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Effect of Stress-Related Neural Pathways on the Cardiovascular Benefit of Physical Activity

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ABSTRACT

BACKGROUND The mechanisms underlying the psychological and cardiovascular disease (CVD) benefits of physical activity (PA) are not fully understood.

OBJECTIVES This study tested whether PA: 1) attenuates stress-related neural activity, which is known to potentiate CVD and for its role in anxiety/depression; 2) decreases CVD in part through this neural effect; and 3) has a greater impact on CVD risk among individuals with depression.

METHODS Participants from the Mass General Brigham Biobank who completed a PA survey were studied. A subset underwent ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomographic imaging. Stress-related neural activity was measured as the ratio of resting amygdalar-to-cortical activity ($AmygA_C$). CVD events were ascertained from electronic health records.

RESULTS A total of 50,359 adults were included (median age 60 years [Q1-Q3: 45-70 years]; 40.1% male). Greater PA was associated with both lower $AmygA_C$ (standardized β: −0.245; 95% CI: −0.444 to −0.046; $P = 0.016$) and CVD events (HR: 0.802; 95% CI: 0.719-0.896; $P < 0.001$) in multivariable models. $AmygA_C$ reductions partially mediated PA's CVD benefit (OR: 0.96; 95% CI: 0.92-0.99; $P < 0.05$). Moreover, PA's benefit on incident CVD events was greater among those with (vs without) preexisting depression (HR: 0.860; 95% CI: 0.810-0.915; vs HR: 0.929; 95% CI: 0.910-0.949; P interaction = 0.011). Additionally, PA above guideline recommendations further reduced CVD events, but only among those with preexisting depression (P interaction = 0.023).

CONCLUSIONS PA appears to reduce CVD risk in part by acting through the brain's stress-related activity; this may explain the novel observation that PA reduces CVD risk to a greater extent among individuals with depression. (J Am Coll Cardiol 2024;83:1543-1553) © 2024 by the American College of Cardiology Foundation.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

^{18}F-FDG-PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

$AmygA_C$ = ratio of amygdalar to ventromedial prefrontal cortex metabolic activity

CVD = cardiovascular disease

MET-min/wk = metabolic equivalent of task minutes per week

PA = physical activity

PRS_{ss} = polygenic risk score for neuroticism, reflecting stress sensitivity

SNA = stress-related neural activity

SUV = standardized uptake value

vmPFC = ventromedial prefrontal cortex

The cardiovascular benefits of physical activity (PA) have long been recognized, but their underlying mechanisms remain incompletely elucidated.[1] PA is known to reduce cardiovascular disease (CVD) risk in part through salutary effects on known cardiovascular risk factors and in part via direct physiological cardiovascular effects. However, those mechanisms only account for roughly 59% of PA's overall CVD benefit.[1] Thus, other mechanisms underlying PA's CVD benefits may also be at play.

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In addition to reducing CVD,[1] PA is associated with lower stress.[2] Furthermore, PA reduces the incidence and symptoms of stress-related syndromes (notably depression and anxiety).[3] Because chronic stress and depression are associated with heightened CVD risk (in part via neurobiological pathways),[4-6] a hypothesis that logically follows is that PA reduces CVD risk in part through its impact on stress-related brain mechanisms. Moreover, it is possible that individuals with stress-related syndromes may derive greater CVD benefits from PA.

The neural network responsible for stress-related activity in the brain comprises several neural centers. Whereas limbic structures (notably the amygdala) are responsible for the detection of potential threats, cortical regions, such as the ventromedial prefrontal cortex (vmPFC), inhibit and regulate these structures.[4,7] In humans, the stress-related activity (SNA) can be objectively measured using imaging of corticolimbic networks. For example, resting ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) provides a measurement of stress-related neural activity as a ratio of amygdalar to vmPFC metabolic activity ($AmygA_C$).[8] Altered activity within these brain regions has long been associated with stress-related syndromes, including anxiety disorders, post-traumatic stress disorder, and depression.[5,9-13] Furthermore, heightened SNA triggers sympathetic nervous system activity and leukopoiesis, leading to atherosclerotic inflammation and atherogenesis.[5,11,12] Moreover, previous studies have shown that chronic stress, and related syndromes, potentiate CVD events through this neural-immune-arterial axis.[5,11,12]

PA induces the production of β-endorphins and alters amygdalar reactivity and connectivity, contributing to PA's short-term mood-enhancing effects.[14-16] Notably, PA also induces long-term stress-related benefits, including chronic reductions in hypothalamic-pituitary-adrenal axis activation and altered stress perception.[17-19] However, the neurobiological mechanisms that may account for PA's chronic stress-reducing effects are not well understood. Moreover, it remains unknown whether PA induces greater CVD benefits among individuals with syndromes that are associated with alterations in stress-related cortico-limbic networks (eg, depression).[13]

Accordingly, we leveraged a large institutional biobank cohort and ^{18}F-FDG-PET-CT brain imaging on a subset to evaluate the impact of PA on neural-immune-arterial pathways. Specifically, we tested the hypotheses that PA: 1) is associated with a reduction in resting SNA; 2) reduces CVD in part through reductions in SNA; and 3) has a greater impact on CVD risk among individuals with depression.

METHODS

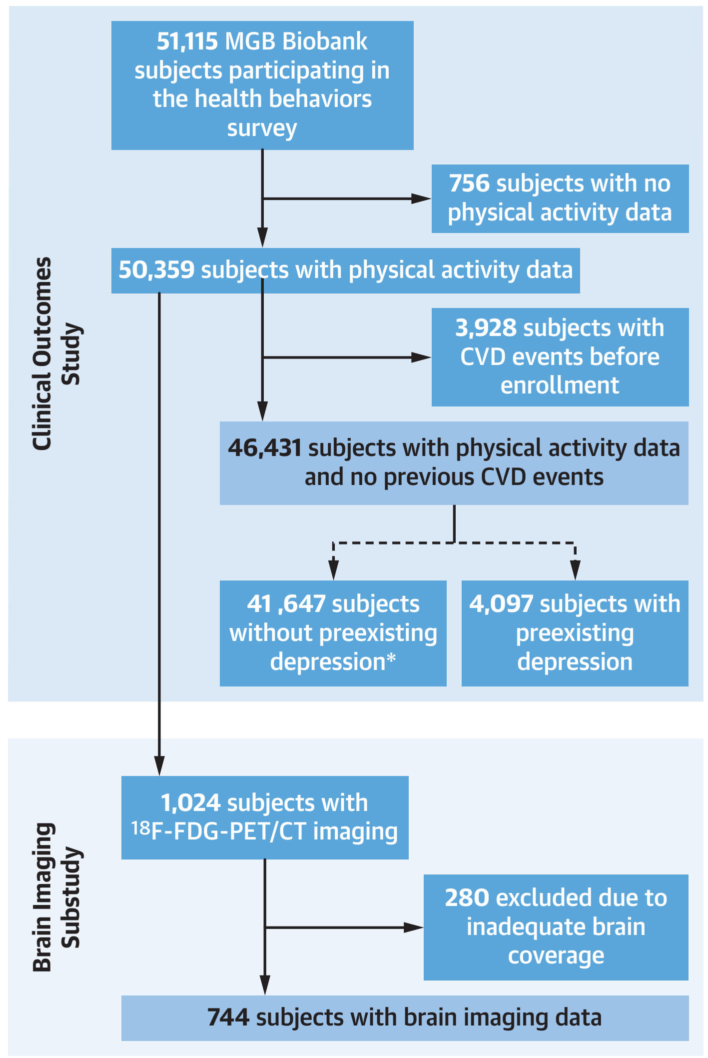
STUDY SAMPLE. The Mass General Brigham (MGB) Biobank is a large repository of data linked to electronic health records and collected from consenting subjects. Given that individuals constantly enroll in the Biobank, September 12, 2020 was an arbitrary date chosen for database lock; thus, only data on participants enrolled in the Biobank before that date were collected. A total of 51,115 adults (aged ≥18 years) completed a health behavior survey (**Figure 1**), of whom 50,359 also completed a PA questionnaire. A subset (n = 20,408) provided genetic data, from which a validated polygenic risk score for neuroticism, which links to stress-sensitivity (PRS_{SS}), was calculated in 9,080 individuals.[20] Clinical ^{18}F-FDG-PET/CT imaging was performed in a subset of those (n = 744), enabling the assessment of brain metabolic activity. All participants provided written informed consent and filled out surveys on enrollment. Thus, the date of consent varies among respondents and marks each respondent's enrollment in the Biobank and date of survey completion. Importantly, although an individual may have enrolled at a certain date, their electronic health records/medical history, even before the date of consent, were available in the Biobank. The study was approved by the MGB Human Research Committee. Additional details are provided in the Supplemental Appendix.

^{18}F-FDG-PET/CT IMAGING. ^{18}F-FDG-PET/CT scanning was performed on an integrated scanner (Biograph 64, Siemens Healthcare or equivalent) using a standard clinical protocol, usually for the purpose of cancer screening or surveillance. ^{18}F-FDG was injected intravenously, and imaging was performed with the patient in a resting state after approximately 1 hour. A low-dose CT scan without contrast material was performed for attenuation correction. An investigator blinded to clinical data measured regional brain activity on the ^{18}F-FDG-PET/CT images. ^{18}F-FDG uptake was measured as mean and maximum standardized uptake values (SUVs). Amygdalar and vmPFC SUVs were reported as the average of their bilateral values, respectively.[5] Thereafter, $AmygA_C$ was derived as mean amygdalar SUV divided by mean vmPFC SUV (**Figures 2A and 2B**).[8] Individuals with intracranial masses were excluded from the brain imaging substudy. Additional details are provided in the Supplemental Appendix. Moreover, measures of atherosclerotic activity and burden (coronary artery calcium and arterial FDG uptake) as well as leukopoietic activity (bone marrow and spleen ^{18}F-FDG uptake) were performed as detailed in the Supplemental Appendix.

PHYSICAL ACTIVITY. Upon enrollment, participants electively completed a health survey that assessed time spent on 8 physical activities during an entire year preceding the survey. Energy expenditure for each activity was derived as a metabolic equivalent-of-task (MET) value.[21] The duration spent on each activity was then multiplied by the MET value, after which the total MET-minute/week (MET-min/wk) for all activities was derived for each respondent. Current guidelines for adults recommend 150 minutes of moderate-intensity activity/week (or 75 minutes of vigorous activity/week) which roughly translates to 500 to 1,000 MET-min/wk.[22] Further details of this measure are provided in the Supplemental Appendix and Supplemental Table 1.

CARDIOVASCULAR EVENTS AND COVARIABLES. Demographic and clinical variables were derived from the MGB Biobank questionnaires and medical records. Cardiovascular and psychiatric diagnoses were evaluated using the International Classification of Disease-10 (ICD-10) criteria. Events constituting major adverse cardiovascular events (CVD events) included myocardial infarction (MI), unstable angina (UA), heart failure, coronary revascularization, peripheral vascular disease, peripheral revascularization, stroke, and transient ischemic attack.[23] Coronary events, a more stringent secondary endpoint, included UA, MI, and coronary revascularization only. The Charlson index, a measure of medical comorbidities,[24] including both solid tumors and malignant hematological conditions, was obtained from the Biobank. Data on alcohol intake, smoking, education, and employment were obtained from Biobank surveys. The median household income was derived from the U.S. Census Bureau, using zip

FIGURE 1 Study Cohort



The study was composed of a clinical outcomes study and a brain imaging substudy. The study cohort was derived from 51,115 Mass General Brigham (MGB) Biobank participants who participated in the health behaviors survey. Of those, 50,359 subjects had physical activity data, among whom 46,431 did not have preexisting cardiovascular disease (CVD) events and were therefore included in the CVD events analysis. Among these subjects, 4,097 had preexisting depression, and 41,647 did not have preexisting depression (*687 patients received diagnoses of depression after study start but before CVD events were excluded from the depression subanalysis). A total of 744 individuals with clinical imaging were evaluated in the brain imaging substudy.

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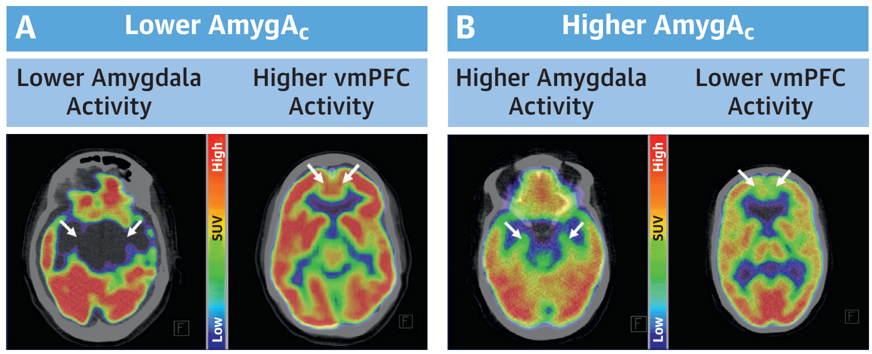
FIGURE 2 Physical Activity, Neuroimaging Measures, and Cardiovascular Risk Reduction



Axial views of the amygdala and ventromedial prefrontal cortex (vmPFC) demonstrating ^{18}F-fluorodeoxyglucose uptake pattern in those with (A) low stress-related neural activity (represented by AmygA$_C$) and (B) high stress-related neural activity. SUV = standardized uptake value.

codes.[25] Data on sleep disorders were derived using ICD-10 codes. Lifestyle factors included alcohol intake, smoking, and sleep disorders, and socioeconomic factors included education, employment, and median income. Additionally, cellular markers and biomarkers of inflammation were derived from medical records. Further details are provided in the Supplemental Appendix and Supplemental Table 2.

STATISTICAL ANALYSES. Statistical analyses were performed using the Statistical Package for Social Sciences, version 28 (IBM Corporation). Data were presented as mean ± SD if normally distributed, or as median (Q1-Q3) if skewed. Continuous variables were compared using independent sample Student's *t*-tests. Categorical variables were compared using chi-square or Fisher exact tests, as appropriate. Covariables that were potential confounders were defined a priori. Multivariable linear regression was used to assess the relationships between PA and neuroimaging, inflammatory, and atherosclerotic measures. Multivariable logistic and Cox regression were used to evaluate relationships between AmygA$_C$ and CVD events and PA and CVD events, respectively. Ten-year CVD events were defined as those that occurred during the 10 years leading up to the date of database lock (September 12, 2010 to September 20, 2020). Additional analyses from the date of consent for each participant to date of database lock were conducted. Interaction terms for event prediction among those with and without depression above and below PA recommendations and across PA quintiles were tested using Cox regression. In both analyses, diagnosis of depression was determined at the start of the observation period; individuals who experienced depression during the observation period were excluded. Additionally, individuals who experienced CVD events before the observation period were also excluded. Mediation analysis was performed using SPSS PROCESS macro v3.4 (IBM Corporation) to test whether PA exerted its cardiovascular benefit via the hypothesized mediator (ie, AmygA$_C$). A 2-sided *P* value <0.05 was used to define statistical significance for all analyses. Further details are given in the Supplemental Appendix.

RESULTS

STUDY COHORT. A total of 50,359 adult Biobank participants (median age 60 years [Q1-Q3: 45-70 years]; 40.1% male) were included in the study, and a subset of 774 provided neuroimaging measures (**Figure 1**). Within the entire cohort (n = 50,359), 35,333 individuals (70.2%) performed PA within guideline recommendations (Supplemental Figure 1). Those who subsequently experienced CVD events had a higher prevalence of traditional CVD risk factors and depression and were less active. Additionally, individuals who achieved greater PA were younger and had a lower prevalence of CVD risk factors and depression (**Table 1**).

PHYSICAL ACTIVITY WAS ASSOCIATED WITH A DOSE-DEPENDENT DECREASE IN STRESS-RELATED NEURAL ACTIVITY. Among subjects with brain imaging data (n = 744), individuals who achieved levels of PA that are recommended by guidelines

TABLE 1 Baseline Characteristics

	Full Cohort (N = 50,359)	Physical Activity <500 MET-min/wk (n = 15,026)	Physical Activity ≥500 MET-min/wk (n = 35,333)	Physical Activity *P* Value	CVD Events[a] + (n = 5,984)	CVD Events[a] − (n = 40,447)	CVD Events[a] *P* Value
Total physical activity (MET-min/wk)							
Median	1,152 (412.5-2,184.5)	212 (53-332)	1,814.5 (1,032.25-2,694)	<0.0001	795 (233.5-1,908)	1,292 (477-2,284)	<0.001
Basic characteristics							
Median age, y	60 (45-70)	63 (51-72)	59 (42-70)	<0.001	68 (59-76)	57 (41-68)	<0.0001
Male	20,178 (40.1)	5,868 (39.1)	14,310 (40.5)	0.002	3,162 (52.8)	14,848 (36.7)	<0.001
Caucasian	44,832 (89)	13,173 (87.7)	31,659 (89.6)	<0.001	5,471 (91.4)	35,835 (88.6)	<0.001
Cardiovascular risk factors							
Smoking[b]	20,598 (40.9)	7,295 (48.60)	13,303 (37.7)	<0.001	3,111 (52)	15,343 (38)	<0.001
Hypertension[c]	23,912 (47.5)	8,704 (57.9)	15,208 (43)	<0.001	4,946 (82.7)	15,438 (38.2)	<0.0001
Diabetes mellitus	7,596 (15.1)	3,409 (22.7)	4,187 (11.9)	<0.001	1,764 (29.5)	4,192 (10.4)	<0.0001
Hyperlipidemia	24,109 (47.9)	8,307 (55.3)	15,802 (44.7)	<0.001	4,531 (75.7)	16,142 (39.9)	<0.0001
Charlson comorbidity index							
98% 10-y survival	7,269 (14.4)	1,331 (8.9)	5,938 (16.8)	<0.001	15 (0.3)	7,243 (17.9)	<0.001
95% 10-y survival	5,193 (10.3)	1,273 (8.5)	3,920 (11.1)	<0.001	156 (2.6)	4,996 (12.4)	<0.001
90% 10-y survival	5,299 (10.5)	1,400 (9.3)	3,899 (11)	<0.001	235 (3.9)	4,969 (12.3)	<0.001
77% 10-y survival	5,329 (10.6)	1,512 (10.1)	3,817 (10.8)	0.013	431 (7.2)	4,751 (11.7)	<0.001
53% 10-y survival	4,737 (9.4)	1,389 (9.2)	3,348 (9.5)	0.420	505 (8.4)	4,059 (10)	<0.001
21% 10-y survival	4,186 (8.3)	1,297 (8.6)	2,889 (8.2)	0.090	521 (8.7)	3,416 (8.4)	0.500
2% 10-y survival	3,318 (6.6)	1,025 (6.8)	2,293 (6.5)	0.170	530 (8.9)	2,486 (6.1)	<0.001
≤0.009% 10-y survival	14,726 (29.2)	5,735 (38.2)	8,991 (25.4)	<0.001	3,591 (60)	8,217 (20.3)	<0.0001
Lifestyle factors							
Sleep disorders	13,819 (27.4)	5,173 (34.4)	8,646 (24.5)	<0.001	2,458 (41.1)	9,495 (23.5)	<0.001
Alcohol intake[d]							
None/low alcohol intake	15,155 (30.3)	6,079 (40.9)	9,076 (25.8)	<0.001	2,201 (37.2)	11,411 (28.4)	<0.001
Moderate alcohol intake	32,846 (65.7)	8,150 (54.9)	24,696 (70.3)	<0.001	3,463 (58.6)	27,227 (67.7)	<0.001
High alcohol intake	1,980 (4)	622 (4.2)	1,358 (3.9)	<0.001	250 (4.2)	1,567 (3.9)	<0.001
Genetic factors							
Neuroticism polygenic risk score (mean Z-score)[e] [20]	-0.045 ± 1.005	-0.015 ± 0.987	-0.060 ± 1.015	0.044	-0.091 ± 0.981	-0.035 ± 1.019	0.058
Psychiatric disorders							
Depression	14,075 (27.9)	5,287 (35.2)	8,788 (24.9)	<0.001	2,023 (33.8)	10,568 (26.1)	<0.001
Socioeconomic factors							
Graduated high school[f]	49,531 (98.7)	14,596 (97.5)	34,935 (99.1)	<0.001	5,824 (97.8)	39,923 (99)	<0.001
Employed[g]	37,918 (75.6)	10,262 (68.6)	27,656 (78.5)	<0.001	3,776 (63.5)	31,925 (79.2)	<0.001
Median income[h]	$84,305 ($64,431-$102,539)	$80,905 ($62,824-$100,157)	$85,336 ($67,471-$103,148)	<0.001	$83,783 ($63,887-$102,008)	$84,479 ($64,509-$102,539)	0.010

Values are median (Q1-Q3), n (%), or mean ± SD. [a]CVD events = 10-year CVD events risk; available for 46,431 participants, after exclusion of patients with preexisting CVD events as reported in **Figure 1**. [b]Available for 50,315 participants. [c]Available on 50,354 participants. [d]Available for 48,001 participants. [e]Available for 9,080 participants. [f]Available for 50,208 participants. [g]Available for 50,171 participants. [h]Available on 48,063 participants,

CVD = cardiovascular disease; MET-Min/wk. = metabolic equivalent task minutes per week.

(>150 minutes week of moderate-intensity PA [ie, ≥500 MET-min/wk] vs others) had lower $AmygA_C$ (standardized $AmygA_C$: −0.111 ± 0.971 vs 0.075 ± 1.018; $P = 0.012$). These differences remained significant in models adjusted for age, sex, socioeconomic and lifestyle factors, genetic influences (PRS_{ss}), and major medical comorbidities (standardized β: −0.0245; 95% CI: −0.444 to −0.046; $P = 0.016$) (Supplemental Table 3). Moreover, dose-dependent reductions in $AmygA_C$ were observed across quintiles of PA (standardized β: −0.085; 95% CI: −0.161 to −0.009; $P = 0.029$) in a similar multivariable-adjusted model (**Central Illustration**). Additionally, we observed that PA was associated with significantly higher vmPFC activity (standardized β: 0.085; 95% CI: 0.011-0.188 corrected for whole brain activity;

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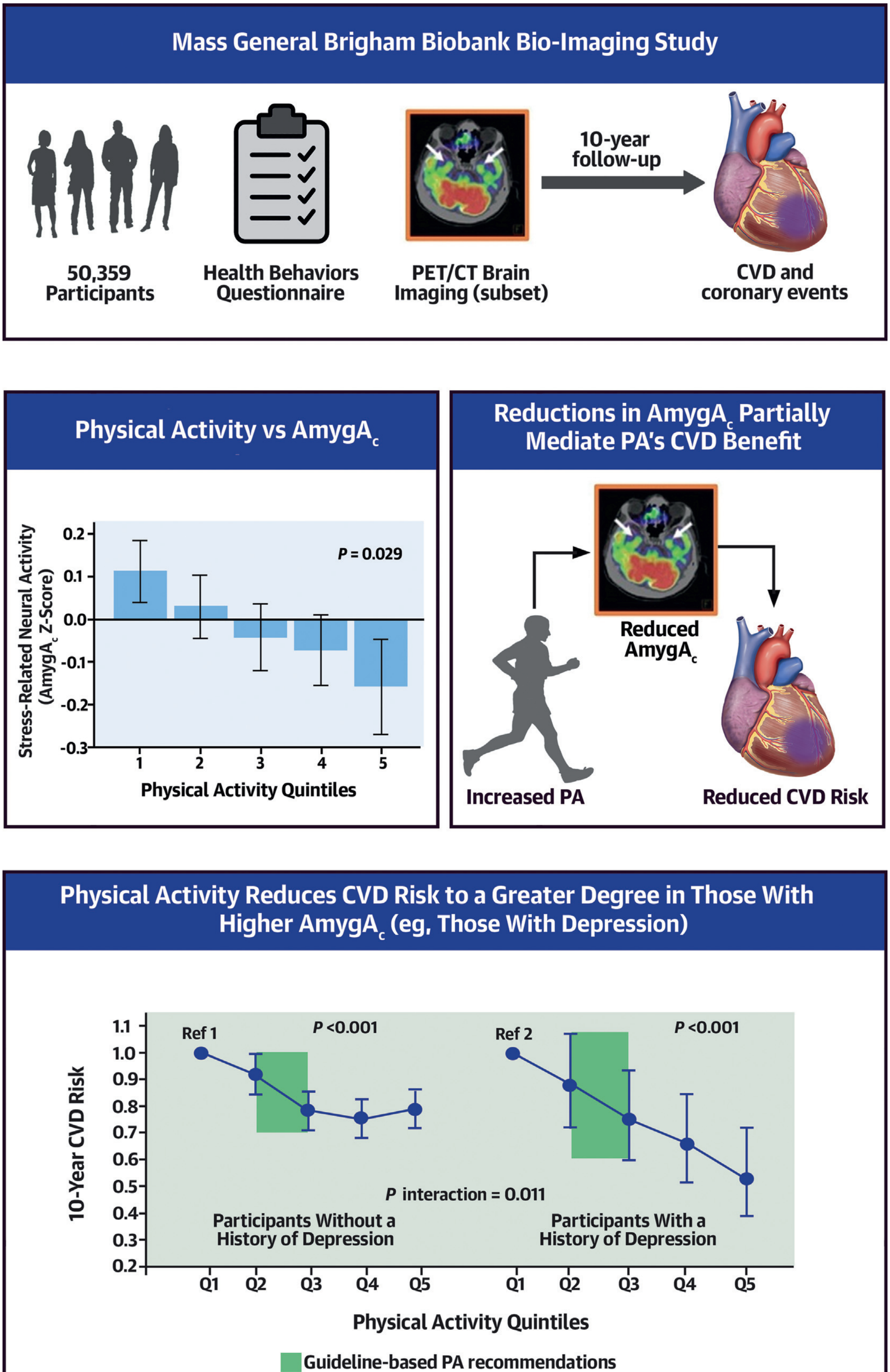
CENTRAL ILLUSTRATION Physical Activity, Stress-Related Neural Activity, and Cardiovascular Risk



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$P = 0.02$) as well as a trend toward reduced amygdalar activity (standardized β: −0.048; 95% CI: −0.144 to 0.029 corrected for whole brain activity; $P = 0.191$). This suggests that PA-related improvements in $AmygA_c$ may be driven by higher vmPFC activity. Absolute SUV values for neurobiological activity and AmygAc values are reported in Supplemental Table 4.

PHYSICAL ACTIVITY WAS ASSOCIATED WITH A DECREASED RISK OF CARDIOVASCULAR EVENTS. We next assessed the relationship between PA and incident 10-year CVD events (median follow-up time: 10.0 years [Q1-Q3: 10.0-10.0 years]). During the 10 years before database lock, among the 46,431 subjects involved in the CVD events analysis, a total of 5,984 individuals (12.9%) experienced CVD events, and, among the 48,409 subjects involved in the coronary events analysis, 2,086 individuals (4.3%) experienced coronary events. Individuals meeting PA guidelines had lower CVD event risk after adjustment for age, sex, and CVD risk factors (HR: 0.765; 95% CI: 0.726-0.806; $P < 0.001$) (Table 2). This relationship remained significant after further adjustment for socioeconomic and lifestyle factors, genetic influences (PRS_{ss}), and major medical comorbidities (HR: 0.802; 95% CI: 0.719-0.896; $P < 0.001$) (Supplemental Table 5). The findings were similar when coronary events were used as the outcome measure (Table 2).

We additionally evaluated associations between $AmygA_C$ and CVD events (as observed previously in other cohorts).[5] Among the 744 patients in the brain imaging cohort, 295 (39.7%) experienced CVD events and 125 (16.8%) experienced coronary events. $AmygA_C$ was associated with heightened CVD events risk in a model adjusted for age, sex, and CVD risk factors (OR: 1.200; 95% CI: 1.008-1.428; $P = 0.040$) (Supplemental Table 6). Furthermore, $AmygA_C$ was positively associated with coronary artery calcium score (standardized β: 0.072; 95% CI: 0.005-0.141; $P = 0.036$) and arterial SUV (standardized β: 0.119; 95% CI: 0.043-0.196; $P = 0.002$) as well as with inflammatory and leukopoietic indices (as high sensitivity C-reactive protein, white blood cell and neutrophil concentrations, and bone marrow and splenic ^{18}F-FDG uptake). PA was generally inversely associated with those measures (Supplemental Table 7).

DECREASED STRESS-RELATED NEURAL ACTIVITY MEDIATED THE CARDIOVASCULAR BENEFIT OF PHYSICAL ACTIVITY. Mediation analysis was used to test the hypothesis that reductions in $AmygA_C$ partially mediate PA's cardiovascular benefit. In this mediation analysis, the indirect pathway of: ↑ **PA** → ↓ **$AmygA_C$** → ↓ **CVD events** was significant (log-odds: −0.035; 95% CI: −0.084 to −0.002; OR: 0.96; 95% CI: 0.92-0.99; $P < 0.05$, adjusted for age and sex) and accounted for 7.9% of PA's total effect on CVD events risk (Figure 3). The direct path linking PA to CVD events (while not involving $AmygA_C$) also remained significant (log-odds: −0.399; 95% CI: −0.711 to −0.087; OR: 0.67; 95% CI: 0.49-0.92; $P = 0.012$).

THE CARDIOVASCULAR BENEFIT OF PHYSICAL ACTIVITY WAS GREATER AMONG INDIVIDUALS WITH DEPRESSION. Because PA reduces CVD risk in part via reductions in $AmygA_C$, we hypothesized that individuals with chronically heightened $AmygA_C$ may derive even greater cardiovascular benefits from PA. In the imaging cohort, we observed that individuals with (vs without) depression (258 vs 486, respectively) had elevated $AmygA_C$ (0.483 vs −0.143; $P = 0.009$). Therefore, within the parent cohort of 50,359, we tested: 1) whether PA's CVD benefits were greater among those with preexisting depression; and 2) whether PA's dose-response in CVD event risk reduction differed between those with and without depression.

CENTRAL ILLUSTRATION Continued

(Top) Study design. (Center left) Participants with physical activity at or above guidelines had significantly lower stress-related neural activity compared with participants with physical activity below guidelines ($P = 0.030$). (Center right) The beneficial effects of physical activity on cardiovascular risk were mediated by the physical activity-induced reduction of stress-related neural activity. (Bottom) HRs for CVD events across quintiles (Q) of physical activity, using Q1 as reference, in individuals without and with preexisting depression with adjustment for age, sex, and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes mellitus, and current/past smoking). *P* values represent the trend. *P* interaction presented in the Figure is that of PA quintiles*preexisting depression for adjusted 10-year CVD event risk benefit. Ranges of MET-min/wk for each PA quintile are Q1 (0-306), Q2 (307-795), Q3 (796-1,538), Q4 (1,539-2,517), and Q5 (2,518-18,720). Guideline PA recommendations of 500-1,000 MET-min/wk lie between Q2 and Q3 (green bars).[22] Error bars represent 95% confidence intervals. $AmygA_C$ = amygdalar to prefrontal cortex activity ratio; CVD = cardiovascular disease; MET-min/wk = metabolic equivalent of task-minutes/week; PA = physical activity; Q = quintile; Ref 1 = reference group (Quintile 1) in those without preexisting depression; Ref 2 = reference group (Quintile 1) in those with preexisting depression.

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TABLE 2 Cardiovascular Risk Reduction Associated With Physical Activity in Those With and Without Preexisting Depression

				Physical Activity Recommendations			Physical Activity Quintiles		
Event/Event Horizon	Group[a]	N[b]	Event Incidence[b]	HR[c] (95% CI)	*P* for Difference	*P* for Interaction[d]	HR† (95% CI)	*P* for Difference	*P* for Interaction[d]
CVD events									
10-y	Full cohort	46,385	5,978 (12.8)	0.765 (0.726-0.806)	<0.001	NA	0.916 (0.899-0.934)	<0.001	NA
	No depression	41,606	4,671 (11.2)	0.796 (0.749-0.845)	<0.001	0.077	0.929 (0.910-0.949)	<0.001	0.011
	Preexisting depression	4,092	620 (15.2)	0.696 (0.594-0.815)	<0.001		0.860 (0.810-0.915)	<0.001	
Consent to last follow-up	Full cohort	42,369	1,968 (4.6)	0.834 (0.760-0.914)	<0.001	NA	0.938 (0.907-0.969)	<0.001	NA
	No depression	33,393	1,391 (4.2)	0.885 (0.791-0.990)	0.033	0.206	0.954 (0.917-0.992)	0.017	0.408
	Preexisting depression	8,844	445 (5.0)	0.768 (0.637-0.927)	0.006		0.924 (0.861-0.991)	0.027	
Coronary events									
10-y	Full cohort	48,363	2,083 (4.3)	0.828 (0.758-0.905)	<0.001	NA	0.951 (0.921-0.982)	0.002	NA
	No depression	43,535	1,596 (3.6)	0.868 (0.783-0.962)	0.007	0.059	0.961 (0.927-0.996)	0.032	0.063
	Preexisting depression	4,576	235 (5.1)	0.668 (0.515-0.865)	0.002		0.871 (0.789-0.962)	0.006	
Consent to last follow-up	Full cohort	46,988	714 (1.5)	0.843 (0.724-0.981)	0.027	NA	0.923 (0.873-0.975)	0.004	NA
	No depression	36,753	486 (1.3)	0.954 (0.791-1.152)	0.625	0.02	0.959 (0.898-1.025)	0.217	0.041
	Preexisting depression	10,176	169 (1.6)	0.608 (0.448-0.825)	0.001		0.824 (0.731-0.930)	0.002	

Values are n (%) unless otherwise indicated. Cox regression model demonstrating cardiovascular event risk reduction in those with preexisting depression (diagnosed before consent date or the 10-year period leading to follow-up) vs those without. Median follow-up time for 10-year analyses: 10.0 years (Q1-Q3: 10.0-10.0 years). Median follow-up time from consent to first CVD event: 3.6 years (Q1-Q3: 2.3-5.0 years) and to the first coronary event: 3.6 years (Q1-Q3: 2.4-5.1 years). Interaction terms were used to test further the statistical significance of the differences observed between the hazard ratios in these 2 subpopulations. Physical activity recommendations (≥ or <500 metabolic equivalents of task-minutes per week (MET-min/wk). [a]Individuals with a new diagnosis of depression after the consent date (for consent to last follow-up analysis) or after 9/12/2010 (for 10-year event analysis) and before event were considered missing values. [b]Differences between numbers in Figure 1 and those in text are due to missing covariables. [c]Adjusted for age, sex, and cardiovascular risk factors (hypertension, diabetes mellitus, hyperlipidemia, and current/past smoking). [d]Interaction term = physical activity (< vs ≥ guideline-recommended amount) x history of depression (yes vs no). Coronary events included myocardial infarction, coronary revascularization, and unstable angina.

CVD = cardiovascular disease.

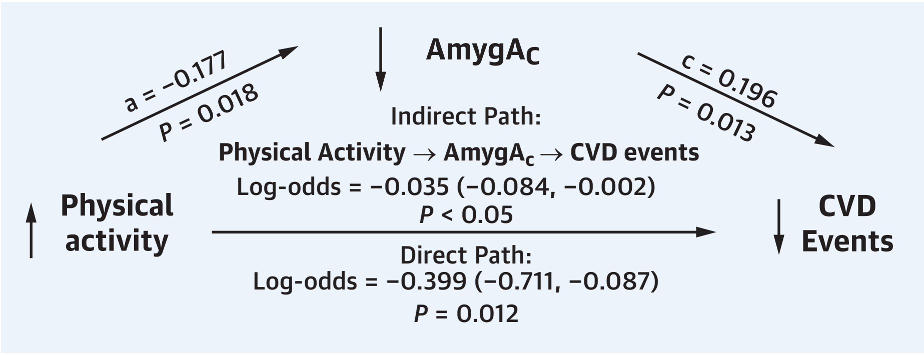
We observed that PA was associated with greater reductions in 10-year CVD event risk among individuals with preexisting depression (interquintile HR: 0.860; 95% CI: 0.810-0.915; vs 0.929; 85% CI: 0.910-0.949; *P* interaction = 0.011) (**Table 2**). Notably, across several CVD endpoints and event horizons, the CVD event risk reduction attained by achieving PA recommendations was approximately twice as great in those with depression (**Table 2**). Moreover, among the entire cohort (Supplemental Figure 2), as well as in those without depression (**Central Illustration**, bottom left), we observed that CVD event risk reduction plateaued after the third quintile of PA, which is roughly equivalent to the upper limit of guideline recommendations, a finding that has been noted in several prior studies.[22] On the other hand, among individuals with preexisting depression, we observed additional reductions in CVD events risk through the highest levels of PA (**Central Illustration**, bottom right). Specifically, individuals without depression achieved no further reductions in CVD event risk beyond the upper limit of the guideline recommendations for PA (approximately 300 minutes of moderate-intensity PA per week; *P* = 0.083). However, in those with preexisting depression, compared with the guidelines' recommended range for PA (which falls roughly between Q2 and Q3 of PA in this study), there was significant additional CVD event risk reduction through the highest quintile of PA (Q2-Q3 vs Q5 HR: 0.633; 95% CI: 0.465-0.861; *P* difference = 0.004; *P* interaction = 0.023).

DISCUSSION

We demonstrate that PA is associated with dose-dependent reductions in SNA and that this impact on SNA may partially mediate PA's cardiovascular benefit. Moreover, we observed that individuals with preexisting depression derive substantially greater CVD risk reduction from PA and continue to further benefit even at higher levels of PA in comparison with individuals without depression (**Central Illustration**). Together, our findings highlight a previously under-recognized impact of PA on the stress-related neural-immune-arterial axis pathway, which provides a mechanistic path underpinning the novel observation that individuals with depression derive greater CVD benefits from PA.

In the current study, we observed that PA's CVD benefits are partially achieved through the modulation of $AmygA_C$. This observation led to the hypothesis that the CVD benefits of PA would be greater among individuals with depression. Indeed, in the larger clinical cohort (n = 50,359), we observed that

FIGURE 3 AmygA$_C$ Mediates the Effect of Physical Activity on Cardiovascular Risk



Mediation analysis using a single mediator to assess whether physical activity (PA) exerts its cardioprotective effect partly through decreasing AmygA$_C$. The indirect and direct pathways are shown. PA was quantified using metabolic equivalents of a task-minutes/week (MET-min/wk) and then categorized into two groups: within or below recommendations (≥500 vs. <500 MET-min/wk). Mediation analysis was adjusted for age and sex. "a" and "c" represent the log-odds of the regression analysis PA → AmygA$_C$ and AmygA$_C$ → MACE, respectively. AmygA$_C$ = amygdalar to prefrontal cortex activity ratio; CVD = cardiovascular disease.

PA was more than twice as effective at reducing CVD risk among those with (vs without) preexisting depression. Notably, this finding provides crucial validation of the smaller imaging cohort's mechanistic observations and has important clinical implications. First, individuals with prior depressive episodes could be advised that, in addition to PA's well-described psychological benefits, PA's CVD benefits may be more than twice as great as in individuals without depression. Second, PA dose recommendations may differ among those with vs without depression. Notably, among those with depression, we observed continued reductions in CVD event risk with increasing PA dose without the plateauing effect that is commonly seen at higher levels of PA.[26] Together, these findings should prompt further study of the impact of PA among those with depression and even other, often concurrent,[27] psychiatric conditions that relate to chronic stress.

Our findings further highlight the role of stress-related neural-immune-arterial pathways in cardiovascular diseases. Notably, the study identifies PA as a potentially effective intervention to reduce the activation of this pathway. Future prospective and randomized trials are needed to evaluate the impact of PA on stress networks and to test the hypothesis that changes in SNA predict downstream changes in leukopoietic, inflammatory, and atherosclerotic disease measures. Moreover, studies identifying the mediators of PA's beneficial neural impacts are also needed, since addressing these mediators may prove effective for reducing SNA, and therefore improving psychological and cardiovascular health.

Importantly, we observed that PA was associated with dose-related increases in vmPFC activity. This increased vmPFC activity (in combination with a trend toward reductions in amygdalar activity) could underlie the observed lower AmygA$_C$ associated with higher PA. Inasmuch as prior studies have shown that higher cortical ^{18}F-FDG uptake is linked to lower risk of cognitive decline[28] and improved adaptive response to stress,[29] the observed increase in vmPFC activity is consistent with the known relationship between PA and cognitive health[30] and provides additional evidence to support the psychological benefits of PA.

STUDY LIMITATIONS. This study carries the inherent limitations of observational studies. The survey data were self-reported at a single time point, limiting the ability to longitudinally assess lifestyle factors that may change over time. Event classification was based on ICD codes, which could result in misclassification, and statistical analyses, despite accounting for many pertinent confounders, may not account for other unmeasured factors. The brain imaging subset underwent ^{18}F-FDG-PET/CT mainly for cancer screening and surveillance, which may limit the generalizability of our findings. Moreover, given the lack of temporal alignment between ^{18}F-FDG-PET/CT imaging and CVD events, a causative effect of AmygA$_C$ on CVD events cannot be derived from this study. However, several previous studies provide evidence of an association between heightened $AmygA_C$ and increased risk of incident CVD events.[5,11,12] Furthermore, mediation analysis findings are consistent with, but do not establish, a causal role for SNA in the relationship between PA and CVD. Nevertheless, the key findings from the mediation analyses are supported by findings in the larger cohort that PA has greater CVD benefits among individuals with preexisting depression. Additionally, although we provided evidence of an association between PA and leukopoietic activity, complete leukocyte characterization is not available in the MGB Biobank, which limits the ability to assess the association between PA and specific cellular subtypes.

CONCLUSIONS

Collectively, our study provides novel insights into the mechanisms underlying the cardiovascular benefit of PA. These findings may help clinicians emphasize the importance of PA for reducing CVD risk, alleviating stress, and enhancing brain health. They also should prompt providers to highlight PA's outsized impact on CVD risk among individuals with preexisting depression.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: PA modifies stress-related neural pathways associated with cardiovascular risk, such that exercise has a greater impact on risk reduction among individuals with higher stress-related neural activity (eg, those with depression).

TRANSLATIONAL OUTLOOK: Prospective studies exploring the role of the brain in mediating the cardiovascular benefit of PA could clarify the mechanisms relating brain activity and cardiovascular health and inform individualized exercise prescriptions.

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APPENDIX For supplemental materials, figures, tables, and references, please see the online version of this paper.