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The moderation of multimorbidity and depressive symptoms on cognition

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Abstract

Background: Multimorbidity, or the occurrence of two or more chronic conditions, is a global challenge, with implications for mortality, morbidity, disability and life quality. Psychiatric disorders are common among the chronic diseases that affect patients with multimorbidity. It is still not well understood whether psychiatric symptoms, especially depressive symptoms, moderate the effect of multimorbidity on cognition. **Methods:** We used a large (n=2681) dataset to assess whether there is a moderation of depressive symptomatology on the effect of multimorbidity on cognition using structural equation modelling. **Results:** It was found that the

more depressive symptoms and chronic conditions, the worse the cognitive performance, and the higher the educational level, the better the cognitive performance**.** We found a significant but weak (0.009; p-value = 0.04) moderation effect. **Conclusions:** We have provided the first estimate of the moderating effect of depression on the effect of multimorbidity on cognition, though it is small. Although this moderation was implicit in numerous previous works, it was never previously estimated.

Introduction

With the increasing ageing of the world's population[1], chronic diseases have become the main challenge of health care around the world. Examples of these are heart disease, diabetes, cancer, and chronic respiratory diseases[2]. The co-occurence of two or more chronic diseases is defined as multimorbidity[3]. The prevalence of multimorbidity is rising, estimated at 35% to 80% of the population[4] , increasing the complexity and costs of treatment for these conditions[4].

Multimorbidity is associated with worse health outcomes, such as increased medication use[4], decline in physical functioning[5], higher suicide risk[6], worse quality of life and higher mortality [7]. These findings have been found in high-income as well as low-income countries[7].

There is evidence that having a mental disorder raises the chance of having one or more chronic physical disorders and vice-versa[8]. Depression[9], psychosis[10] and substance use[11] are related to increased risk of multimorbidity. Mental disorders are themselves chronic conditions with large impacts on quality of life [6] and cognition [5], especially in younger individuals[4]. Furthermore, there is evidence that people living with chronic diseases and mental disorders (including depression) are less compliant with treatment and have higher mortality and more disability than people who have multimorbidity without mental disorders[14]. In 2018, Wei e al. measured cognitive function using a modified version of the Telephone Interview for Cognitive Status (TICS-m) and concluded that cognitive performance wasby multimorbidity [12]. Additionally, a significant association between multimorbidity and mild cognitive impairment has been reported by Vassilaki e al. (2015) (hazard ratio [HR]: 1.38; 95% confidence interval [CI], 1.05–1.82)[13]. People with mental-physical morbidity have worse quality of life, social-economic hardship, and worse outcomes compared to just mental or physical morbidity [8]. These papers often imply that there is an interaction of mental disorders with multimorbidity on some outcomes, including cognition[5].

Depression is the most prevalent mental disorder, with at least 350 million people affected worldwide[15]. It is responsible for more years lost to disability than any other condition [16]. It is underdiagnosed and undertreated, with half of the world's population living in countries with less than two psychiatrists per 100,000 habitants [16]. Maladaptive health risk behaviors and the physiologic imbalance inherent to depression often lead them to develop chronic disorders at an

earlier age [17]. A recent meta-analysis by Read et al. (2017) showed that patients with multimorbidity had twice the risk of depressive disorder compared to those without multimorbidity. Depressive disorders were found across age groups, settings, cultures and regardless of whether depression was measured by a diagnosis or cut-off score [9]. Studies have found patients with major depression to be impaired in executive functions, attention, memory, and psychomotor speed in acute and remitted states [18].

Although the relation between depression and multimorbidity, and of both on cognition is well documented, no estimate of the moderating effect of depressive symptomatology and multimorbidity on cognitive performance has been reported to our knowledge. We set out to provide the first estimate of this effect, hypothesising that depression would have a moderating effect on cognition. We used a large dataset of British subjects (2681) excluding subjects with dementia and severe neurological diseases.

Methods

Data source

The data set included 2681 baseline observations from the Cambridge Centre for Aging and Neuroscience (Cam-CAN) dataset available at https://cam-can.com. Cam-CAN was a large-scale collaborative project, started in 2010, which collected neuroimaging, demographic, and cognitive information on participants in order to evaluate cognitive abilities in aging[19]. The exclusion criteria for CAM-CAN was a mini-mental state examination (MMSE) score 24 or less, missing MMSE scores, severe memory defect, consent difficulties for the next stage, hearing problems, insufficient english language, vision difficulties, dementia diagnosis/Alzheimer's disease, Parkinson's disease, motor neuron disease, multiple sclerosis, cancer, stroke, encephalitis, meningitis, epilepsy, head injury with serious results, recently diagnosed or uncontrolled high blood pressure, pregnancy or trying to become pregnant, current serious psychiatric conditions, restricted mobility which would prevent further participation, inability to walk 10 meters, past or current treatment for drug abuse, current drug usage and refusal to answer substance abuse questions. We did not have access to information about treatment received or use of medication by the participants. This analysis was performed using full information maximum likelihood; therefore all observations were included in the analysis.

Data analysis

Descriptive statistics are reported for all used variables in Table 1. Continuous variables were analyzed with the average of the descriptive measures, median, minimum, maximum and standard deviation (SD) and categorical variables were described with the total number of

observations and their corresponding percentages stratified by sex. All analyses were performed using R version 4.1.1 (https://cran.r-project.org/). To test the hypothesis that depressive symptomatology moderated the effect of multimorbidity on cognitive performance, we performed a structural equation model (SEM). The package umx (version 4.9.5) [20] was used for the SEM analysis, which estimated standardized coefficients and confidence intervals using full information maximum likelihood (FIML) with the CSOLN optimizer. We checked identification using an OpenMx (version 2.19.6) utility (mxCheckIdentification).

Table 1. Descritives analyses stratified by sex. Group comparison was performed using chi-2 tests for the categorical variables and ANOVA for the continuous variables.

	Overall	Female	Male	p
n	2681	1508	1172	
MMSE (mean (SD))	**27.88 (2.44)**	**27.79 (2.57)**	**27.99 (2.26)**	**0.036**
Verbal Fluency (mean (SD))	15.73 (6.10)	15.59 (6.06)	15.90 (6.15)	0.196
Age (mean (SD))	60.57 (20.93)	60.96 (21.46)	60.09 (20.23)	0.285
Marital Status (%)				**<0.001**
Single	507 (19.0)	296 (19.7)	211 (18.1)	
Married	1300 (48.7)	617 (41.1)	683 (58.5)	
Cohabiting	161 (6.0)	89 (5.9)	72 (6.2)	
Divorced	265 (9.9)	164 (10.9)	101 (8.7)	
Widowed	436 (16.3)	336 (22.4)	100 (8.6)	
Total income (%)				**<0.001**

A	483 (18.2)	237 (15.9)	246 (21.1)	
B	596 (22.5)	349 (23.5)	247 (21.2)	
C	513 (19.4)	253 (17.0)	260 (22.3)	
D	657 (24.8)	389 (26.2)	268 (23.0)	
E	247 (9.3)	183 (12.3)	64 (5.5)	
F	155 (5.8)	75 (5.0)	80 (6.9)	
Age last education (mean (SD))	**19.57 (4.39)**	**19.24 (4.17)**	**20.01 (4.62)**	**<0.001**
HADS-A (mean (SD))	**5.16 (3.40)**	**5.51 (3.48)**	**4.71 (3.23)**	**<0.001**
HADS-D (mean (SD))	3.32 (2.91)	3.32 (2.91)	3.32 (2.91)	0.955
NCC (mean (SD))	**2.36 (2.00)**	**2.43 (2.09)**	**2.25 (1.88)**	**0.028**
Asthma = No (%)	433 (16.9)	252 (17.5)	181 (16.2)	0.417
Illicit drug use = No (%)	**165 (6.3)**	**65 (4.4)**	**100 (8.7)**	**<0.001**
Current smoker = No (%)	**264 (10.1)**	**123 (8.4)**	**141 (12.3)**	**0.001**
Daily drinkers = No (%)	**554 (21.2)**	**243 (16.5)**	**311 (27.2)**	**<0.001**
Stroke (%)				0.823

No	2442 (95.3)	1370 (95.0)	1072 (95.6)	
Transient ischemic attack	41 (1.6)	25 (1.7)	16 (1.4)	
Mini-stroke	49 (1.9)	30 (2.1)	19 (1.7)	
Stroke	31 (1.2)	17 (1.2)	14 (1.2)	
Migraine = No (%)	**351 (13.7)**	**258 (17.9)**	**93 (8.3)**	**<0.001**
Parkinson = No (%)	9 (0.4)	5 (0.3)	4 (0.4)	1.000
Epilepsy = No (%)	57 (2.2)	31 (2.1)	26 (2.3)	0.867
Insomnia requiring treatment = 1 (%)	**154 (6.0)**	**105 (7.3)**	**49 (4.4)**	**0.003**
Multiple sclerosis = No (%)	4 (0.2)	3 (0.2)	1 (0.1)	0.802
Chronic bronchitis = No (%)	38 (1.5)	23 (1.6)	15 (1.3)	0.713
Tuberculosis = No (%)	50 (1.9)	29 (2.0)	21 (1.9)	0.910
High blood cholesterol = No (%)	**482 (18.9)**	**247 (17.3)**	**235 (21.0)**	**0.019**
High blood pressure = 1 (%)	759 (29.6)	417 (28.9)	342 (30.4)	0.448
Angina = No (%)	**131 (5.1)**	**54 (3.8)**	**77 (6.9)**	**0.001**
Arrhythmia = No (%)	297 (11.6)	158 (11.0)	139 (12.4)	0.298
Diabetes = No (%)	**148 (5.8)**	**63 (4.4)**	**85 (7.6)**	**0.001**
Thrombosis = No (%)	71 (2.8)	42 (2.9)	29 (2.6)	0.697
Osteoporosis = No (%)	**147 (5.8)**	**123 (8.6)**	**24 (2.1)**	**<0.001**

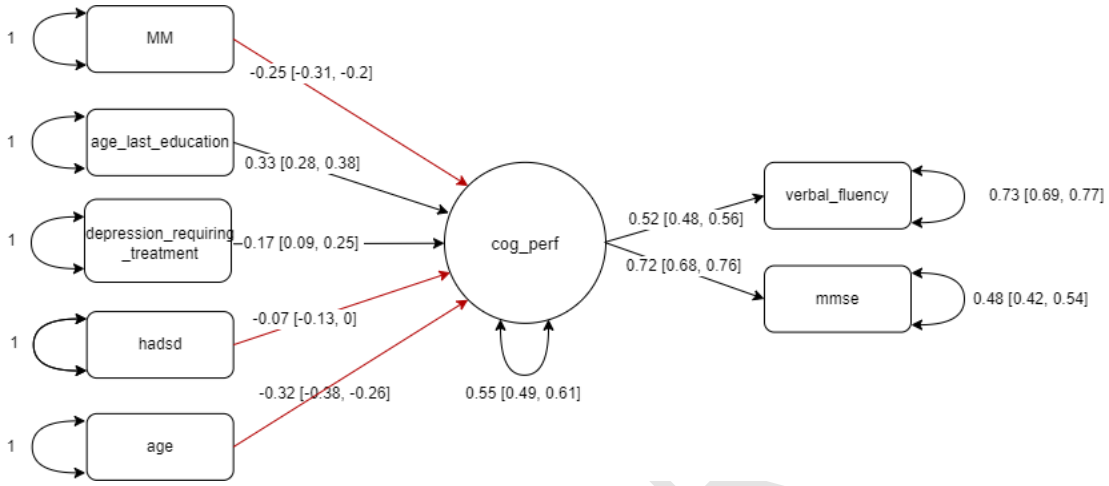
Thyroid = No (%)	**208 (8.1)**	**170 (11.8)**	**38 (3.4)**	**<0.001**
Ulcer = No (%)	62 (2.4)	29 (2.0)	33 (2.9)	0.158
GI polyps = No (%)	**97 (3.8)**	**44 (3.1)**	**53 (4.7)**	**0.037**
Gallstones = No (%)	**157 (6.1)**	**105 (7.3)**	**52 (4.6)**	**0.007**
Varicose vein = No (%)	**294 (11.4)**	**199 (13.8)**	**95 (8.4)**	**<0.001**
Arthritis = No (%)	**567 (22.2)**	**376 (26.2)**	**191 (17.1)**	**<0.001**
Cancer = No (%)	279 (10.8)	156 (10.8)	123 (10.9)	0.942
Depression requiring treatment = No (%)	**410 (16.0)**	**274 (18.9)**	**136 (12.1)**	**<0.001**
Other psychiatric illness = No (%)	65 (2.5)	41 (2.8)	24 (2.1)	0.325

Model specification and variables included in the model

A latent reflexive variable representing cognitive performance was specified, loading from the Mini-Mental State Examination (MMSE) and verbal fluency scores of each individual assessed. A variable representing multimorbidity (the number of chronic conditions each patient presented, starting by the second condition) was also regressed on the latent variable, together with scores (cut-off is 8 out of 21 points) from the Hospital anxiety and depression scale-depression subscale (HADS-D), age, education level, and history of previous depression requiring treatment. Because age and education are known to interfere with MMSE and verbal fluency results, they were added as covariates in the model. The formal specification can be seen in Figure 1. The multimorbidity (MM) variable was defined as numerical, starting with two chronic conditions (those with one chronic condition were counted as zero). The conditions were history of illicit drug use, whether the patient currently smoked, whether the patient drank daily, and the diagnoses of asthma, migraine, Parkinson, epilepsy, insomnia that prompted treatment, multiple sclerosis, chronic bronchitis, tuberculosis, high blood cholesterol, high blood pressure, angina, arrhythmia, diabetes, deep vein thrombosis, osteoporosis, thyroid disease, peptic ulcer, gastrointestinal polyps, gallstones, varicose veins, arthritis, cancer, depression, and

other psychiatric diagnosis. Finally, algebra for the moderation between the multimorbidity (MM) variable and HADS-D scores was included in the model (Supplemental material).

Figure 1. Structural equation model.



The circle represents a latent variable (cognitive performance) and boxes the measured variables. Straight arrows represent the direction of the relationship. Values are the estimated coefficients. Negative coefficients in red lines. The indicators in the left column were allowed to correlate, but we omitted the arrows in the interest of clarity. $\chi^2(2) = 20.12$, $p < 0.001$; Comparative Fit Index (CFI) = 0.993; Tucker-Lewis Index (TLI) = 0.926; Root mean squared error of approximation (RMSEA)= 0.058. Not shown, moderation between hads-d and multimorbidity (MM): 0.009 (p-value = 0.04).

The MMSE is a simple cognitive test used in clinical settings that correlates with the standard cognition test (Wechsler Adult Intelligence Scale) [21]. This variable was used together with categorical verbal fluency (the number of words starting with the letter s recollected in a minute) in the cognitive performance latent variable.

Results

The number of participants in the study was 2681 individuals, 1508 female and 1172 male (Table 1). There were significant differences in anxiety symptom scores and in the mini-mental state examination (MMSE) between the sexes. The mean score for anxiety symptoms for females was 5.51 (SD 3.48, p <0.001), whereas for males it was 4.71 (SD 3.23, p <0.001). The mean mini-mental state examination (MMSE) score for females was 27.79 (SD 2.57, p < 0.05)

and 27.99 (SD 2.26, $p < 0.05$) for males. There were also statistically significant differences with regard to marital status, as most participants are married (Female: 41.1% / Male: 58.5%, $p < 0.001$)), income (shows lower income levels, for example, for income level B 23.5% among female and 21.2% among female, $p < 0.001$), illicit drug use (Female 4.4% / Male 8.7%, $p < 0.001$); current smoking (Female 8.4% and Male 12.3%, $p < 0.001$), daily drinking (Female 16.5% and Male 27.2%, $p < 0.001$), migraine (Female 17.9% and Male 8.3%, $p < 0.001$), insomnia that requires treatment (Female 7.3% and Male 7.4%, $p < 0.05$), high blood cholesterol (Female 17.3% and Male 21.0%, $p < 0.05$), angina (Female 3.8% and Male 6.9%, $p < 0.05$), diabetes (Female 4.4% and Male 7.6%, $p < 0.001$), osteoporosis (Female 8.6% and Male 2.1%, $p < 0.001$), thyroid (Female 11.8% and Male 3.4%, $p < 0.001$), GI polyps (Female 3.1% and Male 4.7%, $p < 0.05$), gallstones (Female 7.3% and Male 4.6%, $p < 0.05$), varicose vein (Female 13.8% and Male 8.4%, $p < 0.001$), arthritis (Female 26.2% and Male 17.1%, $p < 0.001$), depression that requires treatment (Female 18.9%, Male 12.1%, $p < 0.001$), age of last education (Female mean 19.24 SD 4.17 and mean Male 20 .01 SD 4.62, $p < 0.001$) and number of chronic conditions (Female mean 2.43 SD 2.09 and mean Male 2 .25 SD 1.88, $p < 0.05$) between sexes (Table 1).

The SEM (Structure Equation Modelling) model presented a good fit ($\chi^2(2) = 20.12$, $p < 0.001$; Comparative Fit Index (CFI) = 0.993; Tucker-Lewis Index (TLI) = 0.926; Root mean squared error of approximation (RMSEA) = 0.058. The model is locally identified. It was found that for each unit increase in the variable encoding reported multimorbidity there was a reduction of 0.25 in the variance of the latent variable encoding cognitive performance. Also, for each unit increase in depressive symptoms there was a 0.07 decrease in the variance of cognitive performance. Therefore, the more depressive symptoms and chronic conditions, the worse cognitive performance. The variables included as covariates were significantly correlated with the cognitive performance variable. For each unit change in age, there was a reduction of 0.32 in cognitive performance. In the same way, for each unit change in the age at last education, there was a 0.33 rise in cognitive performance. In other words, the higher the educational level, the better the cognitive performance (Figure 1).

The moderation term was estimated at 0.009 ($p = 0.04$), so depressive symptomatology moderated the effect of multimorbidity on cognitive performance, worsening its effect.

Discussion

A large data set of 2681 British individuals with mean age of 60.57 was used to investigate whether presence of depressive symptomatology at baseline moderated the effect of multimorbidity on cognitive performance. We used all information in the set, and controlled for age, education, and previous history of depression. Females had lower MMSE scores than

males, and more depression requiring treatment. It was found that depressive symptomatology was indeed a moderator of MM on cognition.

There is evidence that the relationships between mental disorders and other chronic diseases are complex and bidirectional. Having mental disorders worsens several chronic disease risk factors, like worse lifestyle choices; poor health literacy; poor access to health care; and symptoms such as lack of motivation and energy[14]. Additionally, a number of medications given to patients with mental disorders (notably antipsychotics), can enhance risk for dyslipidemia, obesity and cardiovascular diseases[22]. Furthermore, chronic diseases and mental disorders share similar risk factors, like susceptibility to citokine-mediated inflammatory responses, genetic common factors and social-economic vulnerability (poverty and violence)[14].

Depression is associated with worse cognitive performance [23]. Impaired concentration and indecisiveness are core symptoms of acute depression in DSM-5. Lam and al. found in their 2014 study that psychosocial functioning in depressive patients is moderated by cognitive performance. Deficits in processing speed, attention, executive function, learning, and memory have been demonstrated among depressed individuals in earlier studies [24,25], with some evidence that cognitive deficits persist even in remission of depressive symptoms [25]. On the other hand, multimorbidity is associated with increased risk of mild cognitive impairment and dementia[13]. In a more recent study, Vassilaki and al. (2019) found a stronger association between multimorbidity and neurodegeneration (volume change), than with amyloid deposition[26]. These types of neurodegenerations are more related to cognition symptoms[26].

There is evidence that the rate of accumulation of chronic diseases in multi-morbid patients over time is associated with a faster rate of decline in verbal fluency, independent of baseline morbidity[27]. We examined the possible moderator effect of depressive symptoms on the relation of multimorbidity on cognition, and we confirm that there is a small, albeit significant moderation in this relationship.

This study has limitations that should be acknowledged. The analysis is cross-sectional, therefore not causal. The number of observations is relatively small. We did not include information from the whole set of neuropsychological tests available. There was no information on biomarkers for Alzheimer Disease or vascular diseases in the dataset. We did not include neuroimaging findings such as MRI. Likewise, we did not have access to information about treatment received or use of medication by the participants. The multimorbidity variable used did not permit the examination of patterns of chronic conditions, and instead captures the variance from the number of conditions of each individual. The chronic conditions included were limited by the conditions actually asked about at the baseline interview by the team who lead the original cohort, therefore this is not a thorough investigation of chronic diseases. Although a number of previous papers imply a moderation effect of psychiatric symptomatology on the relationship between multimorbidity and cognition, this has not been

tested directly. Here, we present an estimation of such moderation using depressive symptoms. The relation of depressive symptoms and other chronic diseases to cognition over time is still not known. It is plausible that this effect may be different from the cross-sectional effect of depression on cognition, and multimorbidity on cognition. Future studies in this field should try to incorporate panel data in this analysis to check whether the moderation effect we found changes with time.

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