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Association of Symptoms of Depression With Cardiovascular Disease and Mortality in Low-, Middle-, and High-Income Countries

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IMPORTANCE Depression is associated with incidence of and premature death from cardiovascular disease (CVD) and cancer in high-income countries, but it is not known whether this is true in low- and middle-income countries and in urban areas, where most people with depression now live.

OBJECTIVE To identify any associations between depressive symptoms and incident CVD and all-cause mortality in countries at different levels of economic development and in urban and rural areas.

DESIGN, SETTING, AND PARTICIPANTS This multicenter, population-based cohort study was conducted between January 2005 and June 2019 (median follow-up, 9.3 years) and included 370 urban and 314 rural communities from 21 economically diverse countries on 5 continents. Eligible participants aged 35 to 70 years were enrolled. Analysis began February 2018 and ended September 2019.

EXPOSURES Four or more self-reported depressive symptoms from the Short-Form Composite International Diagnostic Interview.

MAIN OUTCOMES AND MEASURES Incident CVD, all-cause mortality, and a combined measure of either incident CVD or all-cause mortality.

RESULTS Of 145 862 participants, 61 235 (58%) were male and the mean (SD) age was 50.05 (9.7) years. Of those, 15 983 (11%) reported 4 or more depressive symptoms at baseline. Depression was associated with incident CVD (hazard ratio [HR], 1.14; 95% CI, 1.05-1.24), all-cause mortality (HR, 1.17; 95% CI, 1.11-1.25), the combined CVD/mortality outcome (HR, 1.18; 95% CI, 1.11-1.24), myocardial infarction (HR, 1.23; 95% CI, 1.10-1.37), and noncardiovascular death (HR, 1.21; 95% CI, 1.13-1.31) in multivariable models. The risk of the combined outcome increased progressively with number of symptoms, being highest in those with 7 symptoms (HR, 1.24; 95% CI, 1.12-1.37) and lowest with 1 symptom (HR, 1.05; 95% CI, 0.92 -1.19; *P* for trend < .001). The associations between having 4 or more depressive symptoms and the combined outcome were similar in 7 different geographical regions and in countries at all economic levels but were stronger in urban (HR, 1.23; 95% CI, 1.13-1.34) compared with rural (HR, 1.10; 95% CI, 1.02-1.19) communities (*P* for interaction = .001) and in men (HR, 1.27; 95% CI, 1.13-1.38) compared with women (HR, 1.14; 95% CI, 1.06-1.23; *P* for interaction < .001).

CONCLUSIONS AND RELEVANCE In this large, population-based cohort study, adults with depressive symptoms were associated with having increased risk of incident CVD and mortality in economically diverse settings, especially in urban areas. Improving understanding and awareness of these physical health risks should be prioritized as part of a comprehensive strategy to reduce the burden of noncommunicable diseases worldwide.

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Supplemental content

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The Sustainable Development Goals aim to reduce premature mortality from noncommunicable diseases (NCDs) by 30% and improve mental well-being worldwide by 2030.[1] These goals are inextricably linked, and otherwise healthy people with depression have been shown to experience increased risks of incident cardiovascular disease (CVD),[2] cancers,[3,4] and mortality[5] (eTable in the Supplement). Yet, these relationships have been studied almost exclusively in high-income countries[5,6] and in China,[7,8] with a recent multicountry meta-analysis[2] reporting no prospective studies for depression from elsewhere. Even if the associations with CVD and mortality are real in high-income countries, they cannot necessarily be generalized to low- and middle-income countries, where most of the global burden of NCDs and mental disorders exists.[9,10] First, any underlying mechanisms are likely to involve complex behavioral and metabolic pathways[11] (associated with increased smoking behaviors, diabetes, and hypertension for example) that may vary by setting. Second, few people receive treatment that might modify any association in these countries.[12] Despite initiatives to scale-up mental health services worldwide,[13-16] the physical health outcomes of people with depression in resource-poor settings remain a neglected area, and it is therefore crucial for health service planning that we research CVD incidence and mortality in people with depression in these settings. Another especially important question is whether these associations vary between urban and rural settings, given that rapid urbanization is associated with erosion of protective factors for depression such as traditional social support[17] and healthy behaviors.[18,19]

Using data from the Prospective Urban Rural Epidemiological (PURE) study, with standardized information on baseline depression and subsequent physical health outcomes from 21 countries, we ask whether associations reported previously from high-income countries can be found in low- and middle-income countries and in urban and rural areas.

Key Points

Question Does the increased risk of incident cardiovascular disease and mortality in middle-aged adults with depressive symptoms vary across and within countries?

Findings In this cohort study from 21 countries and 145 862 participants, cardiovascular events and death increased by 20% in people with 4 or more depressive symptoms compared with people without. The relative risk increased in countries at all economic levels but was more than twice as high in urban than rural areas.

Meaning Adults with depressive symptoms experience poor physical health outcomes and increased risk of mortality across the world and in different settings, especially in urban areas.

Methods

Study Design and Participants

The design and methods of PURE are described elsewhere[20,21] and in the eMethods in the Supplement. Briefly, PURE is a prospective cohort study in 51 centers in 21 high-, middle-, and low-income countries. When countries joined PURE, we categorized them according to World Bank income groupings, which included 5 low- (Bangladesh, India, Pakistan, Zimbabwe, and Tanzania), 5 lower-middle- (China, the Philippines, Colombia, Iran, and Occupied Palestinian Territory), 7 upper-middle- (Argentina, Brazil, Chile, Malaysia, Poland, South Africa, and Turkey), and 4 high-income countries (Canada, Sweden, United Arab Emirates, and Saudi Arabia) (eMethods in the Supplement). Countries and communities were selected to reflect socioeconomically diverse populations, with broadly representative samples of each community. The final samples were also broadly representative of populations in each country (eMethods in the Supplement). Individuals aged 35 to 70 years with no intention to change address for 4 years were eligible to enroll in the first 2 phases of the PURE core study, which involved detailed baseline data collection and follow-up for subsequent health outcomes. We approached 506 087 individuals from 132 977 households in 997 urban and rural communities, of whom 458 434 (91%) consented to a family census. Of 235 180 who were eligible, 166 762 (71%) enrolled (eMethods in the Supplement). The study was coordinated by the Population Health Research Institute (Hamilton, ON, Canada) and approved by ethics committees at each participating center. Patients provided written informed consent.

Baseline Procedures

Trained field researchers administered standardized, locally translated questionnaires to participants at baseline, recorded anthropometrics, and collected fasting blood samples. The questionnaires included an adapted Short-Form Composite International Diagnostic Interview (CIDI-SF) for major depressive disorders.[22] This has been used previously in large multicountry epidemiologic trials,[23] including in China,[7] and is based on the Composite International Diagnostic Interview (CIDI),[24] which has been validated in low- and middle-income countries.[12] Participants were asked whether they had felt sad, blue, or depressed for 2 weeks or longer in the previous year and if so, whether they experienced loss of interest in pleasurable activities, tiredness, unintentional weight changes, difficulty sleeping or concentrating, feeling worthless, or thoughts about death during the same period. Validation studies from the United States and Canada[25,26] show that 4 or more of these 7 symptoms are predictive of major depressive disorder, and we therefore used this threshold to classify depressive symptoms. We also recorded antidepressant use at baseline and during follow-up.

Follow-up and Outcomes

Three yearly follow-up visits took place between January 2008 and June 2019. At each visit, standardized forms were used to record incident diseases and intervening mortality, using information from household interviews, medical records, death certificates, and other sources. Events were adjudicated centrally in each country (eMethods in the Supplement). Primary outcomes included incidence of major CVD (including

cardiovascular death, myocardial infarction, stroke, or heart failure), all-cause mortality, and a combined outcome, defined as either the incidence of major CVD or all-cause mortality. In secondary analyses, we divided the first 2 categories into incident myocardial infarction, stroke, heart failure and mortality from cardiovascular and noncardiovascular causes, and included incidence of any cancer.

Statistical Analysis

We compared event rates for all outcomes in people with 4 or more and less than 4 depressive symptoms, standardizing directly for the age and sex of the PURE population. Using 2 Cox proportional hazards shared frailty models, we modeled associations between 4 or more depressive symptoms and each outcome, incorporating random intercepts for study center as most clustering was within center or country. In model 1, we adjusted for baseline age, sex, urban/rural residence, educational attainment, use of statins, and self-reported disabilities (0, 1, or ≥2 physical impairments). In model 2, we also included baseline characteristics that were indistinguishable as confounders or mediators including former or current smoking or alcohol use, hypertension, diabetes, and a social isolation index based on the Modified Social Network Index.[27] More detailed descriptions of covariate classifications are in the eMethods in the Supplement. In sensitivity analyses, we adjusted separately for a further 7 variables in addition to those in model 2, including physical inactivity, unhealthy diet,[28] and obesity (where this data was available); relative wealth[29] and adverse life experiences; and antidepressant use. To address concerns about reverse causation, we excluded participants who reported an outcome within 2 years of enrollment, as well as participants who reported chest pain, persistent cough, or jaundice in the 6 months before enrollment, and repeated the analyses for that outcome. We also excluded participants who had been bereaved within the previous year. To determine whether associations with the primary outcomes were dose dependent, we modeled hazard ratios (HRs) for each CIDI-SF score from 1 to 7 (relative to a score of 0), using model 2 and report the *P* value for linear trend.

To study the consistency of the associations between 4 or more depressive symptoms and the combined outcome in different geographical regions; in high-/upper-middle-income countries and lower-middle-/low-income countries; and in urban and rural residents, we compared HRs derived from models 1 and 2, examining coefficients for modifiable risk factors and performing tests for interactions between depression and each setting. To account for potential crosscountry differences in symptom reporting,[30] we also modeled associations between both CIDI-SF score (as a continuous variable) and the presence of 4 or more depressive symptoms (as a binary variable) with the combined outcome in each country, adjusting minimally for age and sex.

Finally, we examined the consistency of the associations between depressive symptoms and CVD, mortality, and the combined outcome in subgroups determined by age, sex, traditional NCD risk factors, and social determinants, again performing tests for interaction in each case. Because of multiple comparisons in this analysis, only 2-sided *P* values over .001 were interpreted as showing significant associations. All analyses were conducted using Stata version 15.0 (StataCorp). Analysis began February 2018 and ended September 2019.

Results

Of 166 762 participants, 164 007 (98%) completed at least 1 round of follow-up, while 2553 (2%) were lost before completing any follow-up visits (displayed by country and by visit number in the eMethods in the Supplement). We included 145 862 participants in the final analysis after excluding 1441 (0.9%) without depression data, 13 846 (9.5%) with baseline CVD or cancer, and 1530 (0.9%) without event data (eMethods in the Supplement).

The age-sex standardized prevalence of depressive symptoms in PURE was 11% (n = 15 983) overall, 15% (n = 8213) in high-/upper-middle-income countries, and 8% (n = 7770) in lower-middle-/low-income countries (**Table 1**). As shown in eResults 1 in the Supplement, prevalence ranged from 2% (n = 645) in China to 40% (n = 527) in Occupied Palestinian Territory (although this was an outlier, with all other countries below 30%). eResults 1 in the Supplement also shows that the CIDI-SF demonstrated reasonable internal consistency, with a Cronbach α of .71 and similar symptom ranking between countries. Prevalence was also higher in urban areas (9601 [13%] vs 6382 [9%] in rural areas), in women (11 409 [13%] vs 4574 [7%] in men), in people with 2 or more disabilities (5475 [22%] vs 10 508 [9%] without), and in people with diabetes (1785 [12%] vs 14 198 [11%] without). People with depressive symptoms were also more likely to smoke (2378 [15%] vs 13 277 [10%]), consume alcohol (4610 [30%] vs 31 514 [24%]), eat unhealthily (5608 [38%] vs 38 175 [32%]),[28] be socially isolated (2140 [13%] vs 8650 [7%]),[27] and were more likely to mistrust others (3230 [25%] vs 16 340 [15%]). Of the people who reported depressive symptoms at baseline, 97 (0.6%) reported using antidepressants at the time, while 1359 (9%) used antidepressants during follow-up.

Over a median (interquartile range) follow-up of 9.3 (7.4-10.7) years, there were 9721 deaths and 7258 major cardiovascular events comprising 11 860 occurrences of the combined outcome. Deaths were mostly cardiovascular (2618 [29%]) and cancer related (1844 [20%]), with fewer due to respiratory diseases (627 [7%]), infections (558 [6%]), and injury or suicide (664 [7%]). After direct standardization for age and sex, event rates for all conditions were higher in people with depressive symptoms compared with people without, except for stroke, for which event rates were similar between groups (**Table 2**).

Table 2 also shows that the HRs for all primary outcomes increased between 17% and 20% in people with 4 or more depressive symptoms, after adjustments for demographics, education, use of statins, and disability and including random intercepts for center (model 1). These risks were not markedly attenuated by further adjustments for traditional risk factors and social isolation (model 2) and remained strong and significant for all-cause mortality (HR, 1.17; 95% CI, 1.11-1.25; $P < .001$), major CVD (HR, 1.14; 95% CI, 1.05-1.24; $P = .001$), and

Table 1. Baseline Prevalence of ≥4 Depressive Symptoms and Sample Characteristics

Prevalence	No. (%)	
	Overall (N = 145 862)	Prevalence (≥4 symptoms) (n = 15 983)
Cross-national[a]		
High-/upper-middle-income countries	53 564 (37)	8213 (15)
Low-/lower-middle-income countries	92 298 (63)	7770 (8)
South Asia	31 232 (21)	3782 (12)
Southeast Asia	16 441 (11)	729 (5)
China	42 691 (29)	645 (2)
Sub-Saharan Africa	6032 (4)	1269 (21)
North America and Europe	17 553 (12)	3280 (19)
Middle East	9982 (7)	1842 (19)
South America	21 931 (15)	4436 (20)
Demographic		
Urban	76 931 (53)	9601 (13)
Rural	68 931 (47)	6382 (9)
Male	61 235 (58)	4574 (7)
Female	84 627 (42)	11 409 (13)
Health-related prevalence		
Disabilities		
<2	121 018 (83)	10 508 (9)
≥2[b]	24 844 (17)	5475 (22)
Diabetes		
No	131 281 (90)	14 198 (11)
Yes[c]	14 581 (10)	1785 (12)
Hypertension		
No	88 297 (61)	9693 (11)
Yes[d]	57 415 (39)	6279 (12)
Abdominal obesity		
No	68 883 (50)	7454 (10)
Yes[e]	68 418 (50)	7786 (12)
Physically		
Active	97 402 (18)	10 059 (10)
Inactive[f]	21 659 (82)	1876 (9)

(continued)

Table 1. Baseline Prevalence of ≥4 Depressive Symptoms and Sample Characteristics (continued)

Prevalence	No. (%)	
	Overall (N = 145 862)	Prevalence (≥4 symptoms) (n = 15 983)
Baseline characteristics	<4 Depressive symptoms (n = 129 879)	≥4 Depressive symptoms (n = 15 983)
Age, mean (SD), y	50.2 (9.7)	49.2 (9.3)
Education		
<Secondary level	54 398 (42)	7613 (48)
Secondary level	50 873 (39)	5083 (32)
>Secondary level	24 304 (19)	3310 (21)
Relative wealth		
Low[g]	40 257 (32)	5250 (34)
Average	42 103 (33)	5476 (35)
High	44 261 (35)	4789 (31)
Current smoker	13 277 (10)	2378 (15)
Current alcohol use	31 514 (24)	4610 (30)
Unhealthy diet[h]	38 175 (32)	5608 (38)
Socially isolated[i]	8560 (7)	2140 (13)
Low trust in others[j]	16 340 (15)	3230 (25)
Bereavement (last 12 mo)	12 848 (10)	4293 (27)

[a] Countries were categorized as follows: Southeast Asia (Bangladesh, India, and Pakistan), South Asia (Malaysia and Philippines), China, the Middle East (Saudi Arabia, United Arab Emirates, Iran, and Occupied Palestinian Territory), Sub-Saharan Africa (South Africa, Tanzania, and Zimbabwe), North America and Europe (Canada, Poland, Turkey, and Sweden), and South America (Chile, Argentina, Brazil, and Colombia).

[b] Disabilities: 0, 1, or ≥2 of difficulty grasping, walking, bending, reading, seeing people, speaking/hearing, and using walking aids.

[c] Diabetes: fasting glucose levels, ≥126.13 mg/dL (to convert to millimole per liter, multiply by 0.0555) or previously diagnosed diabetes or use of glucose lowering medications.

[d] Hypertension: systolic blood pressure, >140 mm Hg, diastolic blood pressure, >100 mm Hg/diagnosed with hypertension or taking hypertension medication.

[e] Abdominal obesity: waist to hip ratio, ≥0.9 (men) or ≥0.85 (women).

[f] Physical inactivity: ≤150 minutes of moderate to vigorous physical activity or ≤600 metabolic equivalent minutes of exercise per week.

[g] Relative wealth: thirds of a validated index of household assets and housing characteristics.[29]

[h] Unhealthy diet: score of ≤31 on the Alternative Healthy Eating index.[28]

[i] Social isolation: a score of ≥4 of 5 on a Modified Social Network Index[27] described in the eMethods in the Supplement.

[j] Low trust: the belief that people were generally not honest and helpful and that doing nice things for someone would be unlikely to be reciprocated. Measurement and classification of other key risk factors are described in more detail in the eMethods in the Supplement.

the combined outcome (HR, 1.18; 95% CI, 1.11-1.24; $P < .001$) (Table 2). In secondary analyses, depressive symptoms were also associated with incident myocardial infarction (HR, 1.23; 95% CI, 1.10-1.37) and noncardiovascular death (HR, 1.21; 95% CI, 1.13-1.31). In sensitivity analyses, these estimates were materially unchanged after further adjustments and removal of recently bereaved participants, and we did not find evidence of reverse causation (eResults 2 in the Supplement). Associations with incident heart failure (HR, 1.09; 95% CI, 0.86-1.31), stroke (HR, 1.05; 95% CI, 0.91-1.21), cardiovascular death (HR, 1.07; 95% CI, 0.94-1.22), and cancer (HR, 1.04; 95% CI, 0.94-1.14) were directionally similar but nonsignificant (Table 2).

The relative risks of all primary outcomes increased progressively with the number of depressive symptoms. Accordingly, risks of the combined outcome increased from HR of 1.05 (95% CI, −0.92 to 1.19) in those with 1 symptom to HR of 1.24 (95% CI, 1.12-1.37) in those with 7 symptoms (P for trend < .001) (**Figure 1**).

Table 3 shows the event rates for the combined outcome and HRs associated with depression in each geographical setting for models 1 and 2. It also shows interaction effects for depression × setting and includes the coefficients for each of the key covariates in the model to show their relative contributions in each setting. These results show that context is important and that in certain settings, adjustments (in model 2)

Table 2. Event Rates and Survival Analyses Showing Associations Between ≥4 Depressive Symptoms and Adverse Clinical Outcomes[a]

Characteristic	Hazard ratio (95% CI)		
	<4 Symptoms (n = 129 879)	≥4 Symptoms (n = 15 983)	*P* value
Primary outcomes			
Major CVD			
Events (n = 7258), No. (%)	6507 (89.6)	751 (10.3)	NA
Event rate/1000 person-years (95% CI)	5.7 (5.5-5.8)	6.4 (5.9-6.9)	NA
Model 1[b]	1 [Reference]	1.17 (1.08-1.27)	<.001
Model 2[c]	1 [Reference]	1.14 (1.05-1.24)	.001
Mortality			
Events (n = 9271), No. (%)	8077 (87.1)	1194 (12.9)	NA
Event rate/1000 person-years (95% CI)	6.9 (6.8-7.1)	1.0 (9.4-1.6)	NA
Model 1	1 [Reference]	1.18 (1.11-1.26)	<.001
Model 2	1 [Reference]	1.17 (1.11-1.25)	<.001
Combined outcome[d]			
Events (n = 13 444), No. (%)	11 860 (88.2)	1584 (11.8)	NA
Event rate/1000 person-years (95% CI)	10.3 (10.1-10.5)	13.3 (12.7-14.0)	NA
Model 1	1 [Reference]	1.20 (1.13-1.27)	<.001
Model 2	1 [Reference]	1.18 (1.11-1.24)	<.001
Secondary outcomes			
Myocardial infarction			
Events (n = 3235), No. (%)	2831 (87.5)	404 (12.5)	NA
Event rate/1000 person-years (95% CI)	2.4 (2.3-2.5)	3.6 (3.2-3.9)	NA
Model 2	1 [Reference]	1.23 (1.10-1.37)	NA
Heart failure			
Events (n = 671), No. (%)	582 (86.7)	89 (13.3)	NA
Event rate/1000 person-years (95% CI)	0.5 (0.5-0.5)	0.7 (0.5-0.9)	NA
Model 2	1 [Reference]	1.09 (.86-1.39)	NA
Stroke			
Events (n = 3317), No. (%)	3073 (92.6)	244 (7.3)	NA
Event rate/1000 person-years (95% CI)	2.7 (2.6-2.8)	2.0 (1.7-2.2)	NA
Model 2	1 [Reference]	1.05 (.91-1.21)	NA
Cardiovascular deaths			
Events (n = 2618), No. (%)	2329 (89.0)	289 (11.0)	NA
Event rate/1000 person-years (95% CI)	2.0 (1.9-2.1)	2.5 (2.2-2.8)	NA
Model 2	1 [Reference]	1.07 (.94-1.22)	NA
Noncardiovascular deaths			
Events (n = 6653), No. (%)	5748 (86.4)	905 (13.6)	NA
Event rate/1000 person-years (95% CI)	4.9 (4.8-5.1)	7.5 (7.0-8.0)	NA
Model 2	1 [Reference]	1.21 (1.13-1.31)	NA
Cancer[e]			
Events (n = 4420), No. (%)	3855 (87.2)	565 (12.8)	NA
Event rate/1000 person-years (95% CI)	3.4 (3.3-3.5)	4.4 (4.0-4.8)	NA
Model 2	1 [Reference]	1.04 (.94-1.14)	NA

Abbreviations: CVD, cardiovascular disease; NA, not applicable.

[a] Separate adjustments for physical inactivity, diet (according to the Alternative Healthy Eating score[28]), waist-to-hip ratio, relative wealth, financial insecurity, conflict, and antidepressant use did not markedly influence the associations for any outcome (eResults 2 in the Supplement). A total of 1441 participants had missing depression scores who were younger, were more likely to live in rural areas, and were more likely to be physically inactive. They were also less educated, ate less healthily, and had lower waist-to-hip ratios. After adjustment for these factors, those with missing data were not at a significantly increased risk of major CVD or mortality. Event rates were directly standardized for age and sex in the Prospective Urban Rural Epidemiology (PURE) study population; the group with less than 4 depressive symptoms was used as the reference group in each Cox proportional hazards model; *P* values are displayed for primary outcomes only.

[b] Model 1 was adjusted for age, sex, educational attainment, urban/rural residence, use of statins, and 1 or ≥2 disabilities and included random intercepts for study center.

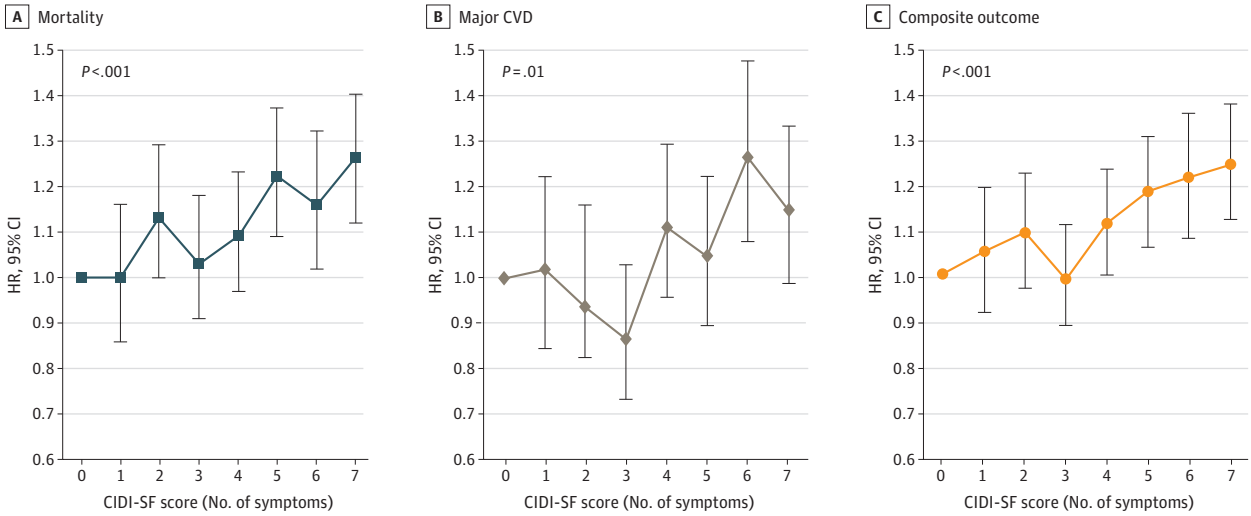
[c] Model 2 was also adjusted for former and current smoking and alcohol use, hypertension, diabetes, and social isolation index (based on the modified Social Network Index [eMethods in the Supplement]).

[d] The combined outcome was defined by the first of either a major cardiovascular event or death.

[e] Hypertension was omitted from Model 2 for cancer because it was not expected to be associated with cancer incidence.

for smoking, alcohol use, hypertension, diabetes, and social isolation led to a 25% to 30% attenuation in the strength of the associations between depression and the combined outcome in specific areas. These settings included the Middle East; North America and Europe; South America; and high-/upper-middle-income countries as well as urban areas. This was mostly attributable to diabetes but not tobacco or alcohol use. Conversely, in other geographical regions, in low-/lower-middle-income countries, and in rural areas, where these risk factors were less common (eResults 3 and 4 in the Supplement), the same adjustments did not attenuate the strength of these associations. Despite these differences, the HRs for depression were similar in all geographical regions (*P* for interaction = .56) and in both country income groups (*P* for interaction = .52) but increased by 2 times in urban (HR, 1.23; 95% CI, 1.13-1.34) compared with rural communities (HR, 1.10; 95% CI, 1.02-1.19; *P* for interaction = .001). The relative contributions of other covariates were fairly similar in different settings.

Figure 1. Associations Between Number of Depressive Symptoms and Primary Outcomes



Relative risks of incident cardiovascular disease (CVD), mortality, and the combined outcome (the first of either incident CVD or death) increased with the number of symptoms of depression. Participants who were either asymptomatic or only reported feeling sad, blue, or depressed received a Short-Form Composite International Diagnostic Interview (CIDI-SF) score of 0. We report hazard ratios (HRs) for each CIDI-SF score from 1 to 7 relative to those with a score of 0, using Cox proportional hazards models adjusted for age, sex, educational attainment, urban/rural residence, use of statins, 1 or 2 or more disabilities, former and current smoking and alcohol use, hypertension, diabetes, social isolation (an index from 0-5), and including random intercepts for study center (model 2). *P* for trend was modeled using the CIDI-SF score as a continuous variable.

In age- and sex-adjusted models, both the CIDI-SF score and having 4 or more symptoms were associated with the combined outcome in most individual countries. Precision of these estimates was greater in countries with more than 3000 participants (eResults 5 in the Supplement). The associations between depression and all primary outcomes were also twice as strong in men compared with women (combined outcome: HR, 1.27; 95% CI, 1.17-1.38 vs HR, 1.14; 95% CI, 1.06-1.23) (*P* for interaction < .001) but were otherwise independent of traditional NCD risk factors and social determinants of health, including education and relative wealth (**Figure 2**).

Discussion

In this prospective study of 145 862 people from urban and rural communities in 21 economically diverse countries, middle-aged adults with 4 or more depressive symptoms are at 14% and 17% increased risks of incident CVD and all-cause mortality, respectively. Our initial question was whether previous research identifying similar patterns of association in mostly Western countries[7,31-33] could be generalized to other parts of the world. Our findings suggest that they can, and we obtained similar results in countries at all economic levels. However, these associations are not the same within countries. After accounting for traditional NCD risk factors and disability, the relative risks of death and CVD were more than twice as high in urban than in rural areas. Men (in whom depressive symptoms were less common) were also at more than double the risk of women. Our analyses of secondary outcomes supports previous research showing that the relative risks of incident CVD are highest for myocardial infarction (23%) when compared with heart failure (9%) and stroke (5%),[7,8,34-36] while the relative risks of all-cause mortality are highest from noncardiovascular (21%) compared with cardiovascular (7%) causes.[31]

These findings are consistent with previous, geographically limited research. For example, the 43% increased risk of death or CVD in China is comparable with the 32% increased risk of ischemic heart disease found in another large study undertaken in China, in which urban residents also experienced greater risks.[7] The elevated urban risk may be partly attributable to the increased prevalence of traditional risk factors, although our results showed that these accounted for only 20% to 30% of the increased risk. It is also possible that consequences of urbanization such as overcrowded housing, lack of green space, widened inequalities,[37,38] and low social cohesion[18] might affect the association between mental health and disease, but this requires further study. Similarly, the stronger associations between depressive symptoms and incident CVD and mortality in men have been reported previously (for both CVD[39,40] and all-cause mortality[41,42]). There are a number of factors that could be responsible for this difference. First, women younger than age 70 years have a longer life expectancy than men, and as the PURE population ages and the mean age increases from 50 years old, we may see these differences attenuate as we do in studies of depression in older populations.[43,44] Second, for a given level of psychological morbidity, men report fewer depressive symptoms than women[40,45] and are also less likely to seek treatment,[46] which could also contribute to the apparent increase in risk.

Direct comparisons within the PURE study show that associations between depressive symptoms and death and CVD are similar to those with smoking, unhealthy eating, and ab-

Table 3. Associations Between ≥4 Depressive Symptoms and the Combined Outcome by Geographical Regions, Country Income Status, and Urban/Rural Communities[a]

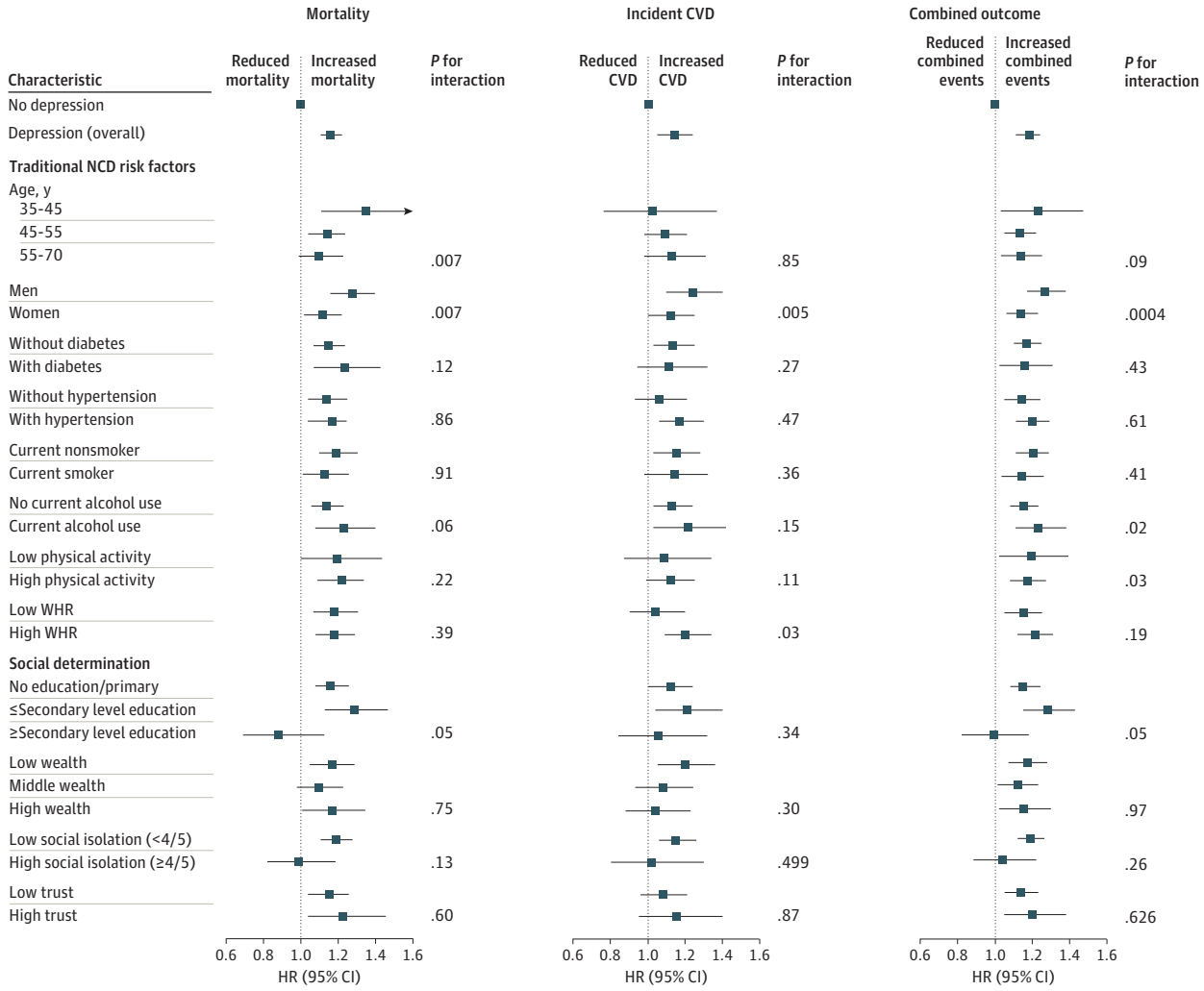
Characteristic	Geographical regions							Country income status		Community	
	South Asia	Southeast Asia	China	Middle East	Sub-Saharan Africa	North America and Europe	South America	High/upper-middle income	Lower/lower-middle income	Urban	Rural
No.	31 232	16 441	42 691	9982	6032	17 553	21 931	52 564	92 298	76 931	68 931
Depression prevalence	12	5	2	19	21	19	20	15	8	13	9
Events, No.	4453	1569	3491	407	849	1105	1570	4342	9102	5545	7899
Event rate/1000 person-years (95% CI)	14.7 (14.2-15.2)	12.8 (12.1-13.4)	9.2 (8.9-9.5)	6.9 (6.2-7.6)	22.2 (20.7-23.8)	6.1 (5.7-6.5)	7.8 (7.4-8.2)	9.2 (8.9-9.5)	11.3 (11.0-11.5)	8.3 (8.1-8.6)	13.0 (12.7-13.3)
Depression, hazard ratio (95% CI)											
Model 1	1.14 (1.04-1.24)	1.21 (0.93-1.56)	1.42 (1.11-1.81)	1.44 (1.11-1.87)	1.21 (1.03-1.43)	1.23 (1.05-1.45)	1.24 (1.10-1.41)	1.22 (1.12-1.33)	1.19 (1.11-1.28)	1.27 (1.17-1.38)	1.12 (1.04-1.21)
Model 2	1.13 (1.03-1.23)	1.20 (0.93-1.56)	1.43 (1.12-1.83)	1.30 (1.01-1.69)	1.20 (1.01-1.41)	1.15 (0.98-1.35)	1.18 (1.04,1.34)	1.17 (1.07-1.28)	1.17 (1.09-1.26)	1.23 (1.13-1.34)	1.10 (1.02-1.19)
P for interaction	.56							.52		.001	
Covariates											
Age	1.07 (1.06-1.07)	1.06 (1.05-1.07)	1.06 (1.06-1.07)	1.07 (1.06-1.08)	1.04 (1.03-1.04)	1.07 (1.06-1.08)	1.07 (1.06-1.08)	1.06 (1.06-1.07)	1.07 (1.06-1.07)	1.07 (1.06-1.07)	1.06 (1.06-1.07)
Male	1.52 (1.41-1.64)	1.82 (1.61-2.05)	1.36 (1.24-1.48)	1.85 (1.42-2.41)	1.89 (1.62-2.20)	2.01 (1.76-2.29)	1.65 (1.48-1.85)	1.83 (1.72-1.96)	1.47 (1.40-1.55)	1.63 (1.53-1.74)	1.55 (1.47-1.64)
Education											
Primary	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Secondary	0.73 (0.67-0.79)	0.77 (0.68-0.87)	0.79 (0.73-0.86)	0.92 (0.70-1.20)	0.85 (0.73-1.00)	0.76 (0.64-0.91)	0.85 (0.75-0.99)	0.80 (0.74-0.87)	0.77 (0.73-0.82)	0.75 (0.70-0.80)	0.80 (0.75-0.85)
>Secondary	0.36 (0.31-0.42)	0.50 (0.39-0.63)	0.73 (0.64-0.83)	0.57 (0.38-0.84)	0.54 (0.30,0.96)	0.76 (0.64-0.90)	0.90 (0.77-1.06)	0.71 (0.64-0.79)	0.53 (0.48-0.58)	0.56 (0.52-0.61)	0.63 (0.54-0.73)
Rural residence	1.11 (1.03-1.19)	1.52 (1.36-1.71)	1.55 (1.43-1.68)	1.22 (0.97-1.53)	1.15 (0.99-1.33)	1.09 (0.96-1.24)	1.08 (0.97-1.21)	1.22 (1.11-1.33)	1.24 (1.18-1.30)	Omitted	Omitted
≥2 Disabilities	1.30 (1.21-1.40)	1.27 (1.11-1.46)	1.28 (1.14-1.44)	1.39 (1.07-1.79)	1.04 (0.88-1.23)	1.48 (1.27-1.73)	1.16 (1.03-1.30)	1.26 (1.17-1.37)	1.26 (1.19-1.33)	1.26 (1.17-1.36)	1.27 (1.20-1.35)
Diabetes	1.79 (1.66-1.94)	1.97 (1.76-2.22)	1.47 (1.32-1.63)	1.74 (1.38-2.18)	1.60 (1.23-2.09)	1.63 (1.38-1.92)	1.88 (1.64-2.14)	1.87 (1.73-2.01)	1.65 (1.56-1.76)	1.68 (1.58-1.80)	1.76 (1.65-1.88)
Hypertension	1.36 (1.27-1.45)	1.37 (1.23-1.53)	1.76 (1.64-1.89)	1.81 (1.46-2.25)	1.06 (0.92-1.23)	1.55 (1.36-1.77)	1.47 (1.31-1.64)	1.41 (1.32-1.51)	1.50 (1.44-1.57)	1.43 (1.35-1.52)	1.48 (1.40-1.55)
Current											
Smoker	1.17 (1.03-1.33)	1.05 (0.88-1.25)	1.31 (1.13-1.51)	1.50 (1.07-2.12)	1.24 (0.95-1.63)	1.24 (1.07-1.44)	1.29 (1.14-1.46)	1.18 (1.08-1.28)	1.21 (1.11-1.31)	1.18 (1.09-1.29)	1.19 (1.09-1.29)
Alcohol consumer	1.19 (1.08-1.31)	0.80 (0.60-1.06)	0.82 (0.74-0.90)	Omitted[b]	0.99 (0.83-1.18)	0.87 (0.75-1.01)	0.82 (0.74-0.91)	0.96 (0.88-1.05)	0.92 (0.87-0.98)	0.94 (0.87-1.01)	0.89 (0.83-0.95)
Socially isolated	1.22 (1.06-1.41)	1.03 (0.83-1.27)	Omitted[c]	1.08 (0.80-1.46)	1.42 (1.23-1.65)	1.22 (1.01-1.47)	1.11 (0.97-1.26)	1.22 (1.11-1.33)	1.20 (1.08-1.33)	1.25 (1.13-1.37)	1.15 (1.04-1.26)

[a] The combined outcome was defined by the first of either a major cardiovascular event or death. This table shows prevalence and event rates, standardized directly for age and sex using the Prospective Urban Rural Epidemiology (PURE) study population as the standard and hazard ratios associated with depression in each geographic setting for model 1 and model 2. We also present the coefficients and 95% CIs for key covariates in model 2. This shows that the relative contributions of each of the covariates were fairly similar in different settings. Model 1 included age, sex, educational attainment, urban/rural residence, use of statins, and 1 or ≥2 disabilities. Model 2 also included current smoking and alcohol use, hypertension, diabetes, and social isolation. All models included random intercepts for center apart from South America, where we included random intercepts for country because of insufficient events in some individual centers.

[b] Alcohol use was omitted from the models in the Middle East, where this question was not asked routinely.

[c] Social isolation was omitted from the model in China, where it was colinear with other variables in the model.

Figure 2. Associations Between ≥4 Symptoms of Depression and Mortality and Incident CVD, in Subgroups Determined by Traditional NCD Risk Factors and Social Determinants of Health



Associations between depression and incident cardiovascular death (CVD), mortality, and the combined outcome (the first of either incident CVD or death) were stronger in men compared with women but were otherwise independent of traditional risk factors after adjustments for age, sex, educational attainment, urban/rural residence, use of statins, 1 or 2 or more disabilities, current smoking, alcohol use, hypertension, diabetes, and social isolation index and including random intercepts for center (model 2). HR indicates hazard ratio; NCD, noncommunicable diseases; WHR, waist-to-hip ratio.

dominal obesity.[21] Although our aim was not to understand the underlying causal mechanisms, we found that the influence of modifiable risk factors and social isolation on the estimated risks of death and CVD in people with depressive symptoms was limited to the Middle East, North America and Europe, South America, high-/upper-middle-income countries, and urban areas, suggesting that these individual risks may be less critical than previously presumed[47] in any causal pathway.

While it is not possible to determine whether the associations between depression and mortality are causal, the temporality, dose response, consistency, and coherence with other research do support such an interpretation. The wide range of cardiovascular and noncardiovascular outcomes associated with depression could point to some common pathways, which previous literature suggests may involve biological mechanisms, including inflammation and autonomic dysregulation.[11,48]

Our findings have several implications for the global NCD agenda. First, they lend credibility to existing World Health Organization (WHO) policies to integrate treatment and prevention of mental disorders into primary care[14] by demonstrating this need in resource-poor parts of the world where the physical health outcomes of depression are poorly understood. Although the evidence to support the use of biopsychosocial treatments for secondary prevention of CVD is weak,[49] collaborative care models that combine treatment for depression with the support to live healthier lives can reduce mortality in older adults with depression by 25%[50] and reduce metabolic risk.[51] Future studies must now examine the potential role for these approaches in primary prevention. Fi-

nally, our results support the position taken by several international organizations[52,53] that depression should be considered a risk factor for ischemic heart disease and provide support for the view articulated by others[54] that it should also be included in future estimates of the burden of disease study, enabling these relationships to be documented globally and over time.

Strengths and Limitations

This is the first study to our knowledge to use standardized methods to collect data on depression, covariates, and health outcomes in 5 continents and to show that longitudinal associations between depressive symptoms and adverse health outcomes exist worldwide. However, there are some limitations. In the absence of a single globally validated screening instrument for depression, we assumed that a CIDI-SF score of 4 or more was predictive of major depressive disorder in each country. However, symptom reporting varied between countries and did not include somatic symptoms, commonly observed in some Asian countries,[55] which could explain the low prevalence in Asia. Nonetheless, while the estimated prevalence of depressive symptoms in PURE was similar to WHO estimates for major depressive disorder[56] in China (2%), Bangladesh (4%), and the Philippines (3%), it may have been less sensitive in some countries (eg, India [5%], Saudi Arabia [5%], Sweden [5%], and Canada [5%]).[30] The risks of incident CVD in people with major depressive disorder may therefore be higher as shown in a recent meta-analysis[2] of mostly high-income countries data, showing risks as high as 72%.

Despite these well-recognized crossnational differences in symptom reporting,[30] we also found that both CIDI-SF score and the presence of 4 or more symptoms consistently predicted mortality or incident CVD in most countries, suggesting that the underlying constructs measured by the instrument are valid crossnationally. Second, we cannot rule out residual confounding, particularly where effect sizes are modest, although by adjusting for potential mediators, we may have underestimated true associations between depression and outcomes. Third, while this is the largest study that we are aware of to examine associations between depression and incident cancer, there were insufficient events to analyze each cancer type separately, which is important because we would expect the mechanisms to vary.[57,58] Finally, we report depressive symptoms at baseline only and cannot therefore evaluate its time-varying effects until these assessments have been repeated.

Conclusions

We confirmed that associations between depressive symptoms and incident CVD and mortality exist in countries at all levels of development. However, the strength of the association varies within countries, being higher in urban areas. This is important because by 2050,[59] most of the global population is expected to live in urban areas, where we found depression was also more common. If governments are to achieve the health-related Sustainable Development Goals, especially in resource-poor settings, they should raise awareness of the physical health risks associated with depression and prioritize an integrated and comprehensive approach to tackling NCDs and mental disorders. Meanwhile, broader public policies should promote mental well-being and healthy behaviors as part of a comprehensive strategy to control NCDs.

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