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Multimorbidity and perceived stress: a population-based cross-sectional study among older adults across six low- and middle-income countries

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ABSTRACT

Background: Stress in chronic conditions or multimorbidity (≥2 chronic conditions) has been reported to affect clinical outcomes but there are no studies on the association between stress and chronic conditions/multimorbidity among older adults in low- and middle-income countries (LMICs). Thus, we investigated this association among adults aged ≥50 years across six LMICs.

Methods: A cross-sectional analysis using data from the World Health Organization's Study on Global Ageing and Adult Health (China, Ghana, India, Mexico, Russia, South Africa) was conducted. A perceived stress score [range 0 (lowest stress) −100 (highest stress)] was computed based on two questions from the Perceived Stress Scale. Thirteen chronic conditions were assessed. Multivariable linear regression analyses were conducted.

Results: 34,129 adults with a mean age of 62.4 (SD = 16.0) years (52.1% females) were included. Overall, 56.6% (95% CI = 55.0%-58.2%) had multimorbidity. In the adjusted model including all countries, compared with those with no chronic conditions, higher numbers of chronic conditions were significantly associated with higher stress levels, dose dependently. In a countrywide meta-analysis, multimorbidity was associated with significantly higher stress levels in all countries (especially India and Ghana) although characterized by moderate heterogeneity (I^2 = 54.6%). For single chronic conditions, notably high stress scores were observed for depression, stroke, and hearing problems.

Conclusion: Chronic conditions and multimorbidity are associated with higher levels of stress in older adults in LMICs. Given that perceived stress and chronic conditions are collectively associated with worse health outcomes, low-cost, population-level integrated interventions to address stress among those with chronic conditions are urgently needed.

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1. Introduction

The recent Lancet Global burden of disease series confirm that whilst the average life expectancy continues to increase, the numbers of years lived with disability are also increasing [1,2]. Of particular concern are the rising number of chronic conditions, such as chronic low back pain, arthritis, diabetes and chronic respiratory conditions which are associated with considerable disability-adjusted life years and healthcare utilization [3–5]. With population ageing, people are now more likely to have multiple chronic conditions simultaneously, a condition often referred to as multimorbidity [6]. Indeed, recent studies have suggested that between 13 and 72% of the general population has multimorbidity [7,8], thus posing one of the greatest challenges in healthcare to our ageing population [6,9]. Multimorbidity is an important risk concept given its associated high healthcare costs, decreased quality of life and ultimately increased mortality [10,11].

To date, most of the research investigating multimorbidity has been limited to a single country and a paucity of data exists from low- and middle-income countries (LMICs). Clearly, this limits the representativeness of the research, and a lack of research considering multimorbidity in LMICs is a concern, given the fact that an increasing proportion of the world's population resides in this setting and the average age continues to rise in this region [12]. Moreover, there is increasing recognition that there is a rising burden of the number of chronic conditions in LMICs, yet the healthcare systems are not well equipped to deal with this public heath demand [13].

Research has also started to consider the mental or emotional health burden of multimorbidity, such as perceived stress [14], a state in which one perceives their life situations stressful [15]. The relationship between some single chronic conditions and perceived stress has been investigated to date, partly driven by the potential deleterious influence of stress on the patient's treatment outcomes and wellbeing. For instance, in patients with asthma, arthritis, chronic back pain or diabetes, stress may intensify the effect of illness by increasing pain, functional limitations, and disability, as well as decreasing adherence to medical treatment protocols [16–18], all of which may further exacerbate stress [19].

Surprisingly, a paucity of multinational research has considered the relationship between multimorbidity and perceived stress. This is an important research gap given that a previous national Danish study identified that perceived stress may contribute to the heightened mortality in those with multimorbidity [11]. Previous research has suggested that multimorbidity is high in LMICs [14,20] and perceived stress levels are high due to considerable economic, environmental and health uncertainties, including less access to physical health care. Thus, this adds to the pressing need to explore this relationship within this context in older adults. One recent study reported the association between chronic conditions, multimorbidity and perceived stress in LMICs using data from the World Health Survey [14]. Whilst novel, the data were older and the study was not restricted to older adults, who are the population typically with the highest levels of chronic conditions and multimorbidity. Furthermore, data from China, India, and Russia, which collectively comprise a large proportion of the global population were not nationally representative. In addition, individual country estimates were not provided despite the potential between-country differences in factors (e.g., underlying disease profile, availability of health insurance and optimal treatment) that may influence stress levels associated with chronic conditions or multimorbidity. Finally, due to a lack of data, important chronic conditions such as hypertension, stroke, and chronic obstructive pulmonary disease (COPD), which are major contributors to the global disease burden [21], could not be included in the previous analysis.

Given the aforementioned gaps in the literature, the aim of the current study was to assess whether a variety of chronic conditions and multimorbidity are associated with higher perceived stress levels among community-dwelling older adults using nationally representative data from six LMICs (China, Ghana, India, Mexico, Russia, South Africa) which broadly represent different geographical locations and levels of socio-economic and demographic transition.

2. Methods

2.1. The survey

Data from the Study on Global Ageing and Adult Health (SAGE) survey was analyzed. This dataset is publically available through the World Health Organization (WHO) website (http://www.who.int/healthinfo/sage/en/). The survey was undertaken in China, Ghana, India, Mexico, Russia, and South Africa between 2007 and 2010. Based on the World Bank classification at the time of the survey, Ghana was the only low-income country, and China and India were lower middle-income countries although China became an upper middle-income country in 2010. The remaining countries were upper middle-income countries. Details of the survey methodology have been published elsewhere [22]. In brief, in order to obtain nationally representative samples, a multistage clustered sampling design method was used. The sample consisted of adults aged ≥18 years with oversampling of those aged ≥50 years. Following a common research protocol across countries, trained interviewers conducted face-to-face interviews using a standard questionnaire to collect information. The questionnaires were translated from English into the local languages, following the WHO translation guidelines. All interviews in Mexico were completed using a computer-assisted personal interview (CAPI), while a paper and pencil interview (PAPI) was used in the remaining countries with the exception of China where both CAPI and PAPI were used. The interviewers also conducted measurements of weight, height, and blood pressure. A stadiometer and a routinely calibrated electronic weighting scale were used to measure height and weight respectively. Blood pressure was measured three times with a one-minute interval using a Boso Medistar Wrist Blood Pressure Monitor Model S.

If a respondent was unable to undertake the interview because of limited cognitive function, then a separate questionnaire was administered to a proxy respondent. These individuals were not included in the current study. The survey response rate ranged from 51% (Mexico) to 93% (China). Sampling weights were constructed to adjust for the population structure as reported by the United Nations Statistical Division. Ethical approval was obtained from the WHO Ethical Review Committee and local ethics research review boards. Written informed consent was obtained from all participants.

2.2. Perceived stress (Outcome)

In line with previous publications [14,23,24], we assessed perceived stress in the last month with the use of two questions which were taken from the Perceived Stress Scale [25]. This validated scale has been widely used to measure perceived stress worldwide. The questions asked were: "How often have you felt that you were unable to control the important things in your life?"; and "How often have you found that you could not cope with all the things that you had to do?" The answer options to these questions were: never (score = 1), almost never (score = 2), sometimes (score = 3), fairly often (score = 4), very often (score = 5). As in a previous study which used the identical questions to measure perceived stress [14], we conducted factor analysis with polychoric correlations to incorporate the covariance structure of the answers provided for individual questions measuring a similar construct. The principal component method was used for factor extraction, while factor scores were obtained using the regression scoring method. These factor scores were later converted to scores ranging from 0-100 with higher values indicating higher levels of perceived stress [14].

Table 1
Sample characteristics

Characteristic	Category	Overall	China	Ghana	India	Mexico	Russia	South Africa
Age (years)	50-59	46.4	44.9	39.7	48.6	48.1	45.2	49.9
	60-69	30.0	31.9	27.5	30.9	25.6	24.6	30.6
	70-79	18.2	18.6	23.1	16.0	17.8	21.8	14.0
	≥80	5.4	4.6	9.7	4.5	8.6	8.4	5.5
	Mean (SD)	62.4 (16.0)	62.6 (16.7)	64.4 (19.9)	61.5 (13.7)	63.0 (18.9)	63.9 (15.4)	61.6 (18.4)
Sex	Male	47.9	49.8	52.4	51.0	46.8	38.9	44.1
	Female	52.1	50.2	47.6	49.0	53.2	61.1	55.9
Education	≤Primary	57.4	63.0	75.3	76.1	79.6	7.5	71.4
	Secondary	35.2	32.5	21.1	18.8	12.3	74.2	22.8
	≥Tertiary	7.4	4.5	3.6	5.1	8.1	18.2	5.7
Wealth	Poorest	17.1	16.3	18.2	18.2	15.3	16.2	20.7
	Poorer	19.0	18.1	19.1	19.5	24.7	19.6	19.9
	Middle	19.5	20.5	20.5	18.8	16.8	19.1	18.2
	Richer	21.3	23.4	20.7	19.6	16.6	20.5	19.8
	Richest	23.1	21.8	21.6	23.9	26.6	24.6	21.3
Type of chronic condition	Angina	17.6	9.4	12.8	17.0	6.7	37.3	8.9
	Arthritis	29.5	26.7	26.2	27.9	14.5	38.2	30.6
	Asthma	7.9	4.3	5.0	12.5	4.9	6.5	7.7
	Cataract	27.3	14.2	18.1	47.4	25.8	20.3	6.4
	Chronic back pain	8.6	5.6	7.5	9.6	8.4	13.0	5.7
	COPD	15.8	11.3	3.7	17.2	13.2	24.4	7.4
	Depression	7.7	1.3	8.0	16.0	16.9	5.6	4.8
	Diabetes	6.8	6.6	3.8	6.9	17.6	7.0	9.2
	Edentulism	12.9	9.1	3.0	15.1	21.7	18.1	8.5
	Hearing problem	5.6	5.5	2.9	5.6	9.3	6.1	5.0
	Hypertension	55.0	60.6	59.6	37.5	61.9	72.1	78.3
	Obesity	11.6	6.0	10.5	2.8	28.5	32.0	47.1
	Stroke	3.0	3.0	2.8	2.0	4.3	4.8	4.0
Number of chronic conditions	0	16.4	19.1	18.0	16.6	7.6	12.6	6.8
	1	27.0	35.0	34.4	24.3	25.2	16.3	28.4
	2	22.6	23.5	26.6	22.3	27.9	19.6	31.3
	3	14.9	12.2	13.1	16.2	22.1	17.4	14.7
	≥4	19.2	10.2	7.9	20.6	17.2	34.0	18.9
Multimorbidity	≥2 Chronic conditions	56.6	46.0	47.6	59.1	67.2	71.0	64.9

Abbreviation: SD Standard Deviation. COPD Chronic Obstructive Pulmonary Disease.
Data are weighted percentages unless otherwise stated.

2.3. Chronic conditions and multimorbidity (Exposures)

We included all 13 chronic conditions (angina, arthritis, asthma, cataract, chronic back pain, COPD, depression, diabetes, edentulism, hearing problems, hypertension, obesity, stroke) for which data was available in the SAGE. These conditions have been included in previous studies on multimorbidity [14,26]. Chronic back pain was defined as having had back pain everyday during the last 30 days. Respondents who answered affirmatively to the question "Have you lost all of your natural teeth?" were considered to have edentulism. The participant was considered to have hearing problems if the interviewer observed this condition during the survey. Hypertension was defined as having at least one of the following: systolic blood pressure ≥140 mmHg; diastolic blood pressure ≥90 mmHg; or self-reported diagnosis. We used the mean of the available measurements for blood pressure. Obesity was defined as BMI ≥ 30 kg/m^2 based on measured weight and height. Diabetes and stroke were solely based on lifetime self-reported diagnosis (Actual question can be found in Web Appendix eTable 1).

For other conditions, the participant was considered to have the condition in the presence of either one of the following: self-reported diagnosis (eTable 1); or symptom-based diagnosis based on algorithms (Details on the algorithms are available in Web Appendix eTable 2). We used these algorithms, which have been used in previous studies using the same dataset, to detect undiagnosed cases [26,27]. Specifically, the validated Rose questionnaire was used for angina [28], and other previously validated symptom-based algorithms were used for arthritis, asthma, and COPD [27,29]. Questions based on the World Mental Health Survey version of the Composite International Diagnostic Interview [30] were used for the endorsement of DSM-IV depression [31]. The total number of chronic conditions was calculated and categorized as 0, 1, 2, 3, and ≥4. Multimorbidity was defined as ≥2 chronic conditions, in line with previously used definitions [26].

2.4. Control variables

These included age (50-59, 60-69, 70-79, ≥80 years), sex, education, and wealth. Education was based on the highest level of education completed and was categorized as primary or less, secondary, and tertiary or higher. Wealth quintiles were created based on country-specific income.

2.5. Statistical analysis

The statistical analysis was performed with Stata 14.1 (Stata Corp LP, College station, Texas). The analysis was restricted to those aged ≥50 years given the focus of this study on older individuals. We conducted multivariable linear regression analysis to assess the association between the number of chronic conditions including multimorbidity (≥2 chronic conditions) or each of the 13 chronic conditions (exposure variables) and perceived stress score (outcome) using the overall and country-wise samples. All models were adjusted for sex, age, education, and wealth [14]. The model using the overall sample was additionally adjusted for country by including dummy variables for each country [32]. For the analyses on the individual chronic conditions, we also adjusted for the presence of other illnesses in order to address confounding by comorbid chronic conditions [14]. The variable on other illnesses included information on whether the individual had any other chronic conditions apart from the chronic condition in question (Y/N).

In order to assess the between-country heterogeneity that may exist in the association between multimorbidity and perceived stress, we

calculated the Higgins' I^2 based on estimates for each country. The Higgins' I^2 represents the degree of heterogeneity that is not explained by sampling error with a value of < 40% often considered as negligible and 40-60% as moderate heterogeneity [33]. A pooled estimate was obtained by random-effect meta-analysis.

All variables were included in the models as categorical variables with the exception of the perceived stress score (continuous variable). Under 5% of the data were missing for all the variables used in the analysis with the exception of number of chronic diseases (7.4%). No attempts to impute missing data were made, as we did not have information about whether these data are missing at random [34]. Thus, complete-case analysis was done. The sample weighting and the complex study design were taken into account in all analyses with the use of the Taylor linearization method. Results from the linear regression models are presented as unstandardized b-coefficients with 95% confidence intervals (CIs). The level of statistical significance was set at $p < 0.05$.

3. Results

After restricting to those aged ≥50 years, the sample size was 34,129 (China 13,175; Ghana 4,305; India 6,560; Mexico 2,313; Russia 3,938; South Africa 3,838). The overall mean (SD) age was 62.4 (16.0) years and 52.1% were females (Table 1). The mean age was similar across countries but the proportion of females was high in Russia (61.1%). The prevalence of individual chronic conditions ranged widely between countries [e.g., depression 1.3% (China) to 16.9% (Mexico); Obesity 2.8% (India) to 47.1% (South Africa)].

The overall prevalence of multimorbidity was 56.6% (95%CI = 55.0%-58.2%) and ranged from 46.0% (China) to 71.0% (Russia). A linear increase in the levels of perceived stress with increasing numbers of chronic conditions was observed in all the samples with the exception of that of Mexico and South Africa (Fig. 1). In the overall adjusted model, compared to those with no chronic conditions, higher numbers of chronic conditions were significantly associated with higher stress levels in a dose-dependent fashion (Table 2). Similar trends were observed for China, Ghana, and India. In Mexico and South Africa, only the highest number of chronic conditions was significantly associated with higher mean stress scores, while no significant associations were observed in Russia (Table 2).

The country-wise adjusted estimates of the associations between multimorbidity and perceived stress are illustrated in Fig. 2. Multimorbidity was associated with significantly higher stress levels in all countries (especially India and Ghana) with the exception of Russia and Mexico, with a moderate level of heterogeneity being observed (I^2 = 54.6%). In terms of the individual chronic conditions, after adjustment, in the overall sample, all conditions were significantly associated with higher stress levels with the exception of edentulism, hypertension, and obesity (Table 3). Particularly high mean stress scores were observed for depression, stroke, and hearing problems. Depression was the only condition significantly associated with higher stress levels across all countries, while hypertension and obesity were not significantly associated with stress in any of the countries. For other conditions, there was a wide variation in the magnitude of the associations.

4. Discussion

To the best of our knowledge, the current paper is the first multinational study specifically in older adults that has investigated the relationship between perceived stress and chronic conditions and multimorbidity. Overall, in our sample of individuals aged ≥50 years from six LMICs, we identified that over a half had multimorbidity, and greater numbers of chronic conditions were associated with higher levels of stress in a dose-dependent fashion. Moreover, we identified that notably high perceived stress was evident for depression, stroke, and hearing problems in the overall sample with the association between depression being consistent across all countries. However, hypertension and obesity were not significantly associated with stress in any of the countries. For most conditions, interestingly, we noted some geographical variations in the relationship with perceived stress. The countrywide meta-analysis indicated a moderate level of between-country heterogeneity in the relationship between perceived stress and multimorbidity. Our results are broadly similar to a previous publication [14] considering perceived stress and multimorbidity across all ages in LMICs, which also found evidence of a dose response

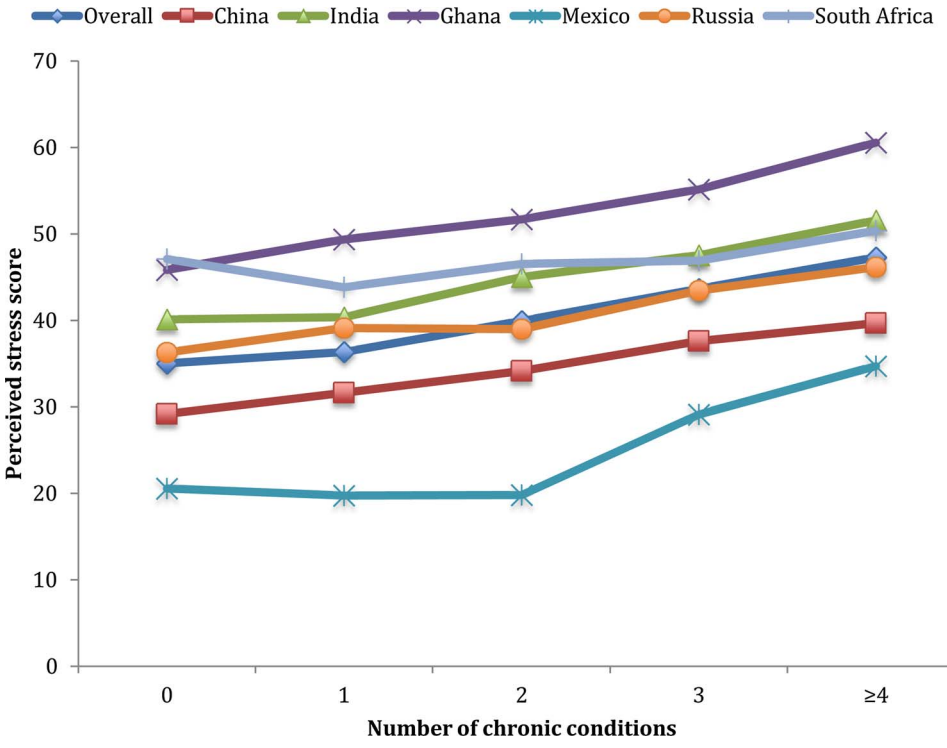

Fig. 1. Mean perceived stress score by the number of chronic conditions and country.
The perceived stress score ranged from 0 to 100 with higher scores indicating higher levels of perceived stress.
Estimates are based on weighted data.

Table 2
The association of number of chronic conditions and sociodemographic characteristics with perceived stress estimated by multivariable linear regression

Characteristic	Category	Overall	China	Ghana	India	Mexico	Russia	South Africa
Number of chronic conditions	0	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	1	1.05 [-0.27,2.37]	1.84** [0.59,3.08]	4.03*** [1.81,6.25]	0.39 [-2.43,3.21]	0.63 [-7.17,8.44]	1.59 [-1.79,4.96]	-1.19 [-6.96,4.59]
	2	3.30*** [1.78,4.82]	3.73*** [2.08,5.37]	6.65*** [4.32,8.97]	4.23** [1.40,7.06]	-0.25 [-7.16,6.67]	0.57 [-3.70,4.83]	1.03 [-4.93,6.99]
	3	6.03*** [4.35,7.71]	6.34*** [4.47,8.21]	9.44*** [6.34,12.54]	7.03*** [3.62,10.45]	8.37 [-0.31,17.05]	3.15 [-1.30,7.59]	3.16 [-2.97,9.30]
	≥4	8.59*** [6.09,11.09]	7.98*** [5.90,10.07]	14.69*** [11.24,18.13]	10.59*** [7.17,14.00]	13.58*** [5.93,21.23]	4.82 [-2.31,11.95]	6.78* [0.17,13.39]
Age (years)	50-59	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	60-69	0.54 [-0.65,1.72]	-0.55 [-1.78,0.68]	0.70 [-1.04,2.43]	0.45 [-1.38,2.27]	-0.77 [-6.43,4.89]	3.57 [-0.24,7.39]	2.57 [-0.94,6.09]
	70-79	1.92* [0.25,3.60]	1.06 [-0.68,2.80]	1.83 [-0.34,4.00]	0.42 [-2.18,3.01]	-2.22 [-8.97,4.52]	7.85*** [3.29,12.41]	1.20 [-3.96,6.36]
	≥80	4.87*** [2.58,7.17]	2.46 [-0.45,5.36]	7.06*** [3.37,10.75]	3.33 [-1.21,7.87]	-2.42 [-7.89,3.04]	12.36*** [7.44,17.28]	2.07 [-5.57,9.71]
Sex	Male	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	Female	1.26* [0.03,2.50]	2.92*** [1.91,3.93]	0.49 [-1.17,2.15]	-1.01 [-3.19,1.17]	2.07 [-3.36,7.49]	3.58 [-0.01,7.16]	-1.11 [-4.34,2.12]
Education	≤Primary	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	Secondary	-1.78** [-3.12,-0.45]	-0.58 [-2.00,0.85]	-3.20** [-5.46,-0.93]	-1.21 [-3.82,1.40]	2.85 [-5.38,11.07]	-3.84* [-7.64,-0.03]	-2.15 [-6.47,2.18]
	≥Tertiary	-1.68 [-4.21,0.86]	0.20 [-2.95,3.34]	-6.35** [-11.05,-1.64]	-3.94 [-8.36,0.48]	-0.52 [-12.87,11.82]	-2.99 [-8.27,2.29]	-3.04 [-9.50,3.43]
Wealth	Poorest	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
	Poorer	-3.32*** [-5.22,-1.42]	-3.13*** [-4.61,-1.65]	-0.99 [-3.11,1.14]	-3.17* [-5.96,-0.38]	-6.96 [-14.28,0.36]	-3.52 [-10.48,3.44]	-4.39 [-9.41,0.64]
	Middle	-4.68*** [-6.39,-2.98]	-6.76*** [-8.75,-4.76]	-2.61* [-5.12,-0.10]	-5.70*** [-9.06,-2.33]	-0.11 [-8.82,8.60]	1.23 [-2.55,5.01]	-8.34** [-13.49,-3.19]
	Richer	-7.99*** [-9.70,-6.29]	-9.35*** [-11.10,-7.60]	-5.37*** [-7.96,-2.78]	-10.23*** [-13.21,-7.24]	-7.39* [-13.08,-1.69]	0.03 [-4.20,4.27]	-13.19*** [-18.84,-7.54]
	Richest	-12.49*** [-14.68,-10.30]	-13.56*** [-15.58,-11.54]	-7.22*** [-10.27,-4.17]	-16.34*** [-20.41,-12.27]	-4.83 [-10.98,1.31]	-1.98 [-7.06,3.10]	-16.57*** [-22.05,-11.09]

Abbreviation: Ref. Reference category
Data are b-coefficient [95% confidence intervals].
Models are mutually adjusted for all variables in the Table. The model including all countries (overall) was additionally adjusted for country.
The perceived stress score ranged from 0 to 100 with higher scores indicating higher levels of perceived stress.
*p < 0.05, ** p < 0.01, *** p < 0.001.

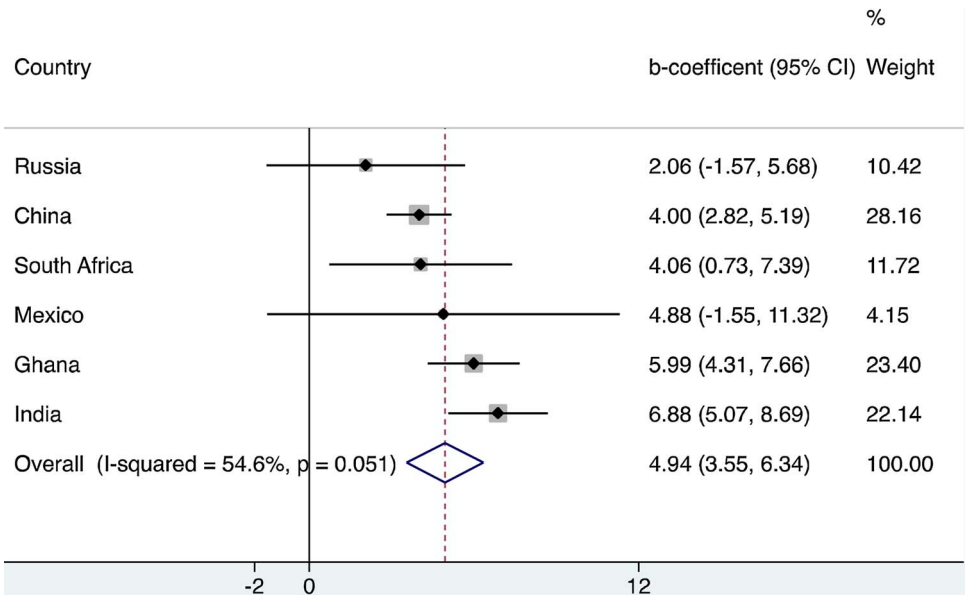

Fig. 2. Country-wise associations between multimorbidity and perceived stress (outcome) estimated by multivariable linear regression.
Abbreviation: CI Confidence Interval
Models were adjusted for age, sex, wealth, and education.
Multimorbidity was defined as ≥2 chronic conditions.
The perceived stress score ranged from 0 to 100 with higher scores indicating higher levels of perceived stress.
The overall estimate was obtained by random-effect meta-analysis.

relationship between an increasing number of chronic conditions and higher perceived stress. Regarding individual chronic conditons, both studies found a strong relationship between perceived stress and depression and asthma.

In terms of the individual chronic conditions, the finding that depression was the only consistent chronic condition that was associated with perceived stress in all countries may not be surprising. Depression is known to negatively impact an individual's ability to cope with life, and stress may actually precede the onset of an episode of depression [42]. Alternatively, lack of social support may underlie both

Table 3
The association between the individual chronic conditions and perceived stress estimated by multivariable linear regression

Chronic condition	Overall	China	Ghana	India	Mexico	Russia	South Africa
Angina	2.36*	5.32***	1.91	2.51*	11.84**	-0.91	5.80
	[0.36,4.36]	[3.43,7.20]	[-0.25,4.07]	[0.12,4.91]	[4.38,19.31]	[-4.98,3.17]	[-0.26,11.86]
Arthritis	1.97**	1.60**	4.48***	2.91**	3.19	-0.69	7.16***
	[0.53,3.42]	[0.53,2.68]	[2.50,6.46]	[1.13,4.68]	[-1.48,7.86]	[-5.45,4.07]	[4.12,10.19]
Asthma	5.65***	6.24***	2.68	4.72***	7.68**	4.72*	11.02***
	[3.87,7.44]	[3.58,8.90]	[-0.57,5.92]	[1.97,7.47]	[2.16,13.19]	[1.08,8.37]	[5.64,16.40]
Cataract	3.01***	0.03	5.73***	3.51**	7.82**	4.35**	-0.23
	[1.61,4.41]	[-1.58,1.63]	[3.47,7.99]	[1.19,5.82]	[1.91,13.73]	[1.79,6.91]	[-6.26,5.80]
Chronic back pain	3.67**	4.77***	8.49***	4.61**	5.47	1.38	6.63
	[1.47,5.88]	[2.04,7.50]	[4.18,12.80]	[1.14,8.08]	[-0.60,11.55]	[-2.46,5.21]	[-0.76,14.02]
COPD	4.68***	1.36	6.32*	6.06***	8.50**	5.44***	6.28*
	[3.44,5.92]	[-0.37,3.09]	[1.21,11.44]	[3.93,8.20]	[2.43,14.56]	[2.74,8.14]	[0.22,12.34]
Depression	9.31***	16.49***	9.60***	7.82***	13.65***	9.74***	18.91***
	[6.10,12.52]	[12.15,20.84]	[6.84,12.35]	[3.77,11.88]	[6.85,20.46]	[5.76,13.72]	[11.84,25.97]
Diabetes	2.78**	1.51	3.38	2.97	4.21	7.14**	-3.70
	[0.78,4.77]	[-1.18,4.20]	[-0.17,6.93]	[-0.65,6.58]	[-1.42,9.84]	[2.04,12.23]	[-8.72,1.32]
Edentulism	0.92	3.13***	9.22***	0.98	2.69	-0.86	-0.29
	[-0.83,2.67]	[1.34,4.92]	[4.41,14.02]	[-1.58,3.53]	[-3.86,9.25]	[-4.23,2.50]	[-5.89,5.31]
Hearing problem	6.75***	5.33***	5.54*	6.87*	16.36***	10.48***	1.16
	[4.18,9.32]	[3.10,7.57]	[0.76,10.32]	[1.41,12.33]	[9.03,23.69]	[4.67,16.28]	[-8.03,10.35]
Hypertension	0.29	0.73	1.39	1.16	-2.35	-0.80	-2.10
	[-0.60,1.19]	[-0.25,1.71]	[-0.13,2.91]	[-0.53,2.85]	[-8.57,3.87]	[-3.62,2.03]	[-4.94,0.75]
Obesity	1.09	0.30	-0.11	2.38	-4.23	1.30	0.87
	[-1.24,3.43]	[-1.53,2.13]	[-2.78,2.55]	[-1.62,6.38]	[-10.34,1.87]	[-3.04,5.65]	[-2.41,4.15]
Stroke	7.64***	11.68***	10.35***	5.30	1.20	4.54	4.69
	[5.03,10.25]	[8.01,15.35]	[5.28,15.41]	[-1.40,12.00]	[-5.62,8.02]	[-0.35,9.43]	[-2.68,12.06]

Abbreviation: COPD Chronic Obstructive Pulmonary Disease
Data are b-coefficient [95% confidence intervals].
Models are adjusted for sex, age, wealth, education, and other illnesses. The model including all countries (overall) was additionally adjusted for country.
The perceived stress score ranged from 0 to 100 with higher scores indicating higher levels of perceived stress.
*p < 0.05, ** p < 0.01, *** p < 0.001.

depression and perceived stress [43]. Moreover, depression is known to be associated with a range of changes in inflammation [44,45] which may potentially account for this observed relationship. One should also consider that the strong relationship between depression and stress may in part be accounted for by some overlap in core symptoms [46]. Finally, depression itself is associated with increased cardiovascular disease [47], which in turn is *per se* associated with higher perceived stress.

For all chronic conditions, it is also possible that the symptoms of the diseases *per se* or the associated disability increase stress levels by restricting an individual's ability to engage in daily activities etc. Alternatively, for some diseases such as stroke and cardiovascular disease, previous studies have shown that perceived stress may lead to the future occurrence of these conditions [48]. It may also be that the high treatment costs associated with some of these conditions lead to high levels of stress, although no study has investigated such an association. The reasons for the between-country differences in the association between some physical conditions and stress are unknown, but it may partly be explained by differences in insurance coverage, availability of treatment, and years lived with disability. For example, in some countries such as India, out-of-pocket payment and catastrophic expenditure for health care is common, and it is possible that having a chronic condition is particularly stressful in this setting due to the economic consequences [49]. In addition, in some counties where there may be high treatments costs, it is conceivable that patients forgo needed treatment, in particular when there is a need for multiple medications, which are often prescribed to treat chronic diseases and multimorbidity. Untreated chronic conditions may increase the severity of the chronic condition or lead to further complications, which may increase levels of perceived stress. Next, it is also possible that treatment options are limited especially in resource-limited settings and that the same condition may not result in the same level of disability and stress in all settings. For example, in the case of edentulism, dentures and dental implants, which are known to substantially improve the negative consequences of edentulism, may be prohibitively expensive or unavailable in some settings. It is also worthy of noting that we found no evidence in any country of a relationship between perceived stress and hypertension or obesity. This may be of no surprise given that of all the chronic conditions assessed, these are the only two which may potentially be asymptomatic. Nonetheless, a previous small (n = 101) study among low income females in the United States found that perceived stress was associated with excessive eating behaviors and poor diet [50]. However, the availability of poor quality and excessive food, commonly associated with obesity in western cultures, may not be so widely available and used as a coping mechanism in LMICs.

The current study is cross sectional an no causal inferences can be ascertained from our data and an important first step is to conduct prospective research to disentangle the relationship between multimorbidity and stress. However, several hypotheses can be suggested regarding the underlying mechanisms of this association. First, chronic stress is known to lead to neuroendocrine dysregulation of the hypothalamic-pituitary-adrenal axis, which in turn may cause changes in the immune and inflammation system, and consequently lead to the development of chronic conditions and multimorbidity [35], commonly conceptualized as allostatic load [36,37]. Even subclinical perceived stress has been linked to changes in cortisol levels, the immune system response, and cortical reactivity [38]. Such processes may underpin the relationship between stress and chronic conditions such as stroke. Finally, perceived stress may also lead to unhealthy behaviors, such as smoking, excess alcohol consumption, unhealthy dietary choices [39,40] and physical inactivity [41], which might also be implicated in the development of chronic conditions and multimorbidity and the associated perceived stress may lead to an increased inflammatory response. Alternatively, chronic conditions and multimorbidity may lead to difficulties undertaking ADL and social restriction which may increase perceived stress. Clearly future longitudinal research is therefore required to better understand the directionality of the relationships we observed and specifically the impact of lifestyle on the stress and

chronic condition trajectory.

Multimorbidity was associated with higher levels of stress in all countries although this relationship was not significant in Russia and Mexico. The meta-analysis showed a moderate level of heterogeneity between countries. This between-country difference may be related with the factors mentioned above such as the availability of health insurance and differing levels of disability associated with the conditions between countries [49]. Apart from these factors, in the case of multimorbidity, it is also likely that the combination of the diseases differed and that that led to a difference in its magnitude of association with stress. A previous study using the same dataset showed that there are distinct patterns of multimorbidity in different countries and that, for instance, a mental-articular pattern is common in China, Ghana and India [26]. Furthermore, based on our finding that there was a large between-country variation in the prevalence of hypertension and obesity, which are conditions unrelated with stress in the current study, we also hypothesized that the association between multimorbidity and stress may have been attenuated especially in countries such as Mexico, Russia, and South Africa where the prevalence of these conditions were particularly high [26]. In order to assess the extent to which the prevalence of obesity and hypertension influenced the between-country differences, we conducted a sensitivity analysis by excluding obesity and hypertension when counting the number of chronic conditions. The results indicate that the strength of the association increased in all countries, especially Mexico, although the association remained non-significant in Russia (Appendix eFigure 1).

Clearly, our research adds to the growing calls for healthcare systems to adapt to the rising issue of multimorbidity and poor mental health. Moreover, perceived stress is associated with increased mortality in those with multimorbidity in Western cultures [11] and it is likely that this combination adds to worse outcomes in LMICs also. Addressing this issue is a unique challenge in LMICs, where resources are often sparse and care may be fragmented. An important first step is raising awareness of the importance of considering chronic conditions and perceived stress among primary and mental health care providers in LMICs, and our research suggests that depression is in particular associated with perceived stress. Better communication with health professionals to identify those with multimorbdity and stress is essential. Future research should seek to identify people with chronic conditions and develop integrated care pathways. Low cost, population level interventions, such as developing a healthy lifestyle may play a pivotal role in the prevention and also management of chronic conditions and ultimately multimorbidity. Moreover, such interventions, including physical activity may also help alleviate stress levels [51]. Given the cross-sectional nature of our work, prospective research should also attempt to disentangle the directionality of the relationships we observed.

Whilst our research is novel, a number of limitations should be noted. The primary limitation is that we cannot deduce the directionality of the associations we observed in our study. Second, whilst we included 13 chronic conditions in our study, clearly there may be additional chronic diseases that were not covered by the SAGE database that we did not identify. In particular, we did not have information on HIV, which is known to be particular prevalent and deleterious for people in LMICs [52] and perceived stress [53]. In addition, we did not have information on important geriatric syndromes such as malnutrition or frailty. Thus, future research is required to investigate the relationship with these outcomes and perceived stress. Third, whilst the use of self-report medical diagnoses is valid in western settings, the validity and reliability in LMICs has not been fully established [26]. Nonetheless, despite the aforementioned, our study is the first multinational study to investigate the relationship between perceived stress and chronic conditions/multimorbidity in older adults. Furthermore, the study used nationally representative data from six countries which represent a large proportion of the world population, while it included a large number of chronic conditions.

5. Conclusion

Our study illustrates that older individuals with chronic conditions or multimorbidity are exposed to higher levels of stress in LMICs although some between-country differences exist. Given that previous research has demonstrated that perceived stress and chronic conditions are collectively associated with worse outcomes, our findings highlight the growing need to develop low cost, population-level integrated interventions to address stress among those with chronic conditions in this region.

Contributors

All authors contributed to the conception and design of the study, the data analysis and interpretation, and the writing of the paper. BS and DV are joint first authors.

Conflict of interest

The authors declare that they have no conflict of interest.

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Ethical approval

This project is a secondary analysis of a publically available data set. Ethical approval was obtained from the WHO Ethical Review Committee and local ethics research review boards. Written informed consent was obtained from all participants.

Provenance and peer review

This article has undergone peer review.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.maturitas.2017.10.007.

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