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Multimorbidity patterns are differentially associated with functional ability and decline in a longitudinal cohort of older women

Caroline A. Jackson[1], Mark Jones[1], Leigh Tooth[1], Gita D. Mishra[1], Julie Byles[2], Annette Dobson[1]

[1]School of Public Health, University of Queensland, Brisbane, QLD 4006, Australia
[2]University of Newcastle—Research Centre for Gender, Health and Ageing, The University of Newcastle Callaghan, Newcastle, NSW 2308, Australia

Address correspondence to: C. Jackson. Tel: +61 (07) 33464724. Email: caroline.jackson@uq.edu.au

Abstract

Background: we aimed to identify multimorbidity patterns and relate these patterns to functional ability and decline.
Methods: we included 7,270 participants of the older cohort of the Australian Longitudinal Study on Women's Health, who were surveyed every 3 years from 2002 to 2011. We used factor analysis to identify multimorbidity patterns from 31 self-reported chronic conditions among women aged 76–81 in 2002. We applied a linear increments model to account for attrition and related the multimorbidity patterns to functional ability and decline at subsequent surveys, as measured by activities of daily living (ADL) and instrumental activities of daily living (IADL). For each pattern, we determined mean ADL and IADL scores in the middle and highest third of factor score in comparison to a reference group.
Results: we identified three multimorbidity patterns, labelled musculoskeletal/somatic (MSO), neurological/mental health (NMH) and cardiovascular (CVD). High factor scores for NMH, MSO and CVD were associated with significantly higher mean ADL and IADL scores (poorer functional ability) in 2005 compared with the reference group of low factor scores for all three factors. The CVD pattern was associated with the greatest decline in ADL between 2005 and 2011, whereas the NMH pattern was associated with the greatest decline in IADL.
Conclusions: distinct multimorbidity patterns were differentially associated with functional ability and decline. Given the paucity of studies on multimorbidity patterns, future studies should seek to assess the reproducibility of our findings in other populations and settings, and investigate the potential implications for improved prediction of functional decline.

Keywords: *multimorbidity, co-morbidity, chronic disease, disability, ageing, older people*

Introduction

The number of people aged over 60 years is projected to reach 2 billion by 2050 [1]. This increasing longevity heralds new public health challenges, given the growing burden of co-existing chronic conditions or 'multimorbidity'.

One-dimensional and multidimensional indices (e.g. total numbers or severity of chronic conditions) have been created to measure multimorbidity [2] and shown to be associated with health outcomes including quality of life and mortality [3]. However, such indices appear to be inadequate in predicting all health and healthcare utilisation outcomes [4, 5]. Furthermore, a single index may be too crude to fully understand how morbidities relate to and predict functional ability. Groups of conditions may have a synergistic effect on disability, and specific diseases may be associated with difficulties in different functional tasks [6]. Particular combinations of diseases may have differing effects on disability [7], a complexity not captured through a one-dimensional index of multimorbidity. Therefore, improved understanding of multimorbidity patterns may be particularly useful in predicting various health states.

Existing studies generally investigated the co-existence of major diseases, with less focus on the whole range of morbid conditions and symptoms affecting older people and how morbidities group together. Some studies have used cluster

analysis to investigate the latter [8–10], but this does not allow conditions to cross-cluster, which is more often the reality. More recent studies have used factor analysis as an alternative approach to identify morbidity 'patterns' [8, 10–13], an approach that has been successfully applied in other areas, for example in nutritional epidemiology to identify dietary patterns [14].

The aims of our study were to identify morbidity patterns in a longitudinal cohort of elderly women and relate these patterns to functional ability and decline.

Methods

Study population

Participants were from the Australian Longitudinal Study on Women's Health (ALSWH), a population-based study of women born in 1921–26, 1946–51 and 1973–78 randomly selected from the Medicare database, which covers all citizens and permanent residents of Australia, including refugees and immigrants. The 1921–26 cohort included 12,432 women surveyed using self-completed questionnaires in 1996 and re-surveyed triennially until 2011. Full details of the recruitment and response rates are reported elsewhere [15]. For this study, we included 7,270 women with complete data on conditions at Survey 3 (S3) in 2002 (earlier surveys were less suitable as they listed fewer conditions and symptoms).

Identification of chronic conditions and symptoms

We used information on self-reported symptoms and doctor-diagnosed disease to cover a wide range of conditions (Table 1 lists all conditions) and to more accurately reflect existing morbidity. At S3, women were asked 'In the last 3 years, have you been diagnosed with or treated for listed diseases'. They were also asked about the frequency of symptoms—'Have you had any of the following problems in the last 12 months?'—and could respond: never, rarely, sometimes or often. We dichotomised the response to yes (often) and no (never/rarely/sometimes). The exception was chest pain, which was considered present if reported as occurring 'sometimes' or 'often', given the serious nature of chest pain, especially within this age group. If women reported experiencing depression or anxiety/panic attacks 'often' in the past 12 months, this was incorporated into the depression and anxiety/nervous disorders disease variables. We identified vision and hearing problems by asking, 'Do you have difficulty seeing newspaper print, even with glasses?' and 'Do you have difficulty in hearing a conversation, even with a hearing aid?', to which participants responded 'yes' or 'no'.

Table 1. Distributions of demographic and health characteristics, self-reported doctor-diagnosed chronic conditions and symptoms at Survey 3 in 2002

Characteristic	*n* = 7,270, %
Age (mean ± SD, years)	78.3 ± 1.45
Married	44.9
High school education or higher[a]	69.9
Australian born[a]	78.9
Current smoker[a]	6.0
Low-risk drinker	97.2
Obese	14.3
Nil exercise/sedentary	39.2
Conditions	
Hypertension	60.5
Arthritis	54.6
Skin cancer	37.3
Osteoporosis	30.1
Stiff or painful joints[b]	27.9
Back pain[b]	23.4
Urinary problems[b,c]	23.1
Heart attack	20.3
Bronchitis/emphysema	18.9
Problems with one or both feet[b]	17.0
Vision problems[b]	16.6
Asthma	14.8
Hearing problems[b]	13.5
Diabetes	12.4
Bowel problems[b,d]	12.2
Other cancer	12.2
Other heart disease	11.9
Angina	10.1
Chest pain[b]	9.5
Allergies/hay fever/sinusitis[b]	8.5
Indigestion/heartburn[b]	8.2
Poor memory[b]	7.5
Stroke	7.3
Depression	6.8
Breathing difficulties[b]	6.2
Low iron[b]	6.1
Anxiety/nervous disorder	6.0
Dizziness[b]	5.6
Severe headache/migraine[b]	4.4
Clumsiness[b]	2.1
Alzheimer's disease/dementia	1.0
Median (inter-quartile range) number of self-reported conditions; [range]	4 (2–7) [0–24]

[a]Based on responses to Survey 1, because the question was not asked subsequently.
[b]Self-reported symptoms (reported as occurring 'often' in the past 12 months, or for chest pain, 'sometimes' or 'often').
[c]A single symptom of 'urinary problems' was created based on any of the following symptoms reported as having occurred 'often': urine that burns or stings; needing to rush to the toilet to pass urine; leaking urine.
[d]A single symptom of 'bowel problems' was created based on any of the following symptoms being reported to have occurred often: constipation; haemorrhoids; other bowel problems.

Outcomes

At Surveys 4 (2005; S4), 5 (2008; S5) and 6 (2011; S6), women were asked about their ability to perform eight basic activities of daily living (ADL) (grooming, eating, bathing, dressing upper body, dressing lower body, getting up from chair, walking, toileting) and eight instrumental ADL (IADL) (light housework, heavy housework, managing money, preparing meals, taking medications, using the telephone, doing leisure activities or hobbies) during the past 12 months. They were asked whether they had difficulty in performing these tasks and whether they needed help from another person to

carry out the task [16]. Responses were scored from 0 to 2, and summary ADL and IADL scores, from 0 to 16, were assigned at each survey, with a higher score reflecting poorer functional ability.

Statistical analyses

Factor analysis

We performed exploratory factor analysis [17] to analyse correlations between conditions at S3, using Stata (version 13.0). We applied the principal factor method based on a tetrachoric correlation matrix, since conditions were coded as dichotomous variables [18]. The number of factors identified was based on their interpretability, having an eigenvalue >1, and the shape of the scree plot [17]. We used a varimax rotation of factor loading matrices, with each resulting factor loading representing the strength of association between the condition and the latent factor. To obtain factor scores for each participant, we multiplied the factor loading for each condition by 1 or 0 (i.e. condition present or absent), before summing these to obtain total scores for each participant (standardised to a mean of 0 and standard deviation (SD) of 1). We performed confirmatory factor analysis to determine stability of factors at S4 [17]. For ease of interpretation, we created tertiles of factor scores.

Modelling of disability outcome

Over the study period, 23.7% died, 20.5% withdrew due to frailty or other reasons and 8.9% were lost to follow-up. In SAS version 9.3, we took account of this attrition by using a linear increments model [19] to examine the association between tertiles of factor scores and mean ADL and IADL scores, adjusting for age. We chose this approach based on previous analytical modelling comparisons undertaken with the ALSWH older cohort [20]. The basic linear increments model involves fitting separate linear models for outcome at S4 and then for the difference in outcome at each wave (S4 to S5, S5 to S6) and then cumulating the estimates for outcome at S4 and difference in outcome at S5 and S6. To fit covariates, the GEE models were specified with user defined working correlation structure as illustrated by Farewell [21]. The reference group comprised women who were in the lowest third for all three factor scores. The women in this group therefore did not have multimorbidity or were multimorbid, but their conditions did not group into any of the identified patterns. We determined mean ADL and IADL scores at S4 and changes over time in women in the middle and highest third of factor scores, with comparison to the reference group. A wave effect was fitted as a categorical variable as the change in effect over time was not linear.

Two alternative modelling approaches are linear mixed models and multiple imputation. Linear mixed models, a maximum likelihood method of analysis, are appropriate for missing data that are missing at random and are preferred over multiple imputation when predictor variables have no missing data, which is the case here [22]. When we performed sensitivity analyses using linear mixed models, the direction of effects was similar, but estimates were attenuated compared with the primary analysis. This probably reflects linear increments being more robust to missing data that are missing not at random, an assumption that appears warranted in the case of deaths, because the health of women who die diminishes more rapidly around 6 months prior to death, and this would not always be captured due to the 3-year gaps between surveys.

Results

Of 11,247 women who were alive at S3, 8,646 returned the survey. Of these, 7,270 (84%) had complete data on all self-reported conditions at that survey, with a mean age of 78.3 (±1.45 SD) years. Excluded women (those with incomplete data on conditions at S3) were similar to included women, except that the former were more likely to be current smokers, abstain from alcohol use, be unmarried and report poorer general health (Supplementary data, Appendix S1, available in *Age and Ageing* online). The prevalence of conditions at S3 ranged from 60.5% for hypertension to 1% for Alzheimer's disease/dementia (Table 1). Two or more conditions were reported by 87% of women, with the median being four conditions (inter-quartile range 2–7).

We identified three factors, which explained 61% of the variance. The first factor, labelled musculoskeletal/somatic (MSO), comprised musculoskeletal conditions (joint stiffness/pain, back pain and arthritis), plus somatic conditions, predominantly asthma, breathing difficulties, indigestion/heartburn, severe headache/migraine and anxiety (Table 2). The second factor, labelled neurological/mental health (NMH), was characterised by poor memory, Alzheimer's disease/dementia, clumsiness, depression, anxiety and stroke. The third factor was labelled cardiovascular (CVD). These patterns remained stable in confirmatory factor analysis (data available from authors).

A high factor score for NMH, CVD and MSO was associated with poorer functional ability at S4 (mean ADL 1.48 [± SE 0.15], 0.95 [± SE 0.12] and 1.06 [± SE 0.15], respectively) compared with women in the reference category of 'low factor score for all three factors' (mean 0.49 [± SE 0.06]; Figure 1a; Supplementary data, Appendix S2, available in *Age and Ageing* online). Similarly, women with a high factor score for NMH, MSO and CVD had a significantly higher mean IADL at S4 (mean 3.04 [± SE 0.19], 2.06 [± SE 0.19] and 2.59 [± SE 0.15], respectively) compared with the reference group (mean 1.34 [± SE 0.07]; Figure 1b; Supplementary data, Appendix S3, available in *Age and Ageing* online). Functional ability was also poorer for women in the middle tertile of the NMH pattern, while mean ADL scores for the CVD middle tertile were also significantly higher than the reference group (Supplementary data, Appendices S2 and S3, available in *Age and Ageing* online).

Table 2. Factor loadings[a] for conditions at Survey 3

	Factor		
	Musculoskeletal/somatic	Neurological/mental health	Cardiovascular
Joint stiffness/pain	**0.71**	0.17	0.10
Back pain	**0.68**	0.17	0.10
Allergies	**0.66**	−0.05	0.01
Indigestion/heartburn	**0.60**	0.19	0.07
Breathing difficulties	**0.59**	0.05	**0.38**
Severe headache/migraine	**0.56**	0.28	0.12
Arthritis	**0.58**	0.05	0.09
Feet problems	**0.53**	0.21	0.12
Asthma	**0.45**	−0.12	0.21
Bowel problems	**0.44**	0.27	0.17
Bronchitis/emphysema	**0.36**	−0.01	0.17
Urinary problems	**0.39**	**0.35**	0.19
Poor memory	0.17	**0.85**	0.02
Alzheimer's/dementia	−0.17	**0.85**	0.05
Clumsiness	0.37	**0.71**	0.01
Dizziness	**0.47**	**0.53**	0.25
Depression	0.22	**0.55**	0.12
Stroke	0.04	**0.30**	**0.33**
Chest pain	0.25	0.10	**0.78**
Angina	0.11	0.03	**0.86**
Heart attack	0.04	0.04	**0.85**
Other heart disease	0.03	0.08	**0.65**
Anxiety/nervous disorder	**0.34**	**0.44**	0.14
Vision problems	0.27	0.29	0.22
Osteoporosis	**0.30**	0.16	0.12
Diabetes	0.02	0.04	0.29
Hypertension	0.09	0.03	0.31
Hearing problems	0.25	0.19	0.12
Low iron	0.16	0.22	0.18
Skin cancer	0.12	−0.09	0.05
Other cancer	0.07	0.04	0.04
Eigenvalue	6.85	2.33	1.89

[a]Factor loadings indicate the strength of association between each variable and each factor, with a factor loading of <0.3 (non-bold loadings) generally considered to be weak, and a loading ≥ 0.3 considered to be moderate or strong.

ADL and IADL scores increased over time as women became more disabled. The increase in mean ADL score was significantly greater among women with high CVD and NMH, but not MSO, factor scores, compared with the reference group (Figure 1; Supplementary data, Appendix S2, available in *Age and Ageing* online). This increase was greatest for women with a high CVD score. The greatest increase in mean IADL score occurred in the middle and top tertiles of the NMH factor (Figure 1b; Supplementary data, Appendix S3, available in *Age and Ageing* online).

Discussion

We identified three multimorbidity patterns in our cohort which were differentially associated with functional ability and decline over time. This suggests that specific groups of conditions may be useful in predicting functional ability and decline, which is important for health service planning and identifying opportunities to prevent functional decline, which may reduce burden of care.

The nature of the identified multimorbidity patterns partly reflects common antecedents and disease pathways. The CVD pattern comprised heart disease and related symptoms, which we would expect to group together. The co-occurrence of dementia, depression and cerebrovascular disease, as found in the NMH pattern, has been reported in other studies [10]. Associations between cerebrovascular disease and each of depression [23] and dementia [24] are well-established. There is growing evidence for associations between depression and both dementia and Alzheimer's disease [25–27], although it remains unclear whether depression is a risk factor for dementia or a prodromal symptom of it. The grouping of somatic symptoms with musculoskeletal symptoms and conditions is consistent with other evidence for an association between musculoskeletal pain and non-musculoskeletal symptoms [28].

Few studies have applied factor analysis to identify natural groups of disease [11–13, 29], with just two studies specifically including an older population [13, 29]. Findings from these studies, which identified two to four patterns, show some similarities to our results. Each study identified a CVD

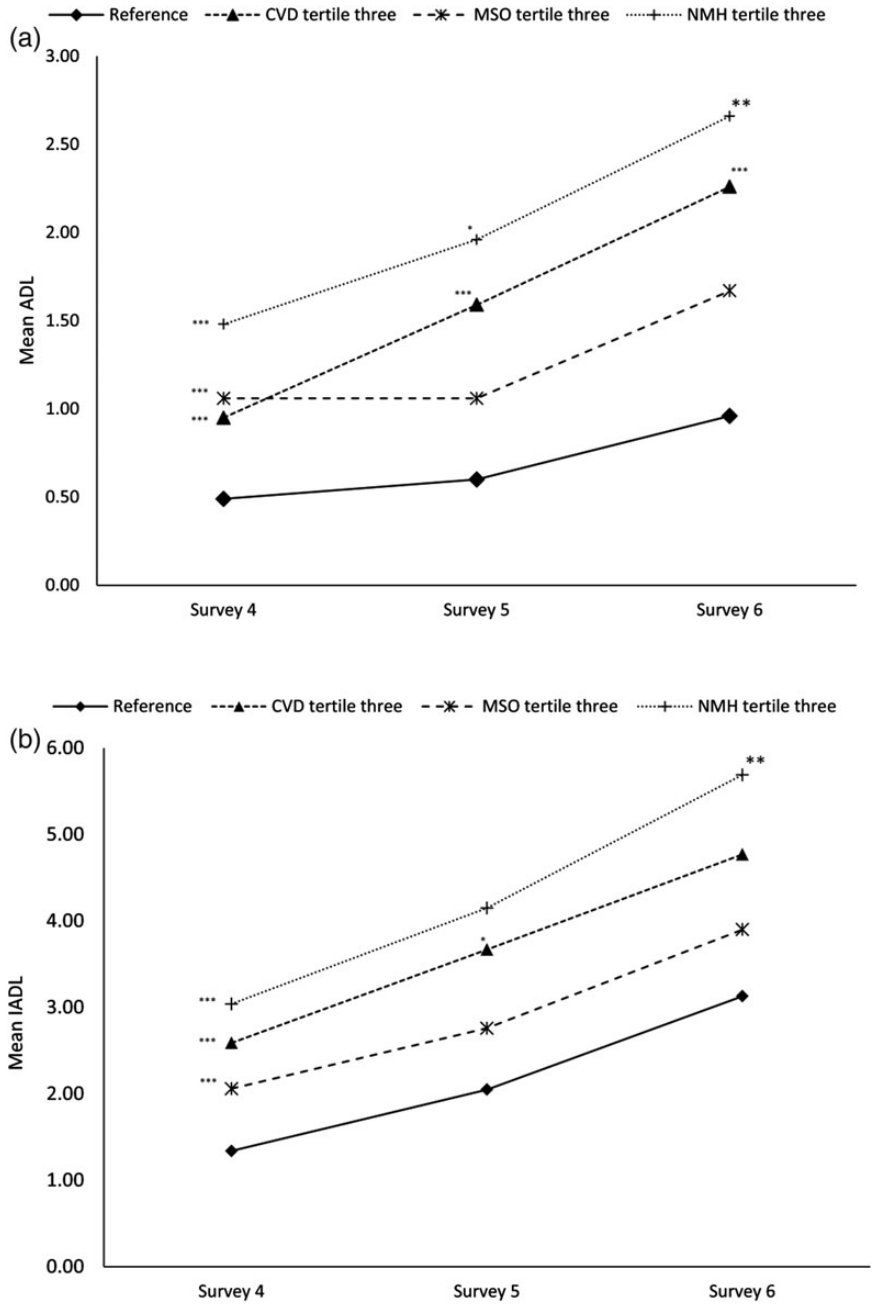

Figure 1. (a) Mean ADL and (b) mean IADL scores at each time point, for those in the lowest third for all three factor scores (the reference category comprised 1,406 women, 1,119 (80%) of whom reported no conditions and 287 of whom reported 2 or 3 conditions) and those in the highest third of each factor score. Asterisks at Survey 4 indicate where the mean ADL or IADL score is significantly different from the reference group. Asterisks at Surveys 5 and 6 indicate where the change in ADL or IADL between Surveys 4 and 5, and 5 and 6, respectively, is statistically significantly different from the change in ADL or IADL between these time points in the reference group; $*P < 0.05$; $**P < 0.001$; $***P < 0.0001$. CVD, cardiovascular; MSO, musculoskeletal/somatic; NMH, neurological/mental health.

pattern, two identified a mental health/neurological disorder pattern [13, 29] and one identified a pattern characterised by osteoporosis/gastro-oesophageal reflux/back pain/anxiety [12], which bears some similarity to the MSO pattern we identified.

Increasing number of co-morbid conditions is known to be associated with decreased functional ability [30]. There is also an established association between increasing number of chronic conditions and increased risk of functional decline [31–33]. Our study makes a further contribution by comparing functional ability and decline across different multimorbidity patterns. Women with a high score for the NMH pattern had the greatest functional decline, while those with a high CVD factor score had a significantly worse decline in

ADL than the reference group, despite having a similar ADL score at S4. In contrast, the decline in the MSO group was similar to that in the reference group. Thus, although certain patterns may be associated with different levels of functional ability, they may not necessarily be associated with subsequent decline. A previous study found that some combinations of co-morbidities involving chronic diseases that affect functional ability through different mechanisms may have a worse effect on functional decline than co-morbidities that share aetiologic factors or pathophysiologic mechanism [33]. This suggests that the functional decline associated with each multimorbidity pattern observed in our study could also differ according to the presence or absence of other, non-grouping morbidities.

Strengths of adopting factor analysis to identify morbidity patterns are that it does not rely on pre-conceived assumptions regarding how particular conditions group together, allows conditions to cross-load and facilitates a better understanding of how conditions (as opposed to individuals) naturally group together. Our study population is the second largest study to investigate multimorbidity patterns among older people using this approach. Furthermore, although the attrition in our cohort was inevitably high, linear increments modelling accounted for this by avoiding underestimation of functional decline over time.

Our study does have some shortcomings. Conditions were based on self-report, which may have introduced some errors. The list of conditions was not exhaustive, and additional patterns may have been identified had additional chronic diseases been included. Unfortunately, we were unable to account for the potential effect of medications on functional ability. Also, our study population reflects a rather 'healthy' group of elderly women (as reflected in the low ADL scores) since it included those still alive by ages 76–81 and who returned S3. The prevalence of conditions such as dementia for instance is lower than in the wider community. However, it is difficult to speculate how this may have affected the grouping of conditions. Functional ability was also based on self-report. It was, however, designed to identify where an individual was on a continuum of disability (from full independence, through preclinical disability and then dependency). Information on functional ability was collected from S4 onwards, which resulted in a 3-year lag between identification of multimorbidity factors and first measure of functional ability, during which time women may have acquired additional morbidities. However, we sought to identify the association between multimorbidity factors and subsequent functional ability. Also, the larger the study population, the more reliable the factor analysis. We therefore carefully considered the trade-off in using S3 to identify the multimorbidity factors, given the attrition in this older cohort. Reassuringly, confirmatory factor analysis at S4 demonstrated the stability of the identified factors. Finally, since our study included women only, we cannot generalise our findings to men.

In conclusion, high scores for distinct multimorbidity patterns were differentially associated with functional ability and decline. Future research should investigate such patterns in different settings and age groups, and examine the association between multimorbidity patterns and individual ADL and IADL tasks, since some are more health service resource intensive than others (e.g. toileting versus grooming). Finally, a better understanding of the temporal nature of how chronic conditions group together may have important implications for management in terms of prevention of additional morbidities.

Key points

- We found three patterns of morbidity in older women.
- These patterns were MSO, NMH and CVD.
- Multimorbidity patterns were differentially associated with functional ability and decline.
- The neurological and mental health pattern was associated with the greatest decline in IADL over time.
- The cardiovascular pattern was associated with the greatest decline in ADL over time.

Conflicts of interest

None declared.

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Supplementary data

Supplementary data mentioned in the text are available to subscribers in *Age and Ageing* online.

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