

Title: Physical multimorbidity predicts the onset and persistence of anxiety: a prospective analysis of the Irish Longitudinal Study on Ageing

Running Head: Physical multimorbidity predicts the onset and persistence of anxiety

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ABSTRACT

Background: The aims of the present study were to examine prospective associations of multimorbidity (i.e., ≥ 2 chronic conditions) at baseline with incident and persistent anxiety over a two-year follow-up period among Irish older adults, and to quantify the extent to which sleep, pain, and disability mediate the multimorbidity-anxiety relationship.

Methods: Data from The Irish Longitudinal Study on Aging (TILDA) conducted between 2009-2011 with a follow-up after two years were analyzed. The baseline survey was anxiety referred to score ≥ 8 on the anxiety section of the Hospital Anxiety and Depression Scale. Lifetime diagnosis of 14 chronic conditions were obtained. Outcomes were incident and persistent anxiety at two-year follow-up.

Results: Data on 5871 adults aged ≥ 50 years at baseline were analyzed [Mean (SD) age 63.3 (9.0) years; 51.2% women]. After adjustment for potential confounders, compared to no chronic physical conditions at baseline, ≥ 3 chronic conditions were associated with a significant 1.89 (95%CI=1.16-3.08) times higher risk for new onset anxiety at follow-up. Furthermore, having 1, 2, and ≥ 3 conditions at baseline were associated with significant 1.48 (95%CI 1.02, 2.14), 1.74 (95%CI 1.19, 2.53), and 1.84 (95%CI 1.27, 2.68) times higher risk for persistent anxiety at follow-up. Sleep problems, pain, and disability were identified as significant mediators, explaining 22.9%-37.8% of the associations.

Conclusion: Multimorbidity was associated with both new onset and persistent anxiety among Irish older adults. Future interventional studies should examine whether addressing the identified mediators may lead to lower risk for incident or persistent anxiety among those with physical multimorbidity.

Keywords: Multimorbidity, Anxiety, Older Adults, Cohort, Epidemiology

INTRODUCTION

Anxiety is an emotion characterized by feelings of tension, worried thoughts, and physical changes (e.g., increased blood pressure). People with anxiety disorders usually have recurring intrusive thoughts or concerns (American Psychological Association, 2021). According to the World Health Organization (WHO), 1 in 13 people suffer from anxiety globally, and anxiety disorders are the most common mental disorders worldwide (World Health Organization, 2021). Anxiety disorders are most common in older adults and have been found in 14–17% of this population (Canuto et al., 2018; Kirmizioglu, Doğan, Kuğu, & Akyüz, 2009; Miloyan & Pachana, 2015; Norton et al., 2012; Wolitzky-Taylor, Castriotta, Lenze, Stanley, & Craske, 2010). Anxiety in old age has been found to be associated with a reduced quality of life (QoL), an increased risk of multiple physical and mental disorders including cognitive decline, impaired functioning, and premature mortality (Carriere et al., 2013). Owing to the high prevalence of anxiety disorder and its associated adverse health outcomes in older adults, risk factors of anxiety in this population need to be identified to inform targeted intervention.

While a myriad of studies on the determinants of anxiety among the older population exist, one factor that has been little studied to date is multimorbidity, which is often defined as the presence of two or more health conditions (NICE | The National Institute for Health and Care Excellence, 2018). Importantly, the prevalence of multimorbidity is increasing and is highest among older adults (Kone et al., 2021). Multimorbidity may increase risk for anxiety via factors such as increased worry of having multiple health conditions and potential difficulty adjusting to the burden of such conditions (De Ridder, Geenen, Kuijer, & van Middendorp, 2008). Furthermore, it is possible for factors such as sleep problems, pain, and disability, which are common consequences of multimorbidity (Ferguson, Svendrovski, & Katz, 2020; Garin et al., 2014; Ruiz-Castell, Makovski, Bocquet, & Stranges, 2019), to increase risk for anxiety (Babson, Trainor, Feldner, & Blumenthal, 2010; Gore et al., 2005; Sareen et al., 2006).

To the best of our knowledge, only two studies specifically on the association between multimorbidity and anxiety exist to date. One cross-sectional study among 4219 participants aged 65 years or older in the US

found that 2 and ≥ 3 medical conditions yielded a 1.96-fold (95% CI=1.13–3.41) and 3.49-fold (95% CI=2.05–5.95) increased odds of anxiety respectively, compared to those with no medical conditions (Gould, O'Hara, Goldstein, & Beaudreau, 2016). In another cross-sectional study including a sample of 181,845 adults aged ≥ 18 years from 42 countries, it was found that compared to those with no physical health conditions, one condition was associated with an almost twofold increased odds of anxiety symptoms (OR = 1.94; 95%CI = 1.76–2.13), while this figure rose to 5.49 (3.73–8.09) in those with ≥ 5 conditions (Vancampfort, Koyanagi, Hallgren, Probst, & Stubbs, 2017). A key limitation of the existing literature is that both studies are cross-sectional in nature. Due to lack of longitudinal data, it is unknown whether multimorbidity increases the risk for new onset anxiety or persistent anxiety. Furthermore, only one of the studies was on older adults and therefore, more studies from diverse settings are necessary. Finally, no study to date has quantified the degree to which factors such as pain, sleep problems, and disability may mediate the multimorbidity-anxiety association, and thus, the underlying mechanisms remain largely unknown.

Given this background, the aim of the present study was to examine associations of multimorbidity at baseline and incident and persistent anxiety over a two-year follow-up period in a large representative sample of Irish adults aged ≥ 50 years. A further aim was to quantify the extent to which sleep problems, pain, and disability mediate the multimorbidity-anxiety relationship.

METHODS

The survey and sample

We analyzed data from two consecutive waves of the Irish Longitudinal Study on Ageing (TILDA) survey. Full details of the survey, including its sampling methods, have been described in detail elsewhere (Barrett et al., 2011; Kenny, Rose Anne et al., 2010; Nolan et al., 2014). Briefly, this was a community-based survey of middle-aged and older adults residing in Ireland conducted by Trinity College Dublin. The first wave (Wave 1) or the baseline survey was conducted between October 2009 and February 2011, and the second wave (Wave 2) was undertaken between April 2012 and January 2013. The target sample consisted of all individuals living in private households aged 50 and over in Ireland. Clustered random sampling was used to obtain

nationally representative samples. The first wave excluded institutionalized individuals, anyone with known dementia or anyone unable to personally provide written informed consent to participate due to severe cognitive impairment. Trained personnel conducted interviews with the use of Computer Assisted Personal Interviewing (CAPI). For sensitive questions, participants were asked to fill in a self-completion questionnaire (SCQ), which was returned after the interview. The response rate of Wave 1 was 62% and that of Wave 2 was 86%. Among those who participated in Wave 1, 84% returned the SCQ. Sampling weights were generated with respect to age, sex, and educational attainment to the Quarterly National Household Survey 2010. Ethical approval for TILDA was obtained by the Faculty of Health Sciences Ethics Committee of Trinity College Dublin. Written informed consent was obtained from all participants.

Anxiety

Anxiety was assessed at Wave 1 and Wave 2 with the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) (Zigmond & Snaith, 1983). This instrument consists of seven items rated on a four-point scale from 0 (not at all) to 3 (very often indeed), with five items reverse coded. The scores of the seven items were summed to create a scale that ranged from 0 to 21, with higher scores indicating more symptoms of anxiety. The HADS-A has been found to have good sensitivity and specificity for assessing anxiety disorders across all ages in the general population (Bjelland, Dahl, Haug, & Neckelmann, 2002), and among specific age groups of older adults (Spinhoven et al., 1997). A positive screen for generalized anxiety disorder (GAD) was defined as a score of ≥ 8 . This cut-off point has been associated with 89% sensitivity and 75% specificity for the screening of GAD (Bjelland et al., 2002; Olsson, Mykletun, & Dahl, 2005). Information on anxiety was obtained via the SCQ in Wave 1 and the standard in-person CAPI interview at Wave 2. Incident anxiety was assessed among those without anxiety at baseline, and referred to new cases of anxiety at follow-up. Next, persistent anxiety was assessed only among those who had anxiety at baseline, and was defined as having anxiety at both baseline and follow-up.

Chronic physical conditions and multimorbidity

Chronic physical conditions were assessed at Wave 1 by the question “Has a doctor ever told you that you have any of the conditions on this card?” The total number of the following 14 conditions were summed: asthma, arthritis, cancer, chronic lung disease (chronic bronchitis or emphysema), cirrhosis, diabetes, eye disease (cataracts, glaucoma, age-related macular degeneration, or other eye disease), heart disease (angina, heart attack, congestive heart failure, heart murmur, abnormal heart rhythm, or other heart disease), high cholesterol, hypertension, osteoporosis, stomach ulcer, stroke, and varicose ulcer. Multimorbidity was defined as having at least two chronic conditions, in line with previously used definitions (Jacob, Haro, & Koyanagi, 2019). The number of chronic conditions was also classified as 0, 1, 2, and ≥ 3 conditions.

Mediators

The potential mediators in the association between multimorbidity and anxiety were selected based on past literature and included sleep problems, pain, and disability (Lenze et al., 2001; Max et al., 2006; Narmandakh, Roest, de Jonge, & Oldehinkel, 2020). A composite sleep score (range 0-7 with higher scores representing more sleep problems) was created based on three questions on the likelihood of dozing off or falling asleep during the day, frequency of trouble falling asleep, and trouble with waking up too early and not being able to fall asleep again (Scarlett, Kenny, O'Connell, Nolan, & De Looze, 2021). Those who answered affirmatively to the question “Are you often troubled with pain?” were considered to have pain. Difficulties with six types of activities of daily living (ADL) (dressing, walking, bathing, eating, getting in or out of bed, and using the toilet) were assessed by asking participants to indicate whether they had difficulty performing these activities. ADL disability was defined as having difficulty with at least one of these ADLs. All these potential mediators were assessed at Wave 1.

Control variables

Control variables included sex, age, education, and marital status (married/cohabiting, never married, separated/divorced/widowed), and these were assessed at Wave 1 with the CAPI. Education was classified as: primary (some primary/not complete, primary or equivalent); secondary (intermediate/ junior/group certificate

or equivalent, leaving certificate or equivalent); and tertiary (diploma/certificate, primary degree, postgraduate/higher degree).

Statistical analysis

The analysis was undertaken using Stata version 14.2 (Stata Corp LP, College Station, Texas). A total of 8163 people aged ≥ 50 years participated at Wave 1. Of these people, follow-up data for 7207 participants were available at Wave 2. We restricted the analysis to: (a) those aged ≥ 50 years at baseline; (b) participants who provided information on anxiety at Wave 1; (c) and those who provided information on anxiety at Wave 2. The sample size after restriction to these individuals was 5871. The association between the number of chronic physical conditions at baseline (exposures) and anxiety at follow-up (outcome) was estimated by multivariable logistic regression. The two outcomes were incident anxiety and persistent anxiety. In order to assess whether there is a statistically significant dose-dependent association between the number of chronic physical conditions and incident or persistent anxiety, we tested for trends by including the variable on number of chronic conditions in the model as a continuous variable. Furthermore, in order to assess whether there is effect modification in the association between number of chronic conditions and incident or persistent anxiety by sex or age groups (i.e., 50-64 years and ≥ 65 years), we conducted interaction analysis by including the product terms of sex X number of chronic conditions and age group X number of chronic conditions in the model. In addition to this, analyses for individual chronic conditions were also conducted.

Finally, in order to assess the degree to which the association between multimorbidity at baseline (i.e., ≥ 2 chronic conditions) and incident or persistent anxiety at follow-up can be explained by sleep problems, pain, and disability at baseline, we conducted mediation analysis using the *khb* (Karlson Holm Breen) command in Stata (Breen, Karlson, & Holm, 2013). This method can be applied in logistic regression models and decomposes the total effect (i.e., unadjusted for the mediator) of a variable into direct (i.e., the effect of multimorbidity on incident or persistent anxiety adjusted for the mediator) and indirect effects (i.e., the mediational effect). Using this method, the percentage of the main association explained by the mediator can also be calculated (mediated percentage). The mediators were included individually in the models, with the

exception of the models where all mediators were included simultaneously. All regression analyses including the mediation analysis were adjusted for sociodemographic variables (i.e., sex, age, education, marital status). All variables were included in the analysis as categorical variables, with the exception of age, sleep problems, and number of chronic conditions only for the test for trend (continuous variables). The sample weighting and the complex study design including clustering within households were taken into account to obtain nationally representative estimates using the Stata *svy* command. Results are expressed as odds ratios (ORs) and their 95% confidence intervals (95% CIs). A P-value <0.05 was considered to be statistically significant.

RESULTS

The analytical sample consisted of 5871 individuals aged ≥ 50 years at baseline. The mean (SD) age was 63.3 (9.0) years and 51.2% were women. The baseline characteristics are provided in **Table 1**. The most common chronic physical conditions were arthritis (26.8%), hypertension (37.1%), and high cholesterol (39.0%). Overall, 26.4%, 22.8%, and 30.1% of participants had 1, 2, and ≥ 3 chronic physical conditions at baseline, while the prevalence of anxiety at baseline was 24.9%. Of those who did not have anxiety at baseline ($n=4457$), 165 developed anxiety at follow-up ($165/4457=3.7\%$), and among those who had anxiety at baseline ($n=1414$), 493 continued to have anxiety at follow-up ($493/1414=34.9\%$). The prevalence of new onset anxiety and persistent anxiety increased with greater number of chronic physical conditions at baseline (**Figure 1**). For example, the prevalence of new onset anxiety was 3.3% among those with no chronic physical conditions but this increased to 4.9% among those with ≥ 3 chronic physical conditions. After adjustment for potential confounders, compared to no chronic physical conditions at baseline, ≥ 3 chronic conditions were associated with a significant 1.89 (95%CI=1.16-3.08) times higher risk for new onset anxiety at follow-up (**Table 2**). In terms of persistent anxiety, compared to no chronic physical conditions, having 1, 2, and ≥ 3 conditions at baseline were associated with significant 1.48 (95%CI=1.02-2.14), 1.74 (95%CI=1.19-2.53), and 1.84 (95%CI=1.27-2.68) times higher odds for persistent anxiety at Wave 2. Test for trend showed that there is a significant dose-dependent association in terms of the number of chronic physical conditions and incident or persistent anxiety ($p<0.05$). Furthermore, no significant interactions were found by sex and age groups in the association between number of chronic physical conditions and incident or persistent anxiety (results not

shown). In terms of individual chronic conditions, most of them were positively associated with new onset anxiety and persistent anxiety (i.e., OR>1) but not all reached statistical significance (**Table S1** of the Appendix).

Based on the mediation analysis, sleep problems (27.4%) and pain (27.7%) each explained more than a quarter of the association between multimorbidity (i.e., ≥ 2 chronic physical conditions) and new onset anxiety, while disability was not a significant mediator (**Table 3**). In terms of persistent anxiety, the mediated percentage for sleep problems, pain, and disability were 37.8%, 23.1%, and 22.9%, respectively. Collectively, these three mediators explained 46.0% and 58.4% of the association between multimorbidity and incident and persistent anxiety, respectively.

DISCUSSION

Main findings

In this longitudinal and representative study of Irish adults aged 50 years and over, it was found that compared to no chronic physical conditions at baseline, ≥ 3 chronic conditions were associated with a significant 1.89 times higher risk for new onset anxiety at follow-up. Furthermore, having 1, 2, and ≥ 3 conditions at baseline were associated with significant 1.48, 1.74, and 1.84 times higher odds for persistent anxiety at follow-up. Importantly, these associations were found to be dose-dependent. Sleep problems (mediated % 27.4%) and pain (27.7%) were significant mediators in the association between multimorbidity and incident anxiety, while disability (22.9%) in addition to sleep problems (37.8%) and pain (23.1%) were significant mediators for persistent anxiety. These mediators collectively explained 46.0% and 58.4% of the association of multimorbidity with incident and persistent anxiety, respectively.

Interpretation of findings

Findings from the present study support findings from previous cross-sectional studies that have identified a positive association between multimorbidity and anxiety (Gould et al., 2016; Vancampfort et al., 2017). Interestingly, a previous cohort study on diabetes-related complications found similar findings with depression

as the outcome. Specifically, in a sample of 1314 adults from Canada, the number of diabetes complications at baseline was positively associated with a greater risk of elevated depressive symptoms, with the highest risk found for those with four to six complications at baseline. Moreover, increases in diabetes complications were associated with increases in depressive symptoms during the course of the follow-up period (5 years) (Deschênes et al., 2017). The present longitudinal study adds to previous literature on this topic by showing that multimorbidity at baseline increases risk for new onset anxiety as well as persistent anxiety. Moreover, for the first time, the present study identified sleep problems, pain, and disability as important mediators in the multimorbidity-anxiety relationship.

There are several plausible pathways that likely explain the multimorbidity-anxiety relationship. First, this may be explained by the mediators identified in our study (sleep problems, pain, disability). Multimorbidity may increase risk of sleep problems via sleep-disordered breathing in conditions such as chronic lung disease, diabetes, and stroke, or symptoms of the chronic conditions per se (e.g., nocturnal symptoms in asthma, COPD, angina or nocturia in diabetes) (Koyanagi et al., 2014). In turn, sleep problems may lead to anxiety via decreased brain activation and decreased functional connectivity between brain regions, which may contribute to a diminished ability to regulate anxiety-related processes (Cox & Olatunji, 2016). Next, multimorbidity likely increases pain owing to a cluster of chronic conditions, reduced functional impairment, symptom severity and burden (Nakad et al., 2020). In turn, previous studies have shown that pain may lead to anxiety (Harvard Health Publishing, 2021). Indeed, chronic pain can lead to avoidance of situations that exacerbate or are believed to exacerbate pain. For example, older adults might avoid time spent in social and recreational activities (e.g., sports) in efforts to avoid pain, which in turn may increase levels of anxiety (Cohen, Vowles, & Eccleston, 2010). Finally, disability is commonly found in individuals with chronic conditions owing to the symptoms of the disease (e.g., stroke, arthritis). Disability may lead to anxiety through stereotypic social and personal attitude; abuse; loss of roles; and stressors related to poverty, environmental barriers, and/ or lack of access to appropriate health care. The finding that disability mediated the association between multimorbidity and persistent anxiety, but not new onset anxiety is interesting. It may be that those who have multimorbidity and anxiety at baseline have more severe disability and this factor may be important

in the persistence of anxiety over time. However, this hypothesis remains untested and future research is needed.

Collectively, sleep problems, pain, and disability explained a substantial proportion the association between multimorbidity and incident (46.0%) or persistent (58.4%) anxiety. However, this means that the remaining proportion is explained by other factors. For example, as previously mentioned, multimorbidity may lead to increased worry for having multiple health conditions, and potential difficulty adjusting to the burden of such conditions (De Ridder et al., 2008). Next, those with multimorbidity have high levels of chronic low-grade inflammation, which has been implicated in the development of anxiety (Friedman, Mroczek, & Christ, 2019; Osimo, Cardinal, Jones, & Khandaker, 2018).

Public health and clinical implications

The present findings suggest that it may be prudent to target those with multimorbidity to reduce the risk of anxiety. Specifically, addressing sleep problems and pain in those with multimorbidity may reduce risk for anxiety onset. Furthermore, among those who have comorbid physical multimorbidity and anxiety, in addition to sleep problems and pain, addressing disability may lead to a lower risk for persistent anxiety. One avenue for intervention may be the utilization of mind-body exercises such as tai chi. Indeed, tai-chi has been shown to be an effective strategy in the management of pain (Wood, 2020), improved sleep quality in those with chronic conditions (Raman, Zhang, Minichiello, D'Ambrosio, & Wang, 2013), and reductions in anxiety per se (Wang et al., 2010). In terms of disability, a multidisciplinary approach may be necessary including physiotherapists who may play a major role in addressing disability through rehabilitation etc. Clinicians should be aware of the high risk for incident and persistent anxiety among patients with multimorbidity and attempt to address the underlying factors that may lead to anxiety, as worse mental health in patients with physical conditions have been associated with worse clinical outcomes (Celano, Daunis, Lokko, Campbell, & Huffman, 2016).

Strength and limitations

The large representative sample of the Irish older adult population, the longitudinal design, the investigation of new onset and persistent anxiety, and the identification of mediating variables are clear strengths of the present study. However, findings must be considered in light of the study limitations. First, all variables assessed in our study were based on self-report and thus, reporting bias is possible. Second, although our list of chronic physical conditions included 14 diseases which are highly prevalent in older age, it is possible that the results would differ with the use of a different list of chronic conditions. Third, baseline data on multimorbidity and other control or mediating variables were used for the analysis. Consequently, it is possible that some conditions or characteristics of the respondents changed between the two waves. Furthermore, multimorbidity and the mediators were both assessed at Wave 1. Theoretically, the mediators are highly likely to be the consequence of multimorbidity but given that they were assessed at the same time, reverse causality cannot be ruled out. In addition, in our study, anxiety was assessed by the HADS-A. While this tool has been reported to have good sensitivity and specificity for assessing anxiety disorders, a diagnostic interview would have been preferred. Next, anxiety was only assessed at two time points, and information on anxiety before Wave 1 or between Wave 1 and 2 were not available. Thus, it should be noted that our definition of new onset anxiety and persistent anxiety is only based on two points of measurement. Finally, it is possible that some level of bias was introduced due to loss to follow-up.

Conclusions

In conclusion, in this large sample of Irish older adults, multimorbidity was associated with both new onset and persistent anxiety. Sleep, pain, and disability (only for persistent anxiety) were identified as important mediators. The present findings suggest that addressing the identified mediators in those with multimorbidity may reduce the risk for incident and persistent anxiety. Future interventional studies may shed light on the effectiveness of such interventions in reducing anxiety risk among those with multimorbidity.

ACKNOWLEDGEMENTS

Researchers interested in using TILDA data may access the data for free from the following sites: Irish Social Science Data Archive (ISSDA) at University College Dublin <http://www.ucd.ie/issda/data/tilda/>; Interuniversity Consortium for Political and Social Research (ICPSR) at the University of Michigan (Kenny, R. A., 2018).

TABLES

Table 1 Baseline characteristics (overall and by anxiety at baseline)

Characteristic		Total (N=5871)	Anxiety at baseline	
			No (N=4457)	Yes (N=1414)
Sex	Female	51.2	48.6	58.9
Age (years)	Mean (SD)	63.3 (9.0)	63.7 (9.1)	60.9 (8.1)
Education	Primary	34.7	34.2	36.3
	Secondary	45.1	45.2	44.7
	Tertiary	20.2	20.6	19.0
Marital status	Married/cohabiting	69.7	69.8	69.5
	Never married	9.4	9.5	9.3
	Separated/Divorced/Widowed	20.8	20.7	21.2
Chronic lung disease	Yes	4.3	3.7	6.0
Arthritis	Yes	26.8	25.5	30.9
Asthma	Yes	9.2	8.3	12.1
Osteoporosis	Yes	9.8	8.9	12.6
Cancer	Yes	5.9	6.0	5.8
Cirrhosis	Yes	0.6	0.5	0.6
Diabetes	Yes	7.3	7.1	8.0
Eye disease	Yes	15.5	15.5	15.5
Heart disease	Yes	18.7	18.2	20.4
High cholesterol	Yes	39.0	38.0	42.3
Hypertension	Yes	37.1	36.5	39.0
Stomach ulcer	Yes	7.0	6.0	10.1
Stroke	Yes	1.4	1.1	2.2
Varicose ulcer	Yes	3.2	3.3	2.9
No. of chronic	0	20.7	21.7	17.6
Physical conditions	1	26.4	27.2	24.2
	2	22.8	22.7	23.1
	≥3	30.1	28.4	35.2
Sleep problems	Mean (SD)	2.2 (1.7)	2.0 (1.6)	2.8 (1.7)
Pain	Yes	36.3	31.7	50.2
Disability	Yes	8.3	7.1	12.1

Abbreviation: SD Standard deviation

Data are % unless otherwise stated.

All data are weighted estimates apart from the Ns which are not weighted.

Table 2 Association between number of chronic physical conditions at baseline and new onset anxiety and persistent anxiety estimated by multivariable logistic regression

Characteristic		New onset anxiety ^a			Persistent anxiety ^b		
		OR	95%CI	P-value	OR	95%CI	P-value
No. of chronic physical conditions ^c	0	1.00			1.00		
	1	1.07	[0.65,1.76]	0.796	1.48	[1.02,2.14]	0.039
	2	1.23	[0.74,2.06]	0.431	1.74	[1.19,2.53]	0.004
	≥3	1.89	[1.16,3.08]	0.010	1.84	[1.27,2.68]	0.001
Sex	Female	1.00			1.00		
	Male	0.48	[0.33,0.69]	<0.001	0.65	[0.51,0.83]	0.001
Age (years)		0.95	[0.93,0.97]	<0.001	0.97	[0.96,0.99]	<0.001
Education	Primary	1.00			1.00		
	Secondary	0.69	[0.44,1.06]	0.089	0.70	[0.52,0.94]	0.018
	Tertiary	0.54	[0.33,0.87]	0.012	0.76	[0.55,1.04]	0.090
Marital status	Married/Cohabiting	1.00			1.00		
	Never married	1.15	[0.63,2.12]	0.642	0.88	[0.57,1.35]	0.549
	Separated/Divorced/Widowed	1.20	[0.75,1.91]	0.452	0.86	[0.62,1.18]	0.350

Abbreviation: OR Odds ratio; CI Confidence interval

Model is adjusted for all variables in the Table.

^a New onset anxiety referred to anxiety at Wave 2 among those who did not have anxiety at baseline (Wave 1).

^b Persistent anxiety referred to anxiety at Wave 2 among those who had anxiety at baseline (Wave 1).

^c Significant test for trend (P<0.05)

Table 3 Mediators in the association between multimorbidity (i.e., ≥ 2 chronic physical conditions) and new onset anxiety or persistent anxiety

Outcome	Mediator	Total effect		Direct effect		Indirect effect		% Mediated ^a
		OR [95%CI]	P-value	OR [95%CI]	P-value	OR [95%CI]	P-value	
New onset anxiety ^b	Sleep problems	1.46 [1.04,2.05]	0.030	1.32 [0.94,1.85]	0.115	1.11 [1.06,1.16]	<0.001	27.4
	Pain	1.49 [1.06,2.10]	0.023	1.33 [0.94,1.89]	0.104	1.12 [1.05,1.19]	0.001	27.7
	Disability	1.50 [1.07,2.10]	0.020	1.46 [1.04,2.05]	0.027	1.02 [0.99,1.06]	0.174	NA
	All mediators	1.46 [1.04,2.07]	0.031	1.23 [0.86,1.74]	0.250	1.19 [1.10-1.29]	<0.001	46.0
Persistent anxiety ^c	Sleep problems	1.44 [1.13,1.83]	0.004	1.25 [0.98,1.60]	0.073	1.15 [1.08,1.22]	<0.001	37.8
	Pain	1.43 [1.12,1.81]	0.004	1.31 [1.03,1.67]	0.026	1.09 [1.02,1.15]	0.009	23.1
	Disability	1.42 [1.11,1.81]	0.005	1.31 [1.02,1.68]	0.034	1.08 [1.03,1.14]	0.002	22.9
	All mediators	1.45 [1.13,1.85]	0.003	1.17 [0.91,1.50]	0.231	1.24 [1.14,1.35]	<0.001	58.4

Abbreviation: OR Odds ratio; CI Confidence interval

Model is adjusted for all variables in the Table.

^a Percent mediated was only calculated in the presence of a significant indirect effect ($P < 0.05$).

^b New onset anxiety referred to anxiety at Wave 2 among those who did not have anxiety at baseline (Wave 1).

^c Persistent anxiety referred to anxiety at Wave 2 among those who had anxiety at baseline (Wave 1).

Models are adjusted for sex, age, education, and marital status

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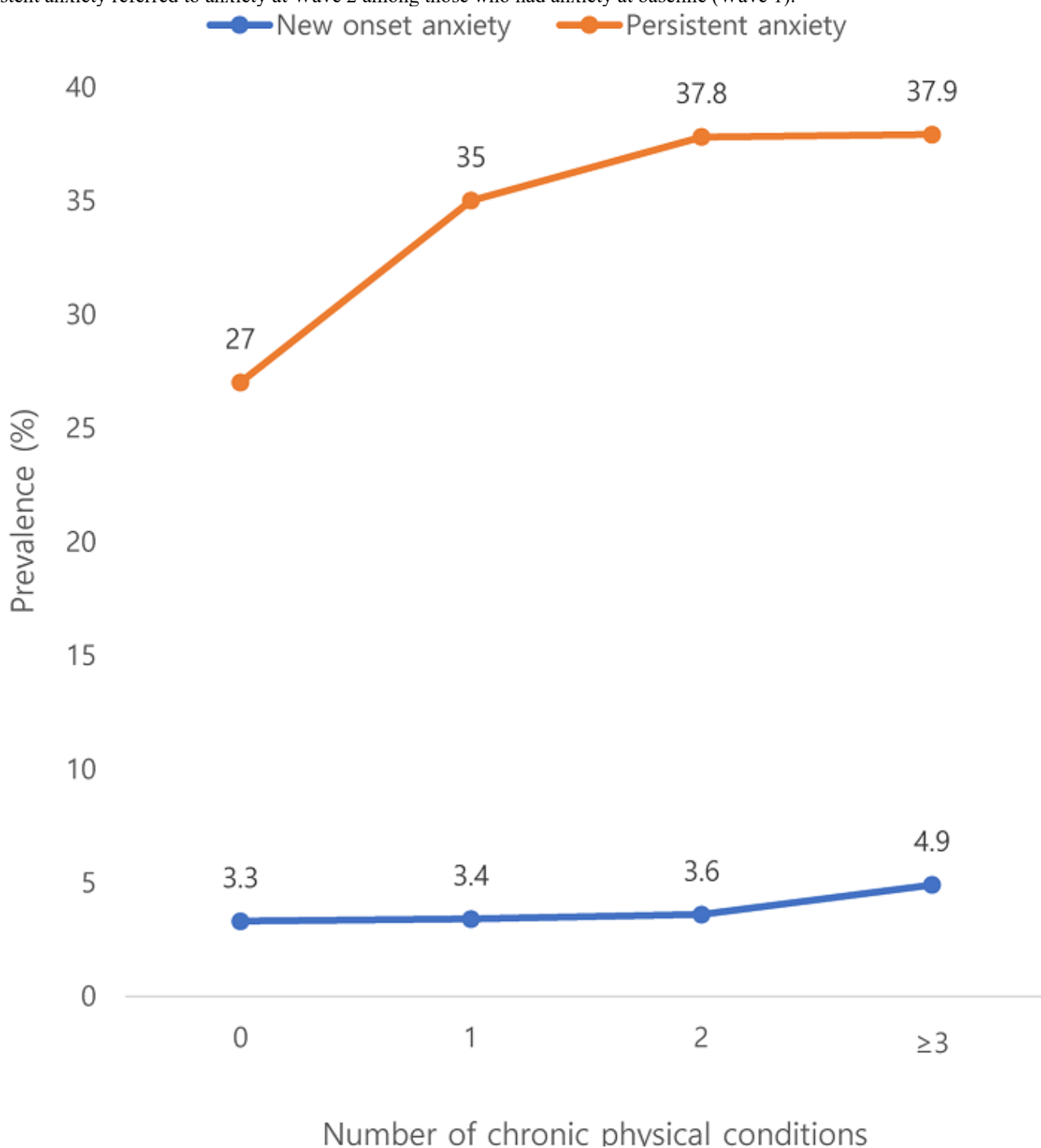
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Figure legend

Figure 1 Prevalence of new onset anxiety and persistent anxiety by number of chronic physical conditions at baseline

New onset anxiety referred to anxiety at Wave 2 among those who did not have anxiety at baseline (Wave 1).

Persistent anxiety referred to anxiety at Wave 2 among those who had anxiety at baseline (Wave 1).



APPENDIX

Table S1 Association between individual physical disease at baseline and new onset anxiety and persistent anxiety estimated by multivariable logistic regression

Chronic physical disease	New onset anxiety ^a			Persistent anxiety ^b		
	OR	95%CI	P-value	OR	95%CI	P-value
Arthritis	1.77	[1.20,2.61]	0.004	1.53	[1.16,2.03]	0.003
Asthma	0.95	[0.51,1.75]	0.870	1.24	[0.88,1.74]	0.225
Cancer	1.47	[0.83,2.62]	0.190	1.02	[0.62,1.68]	0.942
Chronic lung disease	1.27	[0.60,2.71]	0.533	1.60	[1.00,2.58]	0.052
Cirrhosis	NA			1.16	[0.24,5.58]	0.852
Diabetes	0.99	[0.47,2.06]	0.973	1.10	[0.73,1.68]	0.640
Eye disease	0.96	[0.58,1.58]	0.867	1.31	[0.94,1.85]	0.115
Heart disease	1.19	[0.77,1.86]	0.434	1.55	[1.14,2.10]	0.005
High cholesterol	1.23	[0.89,1.70]	0.218	1.07	[0.85,1.35]	0.558
Hypertension	1.31	[0.92,1.87]	0.132	1.15	[0.92,1.46]	0.223
Osteoporosis	1.25	[0.77,2.03]	0.375	1.01	[0.71,1.43]	0.971
Stomach ulcer	1.49	[0.82,2.68]	0.189	0.99	[0.65,1.51]	0.973
Stroke	2.04	[0.48,8.66]	0.335	0.71	[0.29,1.73]	0.456
Varicose ulcer	0.66	[0.20,2.17]	0.496	2.25	[1.03,4.91]	0.042

Abbreviation: OR Odds ratio; CI Confidence interval

Models are adjusted for sex, age, education, and marital status.

^a New onset anxiety referred to anxiety at Wave 2 among those who did not have anxiety at baseline (Wave 1).

^b Persistent anxiety referred to anxiety at Wave 2 among those who had anxiety at baseline (Wave 1).