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BRIEF COMMUNICATION

Time-Varying Depressive Symptoms and Cardiovascular and All-Cause Mortality: Does the Risk Vary by Age or Sex?

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BACKGROUND: Depressive symptoms are associated with mortality. Data regarding moderation of this effect by age and sex are inconsistent, however. We aimed to identify whether age and sex modify the association between depressive symptoms and all-cause and cardiovascular disease (CVD) mortality.

METHODS AND RESULTS: The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study is a prospective cohort of Black and White individuals recruited between 2003 and 2007. Associations between time-varying depressive symptoms (Center for Epidemiologic Studies Depression scale score ≥4 versus <4) and all-cause and CVD mortality were measured using Cox proportional hazard models adjusting for demographic and clinical risk factors. All results were stratified by age or sex and by self-reported health status. Of 29 491 participants, 3253 (11%) had baseline elevated depressive symptoms. Mean age was 65 (9.4) years, with 55.1% of participants female, 41.1% Black, and 46.4% had excellent/very good health. Depressive symptoms were measured at baseline, on average 4.9 (SD, 1.5), then 2.1 (SD, 0.4) years later. Neither age nor sex moderated the association between elevated time-varying depressive symptoms and all-cause or CVD mortality (all-cause: age 45–64 years adjusted hazard ratio [aHR], 1.38; 95% CI, 1.18–1.61 versus age ≥65 years aHR,1.36; 95% CI, 1.23–1.50; *P*=0.05; CVD: age 45–64 years aHR, 1.17; 95% CI, 0.90–1.53 versus age ≥65 years aHR, 1.26; 95% CI, 1.06–1.50; *P*=0.54; all-cause: males aHR, 1.46; 95% CI, 1.29–1.64 versus female aHR, 1.34; 95% CI, 1.19–1.50; *P*=0.35; CVD: male aHR, 1.32; 95% CI, 1.08–1.62 versus female aHR, 1.22; 95% CI, 1.00–1.47; *P*=0.64). Similar results were observed when stratified by self-reported health status.

CONCLUSIONS: Depressive symptoms confer mortality risk regardless of age and sex, including individuals who report excellent/very good health.

Key Words: cardiovascular disease mortality ■ depression ■ mortality

Elevated depressive symptoms is an established risk factor for cardiovascular disease (CVD) and all-cause mortality,[1] but research on whether age and sex moderate this effect is inconsistent. For example, some suggest that depression may increase the risk of all-cause and CVD mortality particularly among men, but is not associated with CVD mortality among women.[2] Others suggest that depression significantly increases the risk of all-cause and CVD mortality among women.[3] Meanwhile, studies demonstrating the strong relationship between depressive symptoms and mortality often focus on older adults, with few studies examining younger or healthier cohorts.[1] Experts also argue that small sample sizes and incomplete adjustment for explanatory covariates also limit prior research on the relationship between depressive symptoms and mortality.[4]

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Depressive symptoms relapse and remit, often by sex and age,[5] and few if any subgroup analyses account for time-varying symptoms, which more accurately represent risk and have the potential to elucidate these subgroup differences. Moise et al (2018) found increased all-cause and CVD mortality risk among individuals with elevated time-varying depressive symptoms and excellent or very good self-reported health status, noting a significant interaction with self-reported health status.[6] Here, we investigate whether age and sex modify the association between time-varying depressive symptoms and all-cause and CVD mortality after adjusting for clinical and behavioral risk factors in the same large, diverse cohort as that of Moise et al.[6]

METHODS

The data that support these findings are available from Dr Monika Safford (mms9024@med.cornell.edu) upon reasonable request. The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study is a prospective cohort study of noninstitutionalized Black and White individuals (≥45 years) recruited between 2003 and 2007.[7] Complete sampling methods, inclusive and exclusion criteria, and data collection methods have been previously described; notably, those with cancer at baseline were excluded.[7] The REGARDS study protocol was approved by institutional review boards at participating centers. As described previously, depressive symptoms were defined using the 4-item Center for Epidemiologic Studies Depression scale (CES-D score ≥4 versus <4),[8,9] which has been found to have similar validity and reliability to the original 20-item depression scale.[9] Associations between depressive symptoms and all-cause and CVD mortality were measured using Cox proportional hazard regression analyses.[6]

The classification of CVD death included participants who died from coronary heart disease, stroke, heart failure, sudden cardiac death, vascular pathology, and other CVD causes. Deaths were ascertained by next-of-kin report, online agencies (eg, Social Security Death Index), or the National Death Index, and adjudicated from death certificates, medical records, and autopsy reports.[7] Depressive symptoms were measured up to 3 times, including at baseline and, on average, both 5 and 7 years later.[6]

Statistical Analysis

The presence of elevated depressive symptoms functioned as time-varying covariates in all models. Time intervals were calculated using the date of in-home examination to the first occurrence of one of the following: death, most recent telephone follow-up, or censoring at the designated end of the study period (December 31, 2012).[6,10] In this analysis, depression status (CES-D score ≥4 versus <4) was treated as a binary, time-dependent variable and the cohort was continually updated to reflect presence or absence of depressive symptoms. Based on a priori hypotheses, we adjusted for demographics, and physiologic (blood pressure, cholesterol, medication, obesity, diabetes mellitus, renal disease, QTc interval, atrial fibrillation, and left ventricular hypertrophy) and behavioral factors (smoking, alcohol use, physical inactivity, and medication adherence), the definitions and cutoffs of which have previously been described.[6]

Analyses were then stratified by age (45–64 years versus ≥65 years) and sex (self-identified male versus female). Moise et al (2018) found that the association between time-varying depressive symptoms and all-cause mortality was moderated by self-reported health (excellent/very good self-reported health versus poor, fair, or good self-reported health status).[6] As such, we reported *P* values for 2-way interaction terms (level of significance <0.05) within each health status strata in addition to 3-way interaction terms.

Exploratory Analysis

Prior studies adjusted for inflammatory and stress-related factors; therefore, we further adjusted for C-reactive protein (log transformed), perceived stress, and physical health component score.[6]

RESULTS

Of 29 491 participants, 11% (3253) had elevated depressive symptoms at baseline. The mean age was 65.0 (9.4) years; 55.1% was female; 41.1% was Black; and 46.4% reported excellent or very good health (Tables S1 and S2). Depressive symptoms were measured an average of 4.8 (SD, 1.5) years following the baseline measurement, and the third measurement occurred on average 2.1 (SD, 0.4) years after the second measurement.

Age

We found that even after adjusting for demographic, clinical, and behavioral risk factors, depressive symptoms similarly confer significant all-cause mortality risk among middle-aged (45–64 years; adjusted hazard ratio [aHR], 1.38; 95% CI, 1.18–1.61) and older (≥65 years; aHR, 1.36; 95% CI, 1.23–1.50) individuals (for age interaction, *P*=0.05) with no significant modification by age. Elevated depressive symptoms were not significantly associated with increased CVD mortality

among middle-aged (aHR, 1.17; 95% CI, 0.90–1.53) individuals, but was significant among older individuals (aHR, 1.26; 95% CI, 1.06–1.50; for interaction, *P*=0.54); however, these effects were not significantly different. When restricting the population to individuals aged 45 to 64 years versus ≥65 years self-reporting excellent or very good health, depressive symptoms similarly increased the risk for all-cause mortality (aHR, 1.63; 95% CI, 1.08–2.47 versus aHR, 1.60; 95% CI, 1.30–1.95; for interaction, *P*=0.58) and CVD specific mortality (aHR, 2.04; 95% CI, 0.98–4.24 versus aHR, 1.44; 95% CI, 1.00–2.07; for interaction, *P*=0.35). Similar trends emerged for those self-reporting poor, fair, or good health. Three-way interactions were not significant (Table).

Sex

Overall, sex (self-reported male versus female) did not appear to moderate the significant relationship between elevated depressive symptoms and all-cause mortality (aHR, 1.46; 95% CI, 1.29–1.64 versus aHR, 95% CI, 1.34; 95% CI, 1.19–1.50; for interaction, *P*=0.35) or CVD mortality (aHR, 1.32; 95% CI, 1.08–1.62 versus aHR, 1.22; 95% CI, 1.00–1.47; for interaction, *P*=0.64). Among individuals self-reporting excellent or very good health, depressive symptoms significantly increased the risk for all-cause mortality similarly in both males versus females (aHR, 1.86; 95% CI, 1.47–2.36 versus aHR, 1.40; 95% CI, 1.07–1.83; for interaction, *P*=0.27), but only among males for CVD-specific mortality (aHR, 2.00; 95% CI, 1.34–2.99 versus aHR, 1.08;95% CI,

Table. Time-Varying Depressive Symptoms and Mortality Stratified by Age and Sex and Self-Reported Health for REGARDS Cohort

	Age 45–64 y	Age >65 y	Age 45–64 y	Age >65 y
	All-cause mortality: excellent/very good health		**All-cause mortality: poor/fair/good health**	
N	6900	6785	7866	7867
Crude HR (95% CI)	2.29 (1.58–3.31)	1.91 (1.57–2.31)	1.69 (1.45–1.98)	1.35 (1.20–1.50)
aHR (95% CI)	1.63 (1.08–2.47)	1.60 (1.30–1.95)	1.28 (1.09–1.51)	1.23 (1.10–1.38)
Events per group†	50	196	163	408
CESD×age	*P*=0.58		*P*=0.16	
Health status×CESD×age	*P*=0.99			
	CVD mortality: excellent/very good health		**CVD mortality: poor/fair/good health**	
Crude HR (95% CI)	3.09 (1.67–5.72)	1.78 (1.25–2.53)	1.41 (1.08–1.86)	1.35 (1.12–1.63)
aHR (95% CI)	2.04 (0.98–4.24)	1.44 (1.00–2.07)	1.04 (0.79–1.39)	1.17 (0.97–1.42)
Events per group†	11	58	59	120
CESD×age	*P*=0.35		*P*=0.76	
Health status×CESD×age	*P*=0.26			
	Female	**Male**	**Female**	**Male**
	All-cause mortality: excellent/very good health		**All-cause mortality: poor/fair/good health**	
N	7097	6588	9104	6629
Crude HR (95% CI)	1.77 (1.36–2.30)	2.68 (2.14–3.36)	1.32 (1.17–1.49)	1.49 (1.31–1.71)
aHR (95% CI)	1.40 (1.07–1.83)	1.86 (1.47–2.36)	1.22 (1.08–1.39)	1.30 (1.13–1.49)
Events per group†	119	128	292	278
CESD×sex	*P*=0.27		*P*=0.52	
Health status×CESD×sex	0.42			
	CVD mortality: excellent/very good health		**CVD mortality: poor/fair/good health**	
Crude HR (95% CI)	1.59 (0.96–2.64)	2.96 (2.02–4.34)	1.25 (1.02–1.55)	1.41 (1.12–1.77)
aHR (95% CI)	1.08 (0.64–1.83)	2.00 (1.34–2.99)*	1.15 (0.92–1.43)	1.13 (0.89–1.44)
Events per group†	36	33	83	96
CESD×sex	*P*=0.27		*P*=0.86	
Health status×CESD×sex	*P*=0.32			

Model was adjusted for the following, age; sex; region; income; health insurance; education; systolic blood pressure; total cholesterol; high-density lipoprotein cholesterol; use of aspirin, statins, antihypertensives, or antidepressants; body mass index; logarithmically transformed albumin-to-creatinine ratio; diabetes mellitus; cardiovascular disease; chronic obstructive pulmonary disease; cognitive impairment; pack-years of cigarette smoking; self-reported alcohol use; physical inactivity; and medication nonadherence. All results presented are from multiply imputed models. aHR indicates adjusted hazard ratio; CESD, Center for Epidemiologic Studies Depression scale; CVD, cardiovascular disease; HR, hazard ratio; and REGARDS, Reasons for Geographic and Racial Differences in Stroke study.

*Statistically significant at *P*<0.05.

†Number of deaths among those with elevated depression within strata.

0.64–1.83; for interaction, *P*=0.27). Similar patterns emerged among those with poor, fair, or good health (Table).

Exploratory Analysis

After adjusting for exploratory factors (C-reactive protein [log transformed], perceived stress, and physical health component score), depressive symptoms remained significantly associated with all-cause mortality among both middle-aged individuals (aHR; 1.20; 95% CI, 1.02–1.42) and older individuals (aHR, 1.24; 95% CI, 1.12–1.37; for interaction, *P*=0.13). Depressive symptoms were no longer significantly associated with CVD mortality among middle-aged individuals (aHR,1.13;95% CI, 0.94–1.35) or older individuals (aHR, 1.09; 95% CI, 0.81–1.45; for interaction, *P*=0.83). Among those with excellent/very good health, depressive symptoms continued to significantly predict all-cause mortality among both individuals middle-aged individuals and older individuals (aHR,1.58; 95% CI, 1.02–2.45 and aHR, 1.52; 95% CI, 1.24–1.87; for interaction, *P*=0.68). Depressive symptoms were no longer significantly associated with CVD mortality among middle-aged individuals or older individuals reporting excellent or very good health (aHR, 1.09; 95% CI, 0.81–1.45 versus aHR, 1.31; 95% CI, 0.90–1.91; for interaction, *P*=0.23).

After adjusting for exploratory factors, depressive symptoms conferred significant increased risk of all-cause mortality among both males and females (aHR, 1.28; 95% CI, 1.30–1.45 and aHR,1.22; 95% CI, 1.08–1.37; for interaction, *P*=0.46). Risk was not significant for CVD mortality among males or females (aHR, 1.17; 95% CI, 0.94–1.45 versus aHR, 1.09; 95% CI, 0.88–1.35; for interaction, *P*=0.94). Among those with excellent/very good health, males versus females both exhibited increased all-cause mortality risk (aHR, 1.70; 95% CI, 1.33–2.18 versus aHR, 1.37; 95% CI, 1.04–1.81; for interaction, *P*=0.36). Risk for CVD mortality among healthy males was significant, but not among females, and the interaction was not significant (aHR, 1.75; 95% CI, 1.14–2.69 versus aHR, 1.04; 95% CI, 0.60–1.79; for interaction, *P*=0.36).

DISCUSSION

Using time-varying analyses in a large diverse cohort, we found that depressive symptoms confer a significant risk for all-cause and CVD mortality in both males and females, and older individuals, but not middle-aged individuals, after adjusting for clinical and behavioral risk factors. However, these effects did not significantly differ by age or by sex. Prior research has shown that individuals with depressive symptoms and excellent or very good self-reported health conferred an increased all-cause and CVD mortality risk compared with those with poor, fair, or good self-reported health. In this follow-up investigation, our stratified analyses revealed that age and sex do not moderate this effect.[6]

Although prior research has shown that depressive symptoms confer mortality risk among older adults,[11] our results suggest that age does not moderate the relationship between depressive symptoms and all-cause or CVD mortality. Depressive symptoms may similarly increase all-cause mortality risk among younger, healthy individuals, in whom symptoms may be less likely to be recognized and treated and who are less likely to be insured.[12] Furthermore, though prior research suggests that depressive symptoms are particularly associated with mortality rates among males, we found similar risk among females. Although the interactions were insignificant, the larger point estimates may support prior evidence of higher risk among males who are also less likely to be recognized and treated.

Finally, our results did not change even after adjusting for causal factors, suggesting the need to explore other explanatory factors (eg, hormonal or other inflammatory factors that may differ by age or sex) in the relationship between depressive symptoms and all-cause mortality.[3] The relationship between depressive symptoms and CVD mortality may be explained by behavioral (eg, exercise) risk factors among middle-aged and female individuals, whereas inflammatory/stress-related factors may drive the relationship among older and male individuals; better powered, formal mediation analyses are needed. It remains unclear whether traditional treatments (eg, antidepressants and therapy) reduce short-term CVD mortality[13]; other modalities such as cardiac rehabilitation should be explored.

Our study was limited by an incomplete adjustment for time-varying covariates (which were not available in this cohort). The low number of CVD events and reduced sample size in stratified groups limited our power to assess 2- and 3-way interactions, given the marked, but nonsignificant differences in point estimates by age and sex among those with self-reported health. There are also potential concerns for overadjustment, particularly in the analysis stratified by self-reported health status. As such, it is possible that we may have missed significant sex and age interactions. However, these covariates were based on a priori hypotheses and were consistent with our prior research.[6,10,14] Future analyses should be considered as more data from the REGARDS study become available to better understand long-term observed patterns in all-cause and CVD mortality risk, though our aim was to assess short-term, time-varying mortality. As we found that age and sex do not moderate the effect of time-varying depressive symptoms on all-cause or CVD mortality, there should be continued focus on improving mental health screening and treatment in all patients, and understanding risk factors for depression across the lifespan, regardless of age or sex.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Tables S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics stratified by age and depressive symptoms.

	Age 45-64		p-value	Age ≥ 65		p-value
	CES-D < 4	CES-D ≥4		CES-D < 4	CES-D ≥4	
N	12853	1937		13371	1316	
Age, mean (SD)	57.4 (4.9)	56.7 (5.0)	<0.001	72.7 (5.9)	73.1 (6.2)	0.035
Female n, (%)	7163 (55.7%)	1367 (70.6%)	<0.001	6818 (51.0%)	889 (67.6%)	<0.001
Black, n (%)	5449 (42.4%)	1045 (53.9%)	<0.001	4973 (37.2%)	657 (49.9%)	<0.001
Less than high school education, n (%)	901 (7.0%)	381 (19.7%)	<0.001	2011 (15.0%)	399 (30.3%)	<0.001
Annual household income <$20,000	1557 (12.1%)	669 (34.5%)	<0.001	2588 (19.4%)	505 (38.4%)	<0.001
No health insurance, n (%)	1372 (10.7%)	372 (19.2%)	<0.001	159 (1.2%)	22 (1.7%)	0.13
Region, n (%)						
Stroke belt	4568 (35.5%)	752 (38.8%)	<0.001	4401 (32.9%)	468 (35.6%)	0.012
Stroke buckle	2777 (21.6%)	468 (24.2%)		2658 (19.9%)	283 (21.5%)	
Non-stroke belt or buckle	5508 (42.9%)	717 (37.0%)		6312 (47.2%)	565 (42.9%)	
General Health Self-reported health, n (%)						
Poor, fair, good	6321 (49.2%)	1545 (79.8%)	<0.001	6890 (51.5%)	977 (74.2%)	<0.001
Excellent, very good	6513 (50.7%)	387 (20.0%)	<0.001	6447 (48.2%)	338 (25.7%)	
CVD, n (%)	1915 (14.9%)	505 (26.1%)	<0.001	3916 (29.3%)	481 (36.6%)	
Diabetes, n (%)	2341 (18.2%)	544 (28.1%)	<0.001	2959 (22.1%)	403 (30.6%)	<0.001
Chronic Obstructive Pulmonary Disease, n (%)	1031 (8.0%)	241 (12.4%)	<0.001	1274 (9.5%)	162 (12.3%)	<0.001
Physical component score on SF-12, mean (SD)	47.7 (10.3)	40.4 (12.5)	<0.001	46.4 (10.0)	41.1 (11.8)	<0.001
Physiologic risk factors						
Body mass index, kg/m^2, mean (SD)	30.0 (6.4)	31.4 (7.5)	<0.001	28.4 (5.6)	29.3 (6.1)	<0.001
Systolic blood pressure, mm Hg, mean (SD)	125.1 (16.0)	126.4 (17.6)	<0.001	129.7 (16.7)	132.1 (18.4)	<0.001
Total cholesterol, mg/dL, mean (SD)	195.6 (39.5)	197.2 (43.6)	0.12	188.0 (39.6)	190.8 (41.8)	0.18
HDL cholesterol, mg/dL, mean (SD)	51.6 (16.0)	52.0 (16.4)	0.29	51.8 (16.4)	53.1 (16.1)	0.008
QT interval, corrected for heart rate, ms, mean (SD)	405.2 (21.7)	408.6 (22.8)	<0.001	409.0 (25.0)	412.0 (25.7)	<0.001
High-sensitivity C reactive protein, mg/L median, IQR	2.2 (0.9, 5.1)	3.3 (1.3, 7.5)	<0.001	2.1 (0.9, 4.7)	2.6 (1.1, 6.3)	<0.001

Urinary Albumin/Creatinine ratio (mg/g), median (IQR)	6.3(4.2, 12.1)	7.1 (4.5, 15.9)	<0.001	8.7 (5.2, 19.8)	10.3 (6.0, 25.7)	<0.001
Medications						
Antihypertensive use, n (%)	5655 (44.0%)	1077 (55.6%)	<0.001	7624 (57.0%)	830 (63.1%)	<0.001
Statin use, n (%)	3267 (25.4%)	569 (29.4%)	<0.001	4973 (37.2%)	478 (36.3%)	0.57
Aspirin use, n (%)	4602 (35.8%)	781 (40.3%)	<0.001	6770 (50.6%)	633 (48.1%)	0.081
Antidepressant use, n (%)	1782 (13.9%)	617 (31.9%)	<0.001	1380 (10.3%)	304 (23.1%)	<0.001
Behavioral risk factors						
Self-reported smoking, pack-years, mean (SD)	11.4 (19.8)	15.2 (24.0)	<0.001	15.1 (25.3)	16.1 (26.2)	0.21
Current smoking, n (%)	2196 (17.1%)	594 (30.7%)	<0.001	1264 (9.5%)	205 (15.6%)	<0.001
Alcohol use, n (%)						
Heavy	569 (4.4%)	70 (3.6%)	<0.001	474 (3.5%)	59 (4.5%)	<0.001
Moderate	4720 (36.7%)	572 (29.5%)		4064 (30.4%)	268 (20.4%)	
None	7335 (57.1%)	1246 (64.3%)		8579 (64.2%)	944 (71.7%)	
Medication non-adherence	3441 (26.8%)	690 (35.6%)	<0.001	3375 (25.2%)	448 (34.0%)	<0.001

Table S2. Baseline characteristics stratified by gender and depressive symptoms.

	Female		p-value	Male		p-value
	CES-D < 4	CES-D ≥4		CES-D < 4	CES-D ≥4	
N	13981	2256		12243	997	
Age, mean (SD)	64.7 (9.4)	63.1 (9.7)	<0.001	65.9 (9.2)	63.8 (10.0)	<0.001
Black, n (%)	6326 (45.2%)	1215 (53.9%)	<0.001	4096 (33.5%)	487 (48.8%)	<0.001
Less than high school education, n (%)	1634 (11.7%)	550 (24.4%)	<0.001	1278 (10.4%)	230 (23.1%)	<0.001
Annual household income <$20,000	2886 (20.6%)	861 (38.2%)	<0.001	1259 (10.3%)	313 (31.4%)	<0.001
No health insurance, n (%)	940 (6.7%)	269 (11.9%)	<0.001	591 (4.8%)	125 (12.5%)	<0.001
Region, n (%)						
Stroke belt	4814 (34.4%)	872 (38.7%)	<0.001	4155 (33.9%)	348 (34.9%)	0.042
Stroke buckle	3159 (22.6%)	539 (23.9%)		2276 (18.6%)	212 (21.3%)	
Non-stroke belt or buckle	6008 (43.0%)	845 (37.5%)		5812 (47.5%)	437 (43.8%)	
General Health Self-reported health, n (%)						
Poor, fair, good	7354 (52.6%)	1750 (77.6%)	<0.001	5857 (47.8%)	772 (77.4%)	<0.001
Excellent, very good	6596 (47.2%)	501 (22.2%)		6364 (52.0%)	224 (22.5%)	
CVD, n (%)	2337 (16.7%)	581 (25.8%)	<0.001	3494 (28.5%)	405 (40.6%)	<0.001
Diabetes, n (%)	2653 (19.0%)	646 (28.6%)	<0.001	2647 (21.6%)	301 (30.2%)	<0.001
Chronic Obstructive Pulmonary Disease, n (%)	1341 (9.6%)	290 (12.9%)	<0.001	964 (7.9%)	113 (11.3%)	<0.001
Physical component score on SF-12, mean (SD)	46.1 (10.7)	40.4 (12.2)	<0.001	48.1 (9.4)	41.3 (12.3)	<0.001
Physiologic risk factors						
Body mass index, kg/m^2, mean (SD)	29.7 (6.8)	31.4 (7.5)	<0.001	28.5 (5.0)	28.7 (5.6)	0.28
Systolic blood pressure, mm Hg, mean (SD)	126.3 (16.8)	127.8 (18.2)	<0.001	128.8 (16.1)	130.7 (17.7)	<0.001
Total cholesterol, mg/dL, mean (SD)	199.7 (39.6)	200.3 (42.7)	0.50	182.8 (38.1)	181.9 (40.6)	0.46
HDL cholesterol, mg/dL, mean (SD)	57.4 (16.2)	55.3 (15.9)	<0.001	45.4 (13.6)	46.1 (15.3)	0.12
QT interval, corrected for heart rate, ms, mean (SD)	410.1 (22.2)	412.0 (23.0)	<0.001	403.8 (24.5)	405.3 (25.7)	0.069
High-sensitivity C reactive protein, mg/L median, IQR	2.7 (1.1, 6.0)	3.4 (1.3, 7.8)	<0.001	1.7 (0.8, 3.8)	2.3 (1.0, 5.2)	<0.001
Urinary Albumin/Creatinine	7.8 (5.0, 15.2)	8.3 (5.2, 18.8)	<0.001	6.8 (4.2, 16.7)	8.1 (4.6, 23.9)	<0.001

ratio (mg/g), median (IQR)						
Medications						
Antihypertensive use, n (%)	7329 (52.4%)	1361 (60.3%)	<0.001	5950 (48.6%)	546 (54.8%)	<0.001
Statin use, n (%)	3881 (27.8%)	694 (30.8%)	0.003	4359 (35.6%)	353 (35.4%)	0.90
Aspirin use, n (%)	5180 (37.1%)	933 (41.4%)	<0.001	6192 (50.6%)	481 (48.2%)	0.15
Antidepressant use, n (%)	2163 (15.5%)	709 (31.4%)	<0.001	999 (8.2%)	212 (21.3%)	<0.001
Behavioral risk factors						
Self-reported smoking, pack-years, mean (SD)	8.9 (18.0)	12.3 (21.2)	<0.001	18.2 (26.4)	22.8 (30.4)	<0.001
Current smoking, n (%)	1831 (13.1%)	512 (22.7%)	<0.001	4355 (35.6%)	283 (28.4%)	<0.001
Alcohol use, n (%)						
Heavy	465 (3.3%)	74 (3.3%)	<0.001	578 (4.7%)	55 (5.5%)	<0.001
Moderate	3649 (26.1%)	489 (21.7%)		5135 (41.9%)	351 (35.2%)	
None	9666 (69.1%)	1637 (72.6%)		6248 (51.0%)	553 (55.5%)	
Medication non-adherence	3804 (27.2%)	796 (35.3%)	<0.001	3012 (24.6%)	342 (34.3%)	<0.001