Use of latent class analysis to identify multimorbidity patterns and associated factors in Korean adults aged 50 years and older

Short title: Identification of multimorbidity patterns and associated factors using latent class analysis

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Abstract

Introduction: Multimorbidity associated with significant disease and economic burdens is common among the aged. We identified chronic disease multimorbidity patterns in Koreans 50 years of age or older, and explored whether such patterns were associated with particular sociodemographic factors and health-related quality-of-life.

Methods: The multimorbidity patterns of 10 chronic diseases (hypertension, dyslipidemia, stroke, osteoarthritis, tuberculosis, asthma, allergic rhinitis, depression, diabetes mellitus, and thyroid disease) were identified via latent class analysis of data on 8,370 Korean adults aged 50+ years who participated in the sixth Korean National Health and Nutrition Examination Survey (2013-2015). The associations between multimorbidity patterns, and sociodemographic factors and health-related quality of life, were subjected to regression analysis.

Results: Three patterns of multimorbidity were identified: 1) a relatively healthy group (60.4% of the population); 2) a 'cardiometabolic conditions' group (27.8%); and, 3) an 'arthritis, asthma, allergic rhinitis, depression, and thyroid disease' group (11.8%). The female (compared to male) gender was associated with an increased likelihood of membership of the *cardiometabolic conditions* group (odds ratio [OR]=1.32, 95% confidence interval [CI]=1.15-1.51) and (to a much greater extent) the *arthritis, asthma, allergy, depression, and thyroid disease* group (OR=4.32, 95% CI=3.30-5.66). Low socioeconomic status was associated with membership of the two multimorbidity classes. Membership of the *arthritis, asthma, allergy, depression, and thyroid*

37   *disease* group was associated with a significantly poorer health-related quality-of-life than was

38   membership of the other two groups.

39   **Conclusion:** The co-occurrence of chronic diseases was not attributable to chance.

40   Multimorbidity patterns were associated with sociodemographic factors and quality-of-life. Our

41   results suggest that targeted, integrated public health and clinical strategies dealing with chronic

42   diseases should be based on an understanding of multimorbidity patterns; this would improve the

43   quality-of-life of vulnerable multimorbid adults.

Introduction

45

46   Given aging populations, advances in medical care and public health policies, and

47   improved living conditions, the co-occurrence of two or more chronic diseases in the same

48   individual (multimorbidity) [1,2] is increasingly common [3-5]. A recent study of Koreans adults

49   aged 50 and older found that more than one in four were multimorbid [6]. Multimorbidity is a

50   public health concern, being associated with higher mortality, impaired functional status, a reduced

51   quality-of-life, increased healthcare utilization, and a greater treatment burden [7-14]. The impact

52   of multimorbidity can be much more complex (being synergistic) than the impact of individual

53   diseases; health outcomes may differ by the disease combinations in play [3,15,16]. Thus, current

54   single-disease-oriented public health strategies and clinical healthcare guidelines may be both

55   incomplete and ineffective for multimorbid patients [17].

56   Certain chronic diseases tend to co-occur more often than expected by chance because they

57   share pathophysiological pathways [18,19]. Identification of patterns of disease combinations and

58   the characteristics of individuals exhibiting similar multimorbidity patterns may provide important

59   information for policymakers and clinicians who seek to integrate strategic public health policy

60   plans and healthcare management to address multimorbidity in at-risk groups more effectively.

61   Even though multimorbidity has attracted increasing attention (because it is becoming the norm in

62   the elderly; [17,20-25]), we still do not know how multiple chronic diseases cluster, the associated

63   socioeconomic factors, and how multimorbidity affects quality-of-life.

64   Multimorbidity is highly complex. The use of a statistical approach to group a population

65   into a limited number of subgroups with similar combinations of chronic diseases is much more

66   practical than analysis of every possible disease combination. Therefore, we performed latent class

67   analysis (LCA) based on the hypothesis that certain chronic diseases cluster. LCA identifies

68   probabilistic rather than deterministic subgroups based on responses to a set of observed variables,

69   and assumes that the pattern is explained by unobserved categorical latent variables of K classes

70   [26,27]. Our objectives were: 1) to identify multimorbidity patterns in the general Korean

71   population aged over 50 years using nationally representative survey data; and, 2) to explore

72   whether such patterns were associated with certain sociodemographic characteristics and quality-

73   of-life.

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Methods

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Data source and sample

78   We used data on adults 50 years of age and older who participated in the sixth Korean

79   National Health and Nutrition Examination Survey (KNHANES) conducted in 2013-2015.

80   KNHANES is a cross-sectional, nationally representative survey of the noninstitutionalized

81   Korean population conducted by the Division of Chronic Disease Surveillance, Korea Centers for

82   Disease Control and Prevention (KCDCP). KNHANES uses a stratified, multistage cluster

83   sampling method based on geographical area, gender, and age. The details have been described

84   previously [28].

85

Measures

87   Chronic disease was based on self-reports, on whether participants had ever been

88   physician-diagnosed with any disease on a pre-specified list. Analysis was limited to the 10 most

89   common chronic diseases (hypertension, dyslipidemia, stroke, osteoarthritis, tuberculosis, asthma,

90   allergic rhinitis, depression, diabetes mellitus, and thyroid disease; the prevalence of each is greater

91   than 3% [29-31]) of the 28 diseases listed in the KNHANES. Multimorbidity was defined as the

92   presence of two or more of these diseases in the same subject.

93   The sociodemographic variables evaluated included age, gender, household income,

94   educational level, and occupation. The household income was the monthly income divided by the

95   square root of household size [32], and was grouped into high and low using the median income

96   as the cut-off. Educational level was categorized as low for those younger than 70 years who were

97   high school graduates or less accomplished, and for those older than 70 years who were middle

98   school graduates or less accomplished. In terms of occupational status, students and housewives

99   were defined as unemployed; service workers. retailers, agriculture or fishery employees,

100   technicians, mechanics, assemblers, and simple laborers were defined as manual workers; and

101   managers, professionals, and office workers were considered to be non-manual workers. The

102   health-related quality of life was assessed using the EuroQol 5 Dimensions (EQ-5D) instrument;

103   this is a generic measure of health status. The EQ-5D features five dimensions (mobility, self-care,

104   engagement in usual activities, pain/discomfort, and anxiety/depression); each dimension has three

105   response options (1 = no problem, 2 = some problems, and 3 = a severe problem). The health-

106   related quality of life was scored as a single value (the EQ-5D index score) using a validated

107   algorithm [33,34].

108

Statistical analysis

110   Disease prevalence, disease co-occurrence in the multimorbid, and the number of co-

111   occurring diseases for each disease, were calculated. We used LCA to explore multimorbidity

112   patterns. The optimal number of latent classes was determined based on the lowest Consistent

113   Akaike Information Criterion (CAIC) and the adjusted Bayesian-Schwarz Information Criterion

114   (adjusted BIC) [35-37], clinical significance, and interpretability [38]. After selection of an optimal

115   model, each respondent was assigned to the class for which s/he had the highest computed

116   membership probability. An average posterior probability greater than 70% indicates an optimal

117   fit [39]. The characteristics of respondents in different latent classes were compared using the chi-

118   squared test for categorical variables and ANOVA for continuous variables. In addition,

119   multinomial logistic regression was performed to assess the association between each

120   sociodemographic factor (age, gender, household income, educational level, and occupation) and

121   latent class membership. Associations were assessed using odds ratios (ORs) with 95% confidence

122   intervals (CIs). Each association was adjusted in terms of the other variables in the multivariate

123 analysis. Regression analysis (using SAS PROC SURVEYREG) was performed to assess whether

124 the health-related quality of life varied by latent class membership. The least square mean of the

125 EQ-5D index score (with the 95% CI) was estimated for each latent class. The adjusted model

126 considered gender, age, household income, educational level, and occupation. Bonferroni post-hoc

127 testing was performed after all pairwise comparisons. As the EQ-5D index score is not normally

128 distributed, it was log-transformed prior to analysis and then back-transformed. All tests were two-

129 tailed, and a p-value <0.05 was regarded as statistically significant. All statistical analyses were

130 performed with the aid of SAS software (version 9.4; SAS Institute, Cary, NC, USA). All estimates

131 were subjected to sample weighting to reflect the complexity of the KNHANES sampling design.

132

Ethics

134 The KNHANES was approved by the institutional review board of the KCDCP (approval

135 nos. 2013-07CON-03-4C, 2013-12EXP-03-5C, and 2015-01-02-6C). Written informed consent

136 was obtained from all participants.

137

Results

139 A total of 8,370 participants aged over 50 years were included in analysis. The mean age

140 was 62.5 years, and 46% were male. Of all respondents, 39% had two or more chronic diseases;

141 the mean number of chronic diseases in multimorbid subjects was 2.6. Table 1 lists the prevalence

142 and the proportions of multimorbidity, and the average number of comorbid diseases for each of

143   the 10 chronic diseases included in the analysis. Hypertension (36.4%), dyslipidemia (22.1%),

144   osteoarthritis (19.8%), and diabetes mellitus (14.4%) were the most prevalent diseases and at least

145   one of the 10 diseases existed as a multimorbidity in over 60% of multimorbid patients; stroke

146   occurred in 87.1% (the highest) and tuberculosis in 63.2% (the lowest). The number of co-

147   occurring diseases varied between 2.2 and 2.9 depending on the index disease. Table 2 summarizes

148   the LCA model fits. When up to four latent classes were considered, the smallest adjusted BIC

149   (two-class model: 929.18; three-class: 797.28; four-class: 801.36) and CAIC (two-class model:

150   1016.91; three-class: 930.97; four-class: 981.01) were those of the three-class model; these classes

151   were *relatively healthy*, those with *cardiometabolic conditions*, and those with *arthritis, asthma,*

152   *allergic rhinitis, depression, and thyroid disease* as revealed by the estimated probabilities of any

153   particular chronic disease given membership of a latent class. Every respondent was assigned to

154   one of the three classes based on the highest membership probability. The *relatively healthy* group

155   included those with a low prevalence of all evaluated chronic conditions. The dyslipidemia

156   response probabilities were very similar for the two multimorbid groups but dyslipidemia was

157   classified as a *cardiometabolic condition* based on the clinical nature of the disease; thus, the

158   *cardiometabolic conditions* group was populated by those with high probabilities of hypertension,

159   dyslipidemia, stroke, and diabetes mellitus. The class membership probabilities were 60.4, 27.8,

160   and 11.8% respectively, and the average posterior probabilities for all three classes exceeded 70%

161   (Table 3). The mean age of the *cardiometabolic conditions* group was the highest (67 years) but

162   the mean number of co-occurring chronic conditions was highest (2.9) in the *arthritis, asthma,*

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163 *allergy, depression, and thyroid disease* group. Both the *cardiometabolic conditions* group (40.2%

164 male vs. 59.8% female) and the *arthritis, asthma, allergy, depression, and thyroid disease* group

165 had higher proportions of females (17.7 vs. 82.3%); males constituted over 50% of the *relatively*

166 *healthy* group (51.4 vs. 48.6%). In particular, most subjects were female in the *arthritis, asthma,*

167 *allergy, depression, and thyroid disease* group (82.3%). Socioeconomic status was similar in the

168 *cardiometabolic conditions* group and the *arthritis, asthma, allergy, depression, and thyroid*

169 *disease* group; both groups evidenced higher proportions (compared to the overall figures) of

170 individuals with lower household incomes, lower levels of education, and of unemployed status

171 (Table 4).

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173 **Table 1. The Prevalence and Characteristics of Certain Chronic Diseases in 8,370**

174 **KNHANES 2013-2015 Respondents Aged 50 Years and Older.**

Disease	Prevalence % (SE)	Cases with multimorbiidty %	Number of co-occurring diseases Mean (SE)
Hypertension	36.4 (0.39)	69.4	2.2 (0.02)
Dyslipidemia	22.1 (0.26)	83.2	2.6 (0.03)
Stroke	4.1 (0.11)	87.1	2.9 (0.07)
Osteoarthritis	19.8 (0.26)	73.9	2.4 (0.03)
Tuberculosis	5.9 (0.14)	63.2	2.2 (0.06)
Asthma	3.6 (0.09)	83.5	2.8 (0.08)
Allergic rhinitis	8.1 (0.12)	67.6	2.3 (0.06)

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Depression	5.6 (0.14)	74.7	2.6 (0.07)
Diabetes mellitus	14.4 (0.18)	84.4	2.7 (0.04)
Thyroid disease	3.9 (0.10)	74.9	2.5 (0.08)

175 KNHANES, Korea National Health and Nutrition Examination Survey; SE, Standard error

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177 **Table 2. A Comparison of the Fit Statistics of Models Featuring Latent Class Analyses.**

Number of latent classes	Likelihood ratio G^2	Degrees of freedom	CAIC	Adjusted BIC
2	806.23	1002	1016.91	929.18
3	609.94	991	930.97	797.28
4	549.61	980	981.01	801.36

178 CAIC, Consistent Akaike Information Criterion; BIC, Bayesian Information Criterion

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180 **Table 3. Class Membership and Item Response Probabilities of the Three Latent Classes.**

	Latent Class		
Characteristics	Relatively healthy	Cardiometabolic conditions	Arthritis, asthma, allergy, depression, thyroid
Class membership probabilities (%)	60.4	27.8	11.8
Item response probabilities (%)			
Hypertension	0.18	0.75	0.42
Dyslipidemia	0.06	0.45	0.49
Stroke	0.01	0.12	0.02
Osteoarthritis	0.12	0.26	0.47

Tuberculosis	0.06	0.07	0.05
Asthma	0.02	0.04	0.14
Allergic rhinitis	0.07	0.04	0.24
Depression	0.03	0.04	0.21
Diabetes mellitus	0.04	0.39	0.13
Thyroid disease	0.02	0.03	0.14

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Table 4. Characteristics of Study Respondents by Latent Class Membership.

Variable	Total	Latent Class			P-value
		Relatively healthy	Cardiometabolic conditions	Arthritis, asthma, allergy, depression, thyroid	
		% (SE) or mean (95% CI)			
Age	62.5 (62.2-62.8)	60.8 (60.5-61.2)	67.0 (66.5-67.5)	63.4 (62.7-64.2)	<0.0001
Gender					
Male	46.3 (0.5)	51.4 (0.7)	40.2 (1.3)	17.7 (1.8)	<0.0001
Female	53.7 (0.5)	48.6 (0.7)	59.8 (1.3)	82.3 (1.8)	
Household income					
Low	52.4 (1.0)	47.4 (1.1)	65.8 (1.5)	57.0 (2.5)	
High	47.6 (1.0)	52.6 (1.1)	34.2 (1.5)	43.0 (2.5)	
Education					
Low	80.9 (0.8)	78.7 (0.9)	85.2 (1.0)	87.1 (1.6)	<0.0001
High	19.1 (0.8)	21.3 (0.9)	14.8 (1.0)	12.9 (1.6)	
Occupation					

Unemployed	46.6 (0.8)	40.0 (0.9)	61.4 (1.3)	61.7 (2.2)	<0.0001
Unmanual	11.4 (0.5)	13.6 (0.7)	6.6 (0.7)	5.2 (1.0)	
Manual	42.0 (0.9)	46.4 (1.0)	32.0 (1.2)	33.1 (2.2)	
Number of co-occurring diseases	1.2 (1.2-1.3)	0.6 (0.6-0.6)	2.6 (2.6-2.7)	2.9 (2.8-3.0)	<0.0001

183   SE, standard error; CI, confidence interval

184   Multinomial logistic regression analysis adjusted for age, gender, educational level,

185 household income, and occupation showed that age increased the risk of being in either of the

186 multimorbid groups compared to the *relatively healthy* group. The risks of membership of the

187 *cardiometabolic conditions* group (OR=1.32, 95% CI=1.15-1.51) and the *arthritis, asthma,*

188 *allergy, depression, and thyroid disease* group (OR=4.32, 95% CI=3.30-5.66) were significantly

189 higher for females than males. Lower household income (OR=1.32, 95% CI=1.14-1.52) and lower

190 educational level (OR=1.25, 95% CI=1.05-1.49) significantly increased the risk of membership of

191 the *cardiometabolic conditions* group. In addition, unemployed status increased the risk of

192 membership of both the *cardiometabolic conditions* group and the *arthritis, asthma, allergy,*

193 *depression, and thyroid disease* group (Table 5).

194

195 **Table 5. Sociodemographic Factors of the Latent Classes as Revealed by Multinomial**

196 **Logistic Regression.**

	Latent Class		
Variable	Relatively healthy	Cardiometabolic conditions	Arthritis, asthma, allergy, depression, thyroid
	Odds Ratio (95% Confidence interval)		
Unadjusted			
Age	1	1.07 (1.07-1.08)	1.03 (1.02-1.04)
Gender (ref=Male)			
Female	1	1.57 (1.39-1.78)	4.90 (3.80-6.32)

Household Income (ref=High)			
Low	1	2.13 (1.88-2.42)	1.47 (1.21-1.80)
Education (ref=High)			
Low	1	1.55 (1.32-1.82)	1.83 (1.40-2.39)
Occupation (ref=Unemployed)			
Unmanual	1	0.32 (0.25-0.41)	0.25 (0.16-0.38)
Manual	1	0.45 (0.40-0.51)	0.46 (0.38-0.57)
Adjusted			
Age	1	1.06 (1.05-1.07)	1.02 (1.01-1.03)
Gender (ref=Male)			
Female	1	1.32 (1.15-1.51)	4.32 (3.30-5.66)
Household Income (ref=High)			
Low	1	1.32 (1.14-1.52)	1.10 (0.88-1.37)
Education (ref=High)			
Low	1	1.25 (1.05-1.49)	1.12 (0.85-1.49)
Occupation (ref=Unemployed)			
Unmanual	1	0.80 (0.61-1.06)	0.56 (0.36-0.86)
Manual	1	0.70 (0.61-0.81)	0.68 (0.54-0.85)

197 CI, confidence interval

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199 Table 6 shows the association between class membership and health-related quality-of-life.

200 When the least-square means of the health-related quality-of-life of the latent classes were

201 compared after adjustment for age, gender, household income, educational level, and occupation,

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202 individuals in the *arthritis, asthma, allergy, depression, and thyroid disease* group evidenced a

203 significantly lower health-related quality-of-life (0.84) than the other two groups (0.93 for the

204 *relatively healthy* group; 0.88 for the *cardiometabolic conditions* group) as revealed by Bonferroni

205 post-hoc analysis.

206

207 **Table 6. Associations between Multimorbidity Patterns and EQ-5D Index Scores.**

	Latent Class			
	Relatively healthy	Cardiometabolic conditions	Arthritis, asthma, allergy, depression, thyroid	*P*-value[a]
Unadjusted	0.92 (0.91, 0.92)	0.84 (0.83, 0.84)	0.80 (0.79, 0.82)	<0.0001
Adjusted				
Model 1	0.91 (0.90, 0.92)	0.86 (0.85, 0.87)	0.82 (0.81, 0.84)	<0.0001
Model 2	0.93 (0.92, 0.94)	0.88 (0.87, 0.89)	0.84 (0.83, 0.86)	<0.0001

208 EQ-5D, European Quality of Life 5 Dimension

209 Values are presented as geometric mean (95% confidence interval)

210 [a]*P*-value was calculated from Bonferroni post-hoc testing

211 Model 1: Age, gender

212 Model 2: Age, gender, household income, education, occupation

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Discussion

215 We used LCA to identify three distinct multimorbidity patterns in the general Korean

216 population: (1) a relatively healthy group; (2) a group with cardiocerebrovascular conditions

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217   including hypertension, dyslipidemia, stroke, and diabetes mellitus; and, (3) a group with arthritis,

218   asthma, allergic rhinitis, depression, and thyroid disease. We found that individuals of the three

219   classes exhibited different sociodemographic characteristics and varied in terms of health-related

220   quality of life. It is difficult to directly compare our results to those of previous studies given the

221   methodological differences in terms of study setting, disease spectrum and number, demographic

222   factors, baseline health status of participants, and the statistical methods used [29], but the

223   multimorbidity patterns we identified are in general agreement with those of prior works. Such

224   similarities may indicate that chronic diseases aggregate because they share underlying risk factors

225   (so one disease increases the risk of another) or that causalities are shared [19]. We found that

226   hypertension, dyslipidemia, stroke, and diabetes mellitus were very likely to co-occur, as have

227   several prior studies evaluating subjects with (predominantly) cardiocerebrovascular conditions

228   [17,19,21,40-42]. It is known that hypertension, dyslipidemia, and diabetes mellitus are risk factors

229   for cerebrovascular diseases, and may precede such diseases [43-46]. Although the mechanism

230   behind the combination of arthritis, asthma, allergic rhinitis, depression, and thyroid disease

231   remains unclear, similar groupings were evident in other studies. Arthritis and depression were co-

232   grouped by Simoes et al. [19], asthma and allergy by Larsen et al. [47], and arthritis, respiratory

233   diseases, and psychiatric symptoms formed a latent class in the work of Islam [17,42].

234   Most previous studies on multimorbidity used a non-model approach such as counts of the

235   most common disease combinations and their observed-to-expected ratios [48-50]; such methods

236   are too simplistic. Recently, several studies have used statistical approaches such as cluster

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237   analysis [31,51,52], factor analysis [21,25,40,41], and LCA [17,22,36,42,53-55] to identify

238   nonrandom multimorbidity clusters. We used LCA to identify subgroups based on structural

239   equation modeling [56]. LCA is better than conventional clustering because LCA employs

240   probability-based classification methods to choose an optimal number of classes based on various

241   diagnostic tests [27,57]. This allowed us to group individuals into a limited number of latent classes

242   and then analyze the differences between the classes. Our analysis not only indicated what other

243   diseases were likely to co-occur in subjects with certain diseases but also allowed us to explore

244   whether individuals with certain sociodemographic characteristics were more vulnerable to

245   multimorbidity and the associated adverse health outcomes. The multimorbid groups were of lower

246   socioeconomic status than the relatively healthy group. Individuals with cardiometabolic

247   conditions were older than individuals in the *relatively healthy* and the *arthritis, asthma, allergy,*

248   *depression, and thyroid disease* groups. In addition, a remarkable female predominance was

249   evident in the *arthritis, asthma, allergy, depression, and thyroid disease* group. Female

250   predominance in a musculoskeletal class and a headache-mental illness class was noted by Larsen

251   et al. [47].

252   Furthermore, we found that older age, being female, and lower socioeconomic status

253   increased the risk of membership of the *cardiometabolic conditions* group and/or the *arthritis,*

254   *asthma, allergy, depression, and thyroid disease* group, as compared to the relatively healthy

255   group. In particular, being female increased the risk of membership of the *arthritis, asthma,*

256   *allergy, depression, and thyroid disease* group more than four-fold; also, individuals assigned to

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257   this latent class had a lower quality-of-life and were younger than members of other groups.

258   Females are thus significantly more likely to develop the disease cluster of arthritis, asthma,

259   allergy, depression, and thyroid disease than males and, thus, endure a lower quality-of-life for

260   longer than males. Such gender inequality in healthy life expectancy, caused by multimorbidity,

261   warrants public health interventions targeting the female elderly.

262   Our study had certain limitations. Analysis was based on a limited number of chronic

263   diseases recorded by the KNHANES only from non-institutionalized Koreans who were able to

264   participate in the survey. In addition, we only considered disease occurrence and, thus, not duration

265   or severity. Finally, we cannot discuss causal relationships between diseases because the survey

266   was cross-sectional in nature. However, using a large and nationally representative sample, we

267   identified multimorbidity patterns, and associations between such patterns and both

268   sociodemographic factors and health-related quality-of-life. Our findings deepen our

269   understanding of non-random associations between diseases; this will aid the design of useful,

270   effective, holistic healthcare and preventative strategies addressing the needs of multimorbid

271   individuals and those at high risk of multimorbidity. In addition, given that the multimorbidity

272   patterns are associated with poor quality-of-life and sociodemographic inequalities, targeted

273   multimorbidity management is important to reduce the burden on the vulnerable population and to

274   address the associated social inequalities.

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