in health-related quality of life (EQ-5D) (n=636) | No | 393 (68.3%) | 39 (63.9%) | 0.443 | 310 (68.0%) | 122 (67.8%) | 0.820 |
| | Yes | 182 (31.7%) | 22 (36.0%) | | 146 (32.0%) | 58 (32.2%%) | |
| Decline in physical functioning (VES-13) (n=673) | No | 525 (87.7%) | 66 (89.2%) | 0.622 | 418 (88.4%) | 173 (86.5%) | 0.768 |
| | Yes | 74 (12.4%) | 8 (10.8%) | | 55 (11.6%) | 27 (13.5%) | |
| Decline in psychological well-being (HADS) (n=649) | No | 501 (86.7%) | 56 (78.9%) | 0.116 | 401 (88.3%) | 156 (80.0%) | 0.017 |
| | Yes | 77 (13.3%) | 15 (21.1%) | | 53 (11.7%) | 39 (19.5%) | |

EQ5D: Euro-Qual 5 Dimensions; VES-13: Vulnerable Elders Survey; HADS: Hospital Anxiety and Depression Scale;

**Table 3: Cluster-adjusted sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) of multimorbidity measures**

| Multimorbidity measure | Sample | Outcome | Sensitivity (%, 95% CI) | Specificity (%, 95% CI) | PPV (%, 95% CI) | NPV (%, 95% CI) |
|---|---|---|---|---|---|---|
| **Patients with ≥ 10 prescribed medication classes** | All patients (n=726) | Death | 28.0% (18.7%-39.8%) | 89.0% (86.0%-91.5%) | 17.1% (9.9%-28.5%) | 94.1% (91.1%-96.2%) |
| | Patients who completed follow-up question-naire (n=673) | Decline in health-related quality of life (EQ-5D) (n=636) | 10.5% (7.6%-14.4%) | 90.9% (86.2% -94.1%) | 36.9% (24.4% – 51.5%) | 68.3% (65.1% -71.3%) |
| | | Decline in physical func-tioning (VES-13) | 8.9% (5.5%–14.3%) | 88.8% (85.2%-91.6%) | 10.1% (5.4%-18.0%) | 87.7% (84.6%-90.2%) |
| | | Decline in physical func-tioning (VES-13) (n=673) | 16.3% (10.4%-24.5%) | 89.9% (86.2%-92.7%) | 21.1% (13.0%-32.4%) | 87.3% (85.1%-89.2%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Patients with >=3 chronic diseases** | All patients (n=726) | Death | 41.6% (33.9%-49.7%) | 70.3% (63.5%-76.3%) | 10.5% (6.6%-16.1%) | 94.0% (91.8%-95.6%) |
| | Patients completing follow-up question-naire (n=673) | Decline in health-related quality of life (EQ-5D) (n=636) | 28.5% (22.1%-35.9%) | 71.9% (64.8%-78.1%) | 32.0% (28.8%-35.3%) | 67.9% (64.4%-71.2%) |
| | | Decline in physical func-tioning (VES-13) | 35.3% (22.9%-50.0%) | 71.1% (64.6%-76.9%) | 12.7% (9.9%-16.2%) | 88.8% (84,4%-92.0%) |
| | | Decline in physical func-tioning (VES-13) (n=673) | 42.8% (31.7%-54.6%) | 72.3% (66,0%-77.9%) | 19.9% (14.8%-26.1%) | 88.4% (85.6%-90.7%) |

EQ5D: Euro-Qual 5 Dimensions; VES-13: Vulnerable Elders Survey; HADS: Hospital Anxiety and Depression Scale; PPV: Positive Predictive Value; NPV: Negative Predictive Value

# Reporting checklist for cohort study.

Based on the STROBE cohort guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the STROBE cohort reporting guidelines, and cite them as:

von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies.

| | | Reporting Item | Page Number |
|---|---|---|---|
| Title | #1a | Indicate the study's design with a commonly used term in the title or the abstract | 1 |
| Abstract | #1b | Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| Background / rationale | #2 | Explain the scientific background and rationale for the investigation being reported | 4 |
| Objectives | #3 | State specific objectives, including any prespecified hypotheses | 4 |
| Study design | #4 | Present key elements of study design early in the paper | 5 |
| Setting | #5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 5 |
| Eligibility criteria | #6a | Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. | 5 |

| | | | |
|---|---|---|---|
| | #6b | For matched studies, give matching criteria and number of exposed and unexposed | NA |
| Variables | #7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 6-8 |
| Data sources / measurement | #8 | For each variable of interest give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Give information separately for for exposed and unexposed groups if applicable. | 6-8 |
| Bias | #9 | Describe any efforts to address potential sources of bias | 8 |
| Study size | #10 | Explain how the study size was arrived at | 8 |
| Quantitative variables | #11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why | 8 |
| Statistical methods | #12a | Describe all statistical methods, including those used to control for confounding | 8 |
| | #12b | Describe any methods used to examine subgroups and interactions | NA |
| | #12c | Explain how missing data were addressed | NA |
| | #12d | If applicable, explain how loss to follow-up was addressed | NA |
| | #12e | Describe any sensitivity analyses | NA |
| Participants | #13a | Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Give information separately for for exposed and unexposed groups if applicable. | 8 |
| | #13b | Give reasons for non-participation at each stage | 8 |
| | #13c | Consider use of a flow diagram | NA |
| Descriptive data | #14a | Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential | 17 |

| | | | |
|---|---|---|---|
| | | confounders. Give information separately for exposed and unexposed groups if applicable. | |
| | #14b | Indicate number of participants with missing data for each variable of interest | 17 |
| | #14c | Summarise follow-up time (eg, average and total amount) | 5 |
| Outcome data | #15 | Report numbers of outcome events or summary measures over time. Give information separately for exposed and unexposed groups if applicable. | 19 |
| Main results | #16a | Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 20-21 |
| | #16b | Report category boundaries when continuous variables were categorized | 20-21 |
| | #16c | If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 20-21 |
| Other analyses | #17 | Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses | 22-23 |
| Key results | #18 | Summarise key results with reference to study objectives | 10 |
| Limitations | #19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. | 10 |
| Interpretation | #20 | Give a cautious overall interpretation considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. | 11 |
| Generalisability | #21 | Discuss the generalisability (external validity) of the study results | 11 |
| Funding | #22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13 |