ESC European Society of Cardiology

European Heart Journal - Cardiovascular Imaging (2019) **20**, 625–632
doi:10.1093/ehjci/jez047

# Association between resting amygdalar activity and abnormal cardiac function in women and men: a retrospective cohort study

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*Received 15 January 2019; editorial decision 27 February 2019; accepted 4 March 2019; online publish-ahead-of-print 9 April 2019*

**Aims** Cardiovascular outcomes of women with coronary artery disease (CAD) are perceived as relatively worse when compared to men. Amygdalar metabolic activity has recently been shown to independently predict cardiovascular events in patients without known cardiovascular disease. Given that traditional algorithms for risk prediction perform worse in women than in men, we sought to assess sex-specific associations between amygdalar metabolic activity and cardiac dysfunction with suspected or known CAD.

**Methods and results** This retrospective study included 302 patients (mean age 66.8 ± 10.2 years, 29.1% women) selected for evaluation of CAD, malignant, or inflammatory disease. All patients had undergone both, myocardial perfusion imaging by single photon emission computed tomography (MPI-SPECT) and whole-body fluoro-18-deoxyglucose ($^{18}$F-FDG) positron emission tomography (PET), within 6 months. $^{18}$F-FDG resting amygdalar uptake was significantly increased in women with abnormal MPI scans (standardized uptake value 33.4 ± 6.5 vs. 30.4 ± 4.7, $P = 0.043$), while no such difference was observed in men ($P = 0.808$). In women, but not in men, a negative association between $^{18}$F-FDG resting amygdalar activity and left ventricular ejection fraction (LVEF) was observed (Pearson $r$ = -0.308, $P = 0.004$). Accordingly, either LVEF [B-coefficient (standard error, SE) = -0.232 (0.109), $P = 0.045$] or abnormal MPI [B-coefficient (SE) = 8.264 (2.449), $P = 0.003$] were selected as significant predictors of high amygdalar $^{18}$F-FDG uptake in a fully adjusted linear regression model in women, and a first order interaction term consisting of sex and LVEF or sex and abnormal MPI was significant ($P = 0.035$ and $P = 0.001$, respectively).

**Conclusion** Resting amygdalar metabolic activity is associated with abnormal cardiac function and perfusion in women, suggesting a link between emotional stress and cardiovascular disease in women.

**Keywords** amygdala • myocardial perfusion imaging • $^{18}$F-FDG positron emission tomography • women • emotional stress

## Introduction

Cardiovascular pathologies are the leading cause of death in the modern world. Increasing knowledge of sex-associated differences in manifestation and pathophysiology of coronary artery disease (CAD) has prompted efforts to reconsider traditional risk stratification models.[1] Indeed, female-specific characteristics of CAD, such as the greater prevalence of non-obstructive CAD, represent a major challenge for cardiovascular risk assessment in women.[2,3] Given that cardiovascular deaths in women presently outrun those in men,

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additional targets are needed in order to improve female cardiovascular risk stratification and early detection of CAD.[4]

The amygdala is an essential component of the neural network involved in stress and emotional responses.[5,6] An increased amygdalar metabolic activity was recently identified as an independent risk predictor of major adverse cardiac events (MACE) in individuals aged 30 years or older and free of cardiovascular disease or active cancer beyond the contribution of known cardiovascular risk factors.[7] An increase in bone-marrow metabolism as well as enhanced arterial inflammation was suggested as a potential mechanism linking enhanced amygdalar activity with an increased risk of cardiovascular events.[7,8] However, a direct association between cardiac function and amygdalar activity is currently unexplored. Further, although a female propensity towards conditions that are elicited from psychological stress is known,[9] it remains unclear whether quantification of amygdalar activity adds prognostic value in the female population.

Thus, the aim of the present study was to investigate the relationship between abnormal cardiac function or perfusion and resting amygdalar activity in a sex-stratified population of patients with suspected or known CAD.

# Methods

## Study population

Between November 2007 and February 2015, a total of 10 148 patients had undergone a 1-day adenosine, dobutamine, or exercise stress/rest $^{99m}$Tc-tetrofosmin single photon emission computed tomography myocardial perfusion imaging (MPI-SPECT) for detection of suspected or known CAD at the Department of Nuclear Medicine, University Hospital Zurich, Switzerland. During the same time period, 25 600 patients had undergone a whole-body (skull to mid-thigh) fluoro-18-deoxyglucose positron emission tomography ($^{18}$F-FDG PET) for screening, staging, or follow-up of malignancies or inflammatory disorders. All exams comprised a non-contrast-enhanced computed tomography (CT) for attenuation correction. In total, 332 patients had undergone both MPI-SPECT and whole-body $^{18}$F-FDG PET/CT within a time frame of 6 months. Of these 332 patients, 24 patients were excluded due to missing clinical data, and 6 patients were excluded because of insufficient image quality. Finally, $n = 302$ patients (mean age 66.8 ± 10.2 years, 29.1% women) were included in the study population. Patients were then stratified by sex, and demographic parameters and key factors of the patient's history were obtained by review of medical records. The mean time interval between MPI-SPECT and whole-body $^{18}$F-FDG PET/CT was 45.3 ± 4.6 (mean ± SEM) days in women and 47.2 ± 3.4 days in men. Three out of 302 patients underwent coronary revascularization between MPI-SPECT and $^{18}$F-FDG PET/CT. Our study is in line with the Declaration of Helsinki (including later amendments) and was approved by the local ethics committee (BASEC No. 2017–01112). The need for informed consent was waived by the ethics committee due to the retrospective and purely observational nature of the study. A flow diagram of patients included in the study is depicted in *Figure 1*.

## $^{99m}$Tc-tetrofosmin MPI-SPECT

Patients underwent an electrocardiography (ECG)-gated 1-day stress/rest protocol as previously described.[10] MPI-SPECT acquisition was conducted using a dual-head camera (Infinia Hawkeye, Ventri or Discovery NM/CT 570c, all GE Healthcare, Milwaukee, WI, USA). The camera consisted of a low-energy, high-resolution collimator at a 20% symmetric window (140 keV; 64 × 64 matrix). Cedars QGS/QPS software (Cedars-Sinai Medical Center, Los Angeles, USA) was applied for MPI-SPECT evaluation according to current guidelines.[11] Each myocardial segment was scored by application of a 20-segment model and a 5-point scoring system (consensus of two experienced readers) as previously reported in detail.[10,12] For coronary calcium scoring (CACS) and attenuation correction, a non-contrast CT exam was conducted using a 64-slice CT scanner (LightSpeed VCT, GE Healthcare) with the following parameters: 64 × 2.5 mm collimation, rotation time 0.35 s, tube voltage 120 kV, and tube current 200 mA.[13] The semi-automatic SmartScore software (GE Healthcare) was applied for quantification of CACS [Agatston units (AU)]. Segments with coronary artery stent implantation or bypass-vessels were excluded from CACS assessment.

## Whole-body $^{18}$F-FDG PET/CT technique and assessment of amygdalar activity

$^{18}$F-FDG is a glucose analogue routinely used in PET/CT imaging for assessment of tissue metabolism (i.e. tumour imaging[14,15]). After measurement of patient's blood glucose (6.2 ± 1.7 mmol/L in women and 6.5 ± 1.7 mmol/L in men, $P = 0.140$ for men vs. women), injection of $^{18}$F-FDG was performed (334.5 MBq, range 180–409 MBq) into a peripheral vein. 45 min–1 hr following injection of the tracer, standardized PET image acquisition protocols (skull to mid-thigh) were applied, including a non-contrast CT scan. Images were registered in 3D mode on various scanners (Discovery VCT or Discovery RX, GE-Healthcare, Milwaukee, WI, USA). PET/CT images were fused on a dedicated workstation (AW 5.0 GE-Healthcare). Whole-body scans were cropped for the skull and quantitative $^{18}$F-FDG uptake was assessed by serially placing regions of interest in the left and right amygdala using PMOD software (version 3.7 to 3.8, PMOD Technologies Ltd.).[16–18] The mean tracer accumulation [standardized uptake value (SUV)] was measured in the areas of interest, normalized for volume, and corrected for cerebellar activity as previously described.[7,19]

## Statistical analysis

Patient baseline characteristics are reported as mean ± standard deviation (SD) or standard error (SE) for continuous and frequencies together with percentages for categorical variables. Prior to analysis, distribution of data was visually assessed by quantile–quantile (Q–Q) and histogram plots. Based on these tests, normal distribution was observed for the variables left ventricular ejection fraction (LVEF) and $^{18}$F-FDG resting amygdalar uptake. Comparative analysis of variables was performed by Student's *t*-test, analysis of variance (ANOVA), or $\chi^2$, as appropriate. Bonferroni correction was applied in multiple comparisons. Correlations were assessed by application of the Pearson product-moment test. Multivariate stepwise linear regression analysis adjusted for age, beta-blocker use, various cardiovascular risk factors [dyslipidaemia, hypertension, positive family history of CAD, body mass index (BMI), diabetes mellitus, known CAD, and current smoking], and active cancer was applied to assess the association of resting amygdalar activity either with LVEF, cardiac scar, or abnormal cardiac perfusion (cardiac ischaemia and/or scar). Missing LVEF values were not included in the final analysis ($n = 12$). All tests were two-sided, and *P*-values below 0.05 were considered statistically significant. Statistical analyses were performed with IBM SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

# Results

## Study population

A total of 302 patients (29.1% women) were assessed for associations between resting amygdalar activity and cardiac function/perfusion. The mean age was 69.0 ± 10.0 years for women and 66.0 ± 10.2 for men ($P = 0.018$). Consistent with many previous reports[20,21]

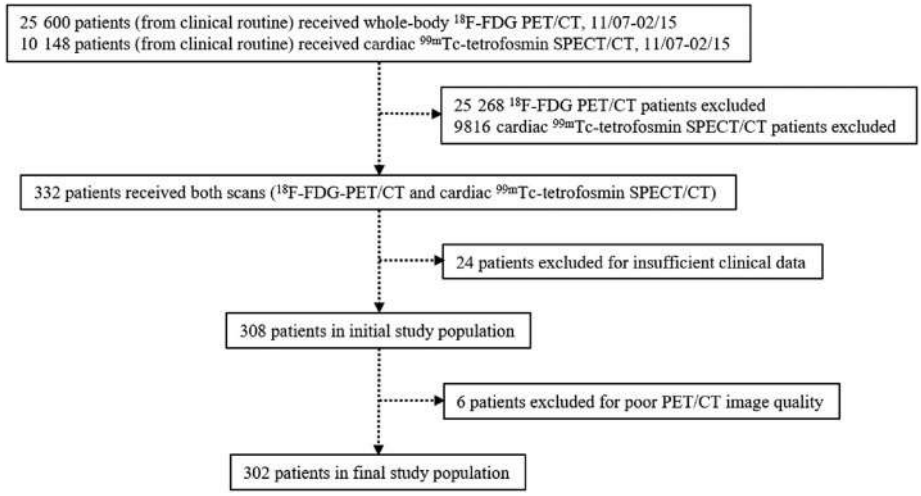


**Figure 1** Study cohort. Flow-chart demonstrating eligible study patients selected on pre-defined criteria. A total of 302 patients entered the final study population.

women showed a significantly higher LVEF than men (64.2 ± 12.9% in women vs. 56.3 ± 12.7% in men, $P < 0.001$). Amongst all patients presenting with reduced (<55%) LVEF, 78.6% of individuals had a fixed myocardial perfusion defect. Women in our study had less often known CAD, prior coronary revascularization procedures, and abnormal cardiac perfusion than men (*Table 1*). The latter is consistent with large-scale epidemiological data reporting a higher prevalence of (visually non-detectable) non-obstructive CAD in women.[22] Notably, following Bonferroni correction for multiple testing, a significant difference between men and women was seen only for LVEF, while other sex differences in baseline characteristics and imaging findings were no longer evident (*Table 1*).

## Association of left ventricular ejection fraction with resting amygdalar activity

LVEF showed a significant and moderate correlation with $^{18}$F-FDG resting amygdalar uptake in women ($r = -0.308$, $P = 0.004$, *Figure 2A*), but not in men ($r = 0.136$, $P = 0.054$, *Figure 2B*). Dichotomous stratification of LVEF by application of a cut-off value of 55% further revealed a significantly increased $^{18}$F-FDG resting amygdalar uptake in women with low LVEF < 55% vs. LVEF ≥ 55% (SUV 33.2 ± 5.3 in women with LVEF < 55% vs. 30.3 ± 5.0 in women with LVEF ≥ 55%, $P = 0.029$, *Figure 2C*). This increase in amygdalar activity was not observed in men with reduced LVEF (SUV 28.4 ± 5.8 in men with LVEF < 55% vs. 29.4 ± 5.2 in men with LVEF ≥ 55%, $P = 0.175$, *Figure 2D*). Clinical characteristics of patients stratified by LVEF and sex are given in Supplementary data online, *Table S1*.

## Association of haemodynamic variables, myocardial perfusion abnormalities, and cardiovascular risk factors with resting amygdalar activity

The presence of abnormal cardiac perfusion (women: $n = 15$, men: $n = 64$) as assessed by MPI-SPECT was associated with significantly higher resting amygdalar activity as compared to normal myocardial perfusion. This difference was observed in women, but not in men (SUV values of 33.4 ± 6.5 vs. 30.4 ± 4.7 in women, $P = 0.043$, *Figure 2C*, 28.9 ± 6.0 and 29.1 ± 5.1 in men, $P = 0.808$, *Figure 2D*). When myocardial perfusion defects were subdivided into reversible (=cardiac ischaemia; women: $n = 6$; men: $n = 31$) and fixed defects (=cardiac scar; women: $n = 11$, men: $n = 49$), an increase in amygdalar activity was only observed in women with fixed defects (SUV values of 35.0 ± 6.3 vs. 30.3 ± 4.7, $P = 0.004$, *Figure 2E*), but not in women with reversible myocardial perfusion defects (SUV values of 29.4 ± 4.4 vs. 31.0 ± 5.2, $P = 0.472$, *Figure 2E*). Again, this difference was not observed in men (fixed defects: SUV values of 28.4 ± 5.7 vs. 29.3 ± 5.3, $P = 0.305$; reversible defects: 28.3 ± 6.7 vs. 29.2 ± 5.1, $P = 0.402$, *Figure 2F*). When resting amygdalar activity was compared between patients with and without cardiovascular risk factors or chronic, non-cardiac, illness, no significant differences were found in both, men and women (*Table 2*). Similarly, no significant association was found between resting heart rate and resting amygdalar activity (total population: $r = -0.027$, $P = 0.668$; women: -0.053, $P = 0.657$; men: -0.032, $P = 0.667$). Clinical characteristics of patients stratified by myocardial perfusion and sex are given in Supplementary data online, *Table S2*.

## Prognostic value of cardiac function/perfusion on female resting amygdalar activity

LVEF was tested in a stepwise linear regression analysis with resting $^{18}$F-FDG amygdalar uptake being the dependent variable, and age, beta-blocker use, cardiovascular risk factors (including dyslipidaemia, hypertension, positive family history of CAD, BMI, diabetes mellitus, known CAD, and current smoking), and active cancer as predictor variables. Only LVEF remained in the model as a significant and independent predictor for female $^{18}$F-FDG resting amygdalar uptake, while other variables were not selected (*Table 3*). Similarly, abnormal

**Table 1 Patient baseline characteristics**

| | Total ($n$ = 302) | Women ($n$ = 88) | Men ($n$ = 214) | $P$-value (women vs. men) |
|---|---|---|---|---|
| Age (years), mean ± SD | 66.8 ± 10.2 | 69.0 ± 10.0 | 66.0 ± 10.2 | 0.018 |
| BMI (kg/m$^2$), mean ± SD | 28.1 ± 17.3 | 29.7 ± 22.8 | 27.4 ± 14.7 | 0.769 |
| Hypertension, *n* (%) | 142 (47) | 42 (47.7) | 100 (46.7) | 0.874 |
| Smoking, *n* (%) | 93 (30.8) | 20 (22.7) | 73 (34.1) | 0.058 |
| Diabetes mellitus, *n* (%) | 56 (18.5) | 14 (15.9) | 42 (19.6) | 0.450 |
| Dyslipidaemia, *n* (%) | 73 (24.2) | 20 (22.7) | 53 (24.8) | 0.707 |
| Family history of CAD, *n* (%) | 25 (8.3) | 11 (12.5) | 14 (6.5) | 0.088 |
| Known CAD, *n* (%) | 117 (38.7) | 25 (28.4) | 92 (43) | 0.018 |
| Previous MI, *n* (%) | 57 (18.9) | 13 (14.8) | 44 (20.6) | 0.243 |
| Previous PCI/CABG, *n* (%) | 82 (27.2) | 17 (19.3) | 65 (30.4) | 0.050 |
| CACS>75th percentile, *n* (%) | 95 (31.5) | 30 (34.1) | 65 (30.4) | 0.896 |
| Cardiac ischaemia, *n* (%) | 37 (12.3) | 6 (6.8) | 31 (14.5) | 0.065 |
| Cardiac scar, *n* (%) | 60 (19.9) | 11 (12.5) | 49 (22.9) | 0.040 |
| Abnormal cardiac perfusion, *n* (%) | 79 (26.2) | 15 (17) | 64 (29.9) | 0.021 |
| Active cancer, *n* (%) | 193 (63.9) | 58 (65.9) | 135 (63.1) | 0.642 |
| Depression, *n* (%) | 19 (6.3) | 5 (5.7) | 14 (6.5) | 0.756 |
| Chronic pain, *n* (%) | 90 (29.8) | 24 (27.3) | 66 (30.8) | 0.491 |
| Beta-blocker, *n* (%) | 146 (48.3) | 34 (38.6) | 112 (52.3) | 0.015 |
| ACE/ARBs, *n* (%) | 156 (51.7) | 44 (50) | 112 (52.3) | 0.547 |
| Statin, *n* (%) | 126 (41.7) | 38 (43.2) | 88 (41.1) | 0.875 |
| P2Y12 inhibitors, *n* (%) | 27 (8.9) | 6 (6.8) | 21 (9.8) | 0.372 |
| ASS, *n* (%) | 128 (42.4) | 30 (34.1) | 98 (45.8) | 0.037 |
| Antidepressants, *n* (%) | 33 (10.9) | 11 (12.5) | 22 (10.3) | 0.601 |
| Corticosteroids, *n* (%) | 40 (13.2) | 12 (13.6) | 28 (13.1) | 0.932 |
| Analgesics, *n* (%) | 135 (44.7) | 40 (45.5) | 95 (44.4) | 0.945 |
| LVEF (%), mean ± SD | 58.7 ± 13.2 | 64.2 ± 12.9 | 56.3 ± 12.7 | <0.001[a] |
| LVEF <55%, *n* (%) | 93 (32.1) | 18 (20.7) | 75 (36.9) | 0.007 |
| Resting heart rate (b.p.m.), mean ± SD | 75.3 ± 15.7 | 77.2 ± 14.1 | 74.6 ± 16.3 | 0.230 |
| Creatinine (μmol/L), mean ± SD | 117.7 ± 150.0 | 85.0 ± 56.1 | 129.8 ± 170.8 | 0.068 |
| NT-proBNP (ng/L), mean ± SD | 1348.3 ± 1729.1 | 973.1 ± 1025.1 | 1523.3 ± 1982.7 | 0.500 |
| Symptoms | | | | |
| Typical angina pectoris, *n* (%) | 30 (9.9) | 6 (6.8) | 24 (11.2) | 0.246 |
| Atypical angina pectoris, *n* (%) | 23 (7.6) | 10 (11.4) | 13 (6.1) | 0.115 |
| Dyspnoea (≥NYHA II), *n* (%) | 39 (12.9) | 17 (19.3) | 22 (10.3) | 0.033 |
| None, *n* (%) | 210 (69.5) | 55 (62.5) | 155 (72.4) | 0.088 |
| Indication for SPECT | | | | |
| Preoperative evaluation, *n* (%) | 186 (61.6) | 60 (68.2) | 126 (58.9) | 0.131 |
| Known CAD, *n* (%) | 60 (19.9) | 14 (15.9) | 46 (21.5) | 0.269 |
| Suspected CAD, *n* (%) | 56 (18.5) | 14 (15.9) | 42 (19.6) | 0.450 |
| Indication for PET | | | | |
| Inflammation, *n* (%) | 46 (15.2) | 11 (12.5) | 35 (16.4) | 0.397 |
| Cancer, *n* (%) | 256 (84.8) | 77 (87.5) | 179 (83.6) | 0.397 |

Data are presented as mean ± standard deviation (SD) or frequencies (percentage). Two-sided $P$-values are reported.
ACE/ARBs, angiotensin converting enzyme/angiotensin II receptor blockers; ASS, acetylsalicylic acid; BMI, body mass index; b.p.m., beats per minute; CABG, coronary artery bypass graft; CACS, coronary artery calcium score; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NT-proBNP, n-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; PET, positron emission tomography; SPECT, single proton emission computed tomography.
[a]Persistent statistical significance after application of Bonferroni method for multiple testing.

cardiac perfusion was tested against the above variables in a stepwise linear regression analysis with $^{18}$F-FDG resting amygdalar uptake being the dependent variable. In this analysis, abnormal cardiac perfusion and hypertension remained as significant predictors for $^{18}$F-FDG resting amygdalar uptake in the model, while other variables were not selected (*Table 3*). Conversely, in men, no significant associations between these independent variables and $^{18}$F-FDG resting amygdalar activity were found (data not shown). Further, when a stepwise linear

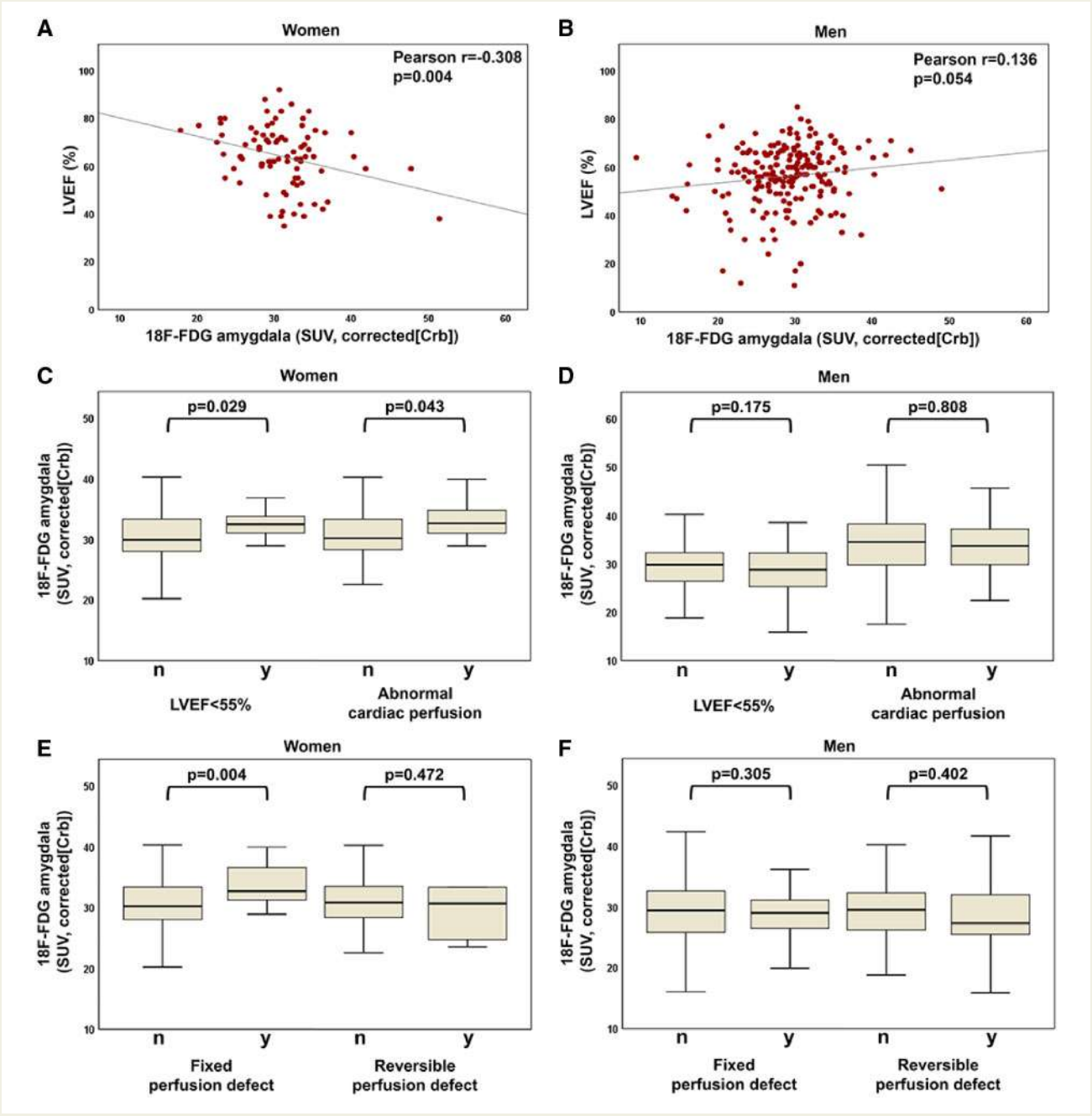


**Figure 2** Association of resting amygdalar activity with cardiac function and perfusion between women and men. Pearson product-moment correlation of left ventricular ejection fraction (LVEF) with $^{18}$F-FDG resting amygdalar uptake (SUV) for female (*A*) and male study patients (*B*). Dichotomous comparison of $^{18}$F-FDG resting amygdalar uptake with LVEF (cut-off value of 55%), presence of abnormal cardiac perfusion, reversible perfusion defect, or fixed perfusion defect for women (*C* and *E*) and men (*D* and *F*). *P*-values are indicated.

regression analysis was performed in the total study population, interaction terms consisting of LVEF and female sex ($P = 0.035$, *Table 4*), abnormal cardiac perfusion and female sex ($P = 0.001$, *Table 4*), and fixed perfusion defect and female sex [B-coefficient (SE) 8.302 (2.393), $P = 0.001$, data not shown] were selected as the only significant predictors of $^{18}$F-FDG resting amygdalar activity thereby confirming that this association is dependent on patient's sex. The complete list of predictor variables used in these models is provided in Supplementary data online, *Tables S3A* and *S3B*.

## Discussion

In the present study, we found evidence of sex differences in the association between impaired cardiac function and increased resting

**Table 2 Impact of (cardiac) risk factors on resting amygdalar activity**

| | Women ($n = 88$, SUV) | | *P*-value | Men ($n = 214$, SUV) | | *P*-value |
|---|---|---|---|---|---|---|
| **Risk factors** | **Absent** | **Present** | | **Absent** | **Present** | |
| Age > 70 (years) | 31.4 ± 5.2 | 30.4 ± 5.1 | 0.376 | 29.6 ± 4.7 | 28.2 ± 6.3 | 0.055 |
| Obesity (BMI > 25 kg/m$^2$) | 31.0 ± 4.4 | 30.7 ± 7.3 | 0.830 | 28.8 ± 5.4 | 30.0 ± 5.4 | 0.168 |
| Hypertension | 31.8 ± 5.1 | 29.9 ± 5.0 | 0.104 | 28.8 ± 5.5 | 29.3 ± 5.3 | 0.489 |
| Smoking | 31.0 ± 5.6 | 30.3 ± 3.6 | 0.588 | 28.8 ± 5.7 | 29.7 ± 4.7 | 0.254 |
| Diabetes | 31.2 ± 4.7 | 29.4 ± 7.0 | 0.238 | 28.8 ± 5.6 | 30.4 ± 4.3 | 0.084 |
| Dyslipidaemia | 30.9 ± 4.8 | 31.0 ± 6.2 | 0.915 | 29.1 ± 5.5 | 29.0 ± 5.1 | 0.945 |
| Family history of CAD | 30.8 ± 4.9 | 31.7 ± 6.7 | 0.589 | 29.2 ± 5.5 | 27.8 ± 3.2 | 0.368 |
| CACS > 75th percentile | 30.4 ± 4.7 | 30.2 ± 5.6 | 0.856 | 28.9 ± 4.7 | 28.9 ± 5.0 | 0.945 |
| Depression | 31.0 ± 4.8 | 27.8 ± 9.1 | 0.172 | 29.2 ± 5.5 | 26.4 ± 3.3 | 0.058 |
| Chronic pain | 31.3 ± 4.7 | 29.8 ± 6.1 | 0.213 | 28.9 ± 5.6 | 29.3 ± 5.1 | 0.623 |
| Active cancer | 30.4 ± 6.1 | 31.2 ± 4.6 | 0.492 | 28.9 ± 4.9 | 29.2 ± 5.6 | 0.731 |
| LVEF < 55% | 30.3 ± 5.0 | 33.2 ± 5.3 | 0.029 | 29.4 ± 5.2 | 28.4 ± 5.8 | 0.175 |
| Reversible perfusion defect | 31.0 ± 5.2 | 29.4 ± 4.4 | 0.472 | 29.2 ± 5.1 | 28.3 ± 6.7 | 0.402 |
| Fixed perfusion defect | 30.3 ± 4.7 | 35.0 ± 6.3 | 0.004 | 29.3 ± 5.3 | 28.4 ± 5.7 | 0.305 |
| Abnormal cardiac perfusion | 30.4 ± 4.7 | 33.4 ± 6.5 | 0.043 | 29.1 ± 5.1 | 28.9 ± 6.0 | 0.808 |

Data are presented as mean ± SD. Two-sided *P*-values are indicated.
BMI, body mass index; CACS, coronary artery calcium score; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; SUV, standardized uptake value.

**Table 3 Stepwise linear regression model for $^{18}$F-FDG resting amygdalar uptake in women ($n = 88$)**

| Independent variables | B-coefficient (SE) | *P*-value |
|---|---|---|
| Model 1 | | |
| Left ventricular ejection fraction (%) | -0.232 (0.109) | 0.045 |
| Model 2 | | |
| Abnormal cardiac perfusion | 8.264 (2.449) | 0.003 |
| Hypertension | -5.193 (2.053) | 0.020 |

Stepwise method was performed among age, beta-blocker, cardiovascular risk factors (including hypertension, diabetes mellitus, dyslipidaemia, positive family history of coronary artery disease, body mass index, known coronary artery disease, and current smoking), active cancer, left ventricular ejection fraction, or abnormal cardiac perfusion. Only variables staying in the final model are presented.
SE, standard error.

amygdalar metabolic activity in patients with known or suspected CAD. Impaired LV function or abnormal myocardial perfusion was selected as significant predictors of enhanced amygdalar activity by a fully adjusted linear regression model in women, but not in men. As the amygdala is the key component of the brain's limbic network involved in the emotional perception and generation of stress,[5] our data indicate that the neural stress response to chronic cardiovascular illness differs substantially between men and women, with a stronger reaction being observed in women. To the best of our knowledge, this is the first study to demonstrate such an association.

Chronic emotional stress is a well-known and important health issue and has been related to an increased susceptibility to cardiovascular mortality.[23] An enhanced sympathetic activity and subsequent adverse haemodynamic changes have been suggested to account for this association.[24] Importantly, sexual dimorphism in sympathetic activity is currently gaining increasing attention in the context of Takotsubo cardiomyopathy or microvascular dysfunction, both conditions being primarily observed in women.[9,25–28] Further, the worse outcomes observed in females with cardiovascular pathologies as well as their higher susceptibility to cardiac injury during high-stress situations implies that sex differences in cardiovascular sympathetic control might be pathogenetic.[29,30] Indeed, acute coronary syndromes (ACS) have been shown to trigger a stronger sympathetic response in women as compared to men which lasts for 9 months[31] and adds to an unfavourable outcome.[32] Similarly, recent data indicate that women are more likely than men to develop mental stress-induced myocardial ischaemia, and that women presenting with an ACS perceive greater psychological stress than men, which, in turn, is associated with worse recovery and prognosis.[29,33,34] Given that the amygdalar efferent projections leading to the brainstem are involved in stress-induced sympathetic activation[6] and are upregulated in anxiety or post-traumatic stress disorders,[35,36] our data further support an important pathogenetic role of sympathetic modulation in women with cardiovascular disease by linking impaired left ventricular function with enhanced metabolic activity in the amygdalar region. Indeed, taken together with previous data from Tawakol *et al.*[7] who report higher MACE rates in patients with enhanced amygdalar activity, our results support the theory that a disproportionate burden of mental stress might account, at least in part, for the worse outcomes observed in women with cardiovascular disease.

Interestingly, in their study Tawakol *et al.*[7] found a positive association between enhanced tracer uptake in the amygdalar region and increased bone marrow activity suggesting an enhanced, sympathetic-driven bone marrow activation triggering a potential inflammatory response which might contribute to their observation of

**Table 4 Stepwise linear regression model for $^{18}$F-FDG resting amygdalar uptake in total population ($n$ = 302)**

| Independent variables | B-coefficient (SE) | *P*-value |
|---|---|---|
| Model 1 | | |
| Female sex × left ventricular ejection fraction (%) | -0.216 (0.101) | 0.035 |
| Model 2 | | |
| Female sex × abnormal cardiac perfusion | 8.302 (2.393) | 0.001 |

Stepwise method was performed among female sex, age, beta-blocker, cardiovascular risk factors (including hypertension, diabetes mellitus, dyslipidaemia, positive family history of coronary artery disease, body mass index, known coronary artery disease, and current smoking), active cancer, left ventricular ejection fraction or abnormal cardiac perfusion, and interaction terms of female sex and left ventricular ejection fraction or abnormal cardiac perfusion. Only variables staying in the final model are presented.
SE, standard error.

an increased cardiovascular risk in patients with enhanced amygdalar activity. As atherosclerosis is largely accepted as a chronic low-grade inflammatory condition, a link between emotional stress, high sympathetic activity, and enhanced inflammation might explain the relation between abnormal cardiac perfusion and increased tracer uptake in the amygdalar region observed in our female study population. Notably, amygdalar activity was not altered in patients with a high CACS (>75th percentile), suggesting that the presence of myocardial injury rather than the amount of plaque burden triggers a neural stress response in women. In addition, in contrast to previous reports demonstrating induction of acute ischaemia in women exposed to mental stress,[29,34] we did not observe an increase in amygdalar activity in women with reversible perfusion defects. Different study populations and a higher percentage of older women and women with known CAD in our study might account for these discrepancies. Further, our findings of an enhanced amygdalar activity in women with fixed myocardial perfusion defect, as well as the lack of association between resting heart rate and amygdalar activity in our study, support the hypothesis that a chronic disease process rather than acute ischaemia is the major trigger of an enhanced stress response in women. Altogether, our findings emphasize the importance of implementing measures to reduce psychological stress and negative affective states in women with cardiac conditions. Whether a targeted anti-inflammatory treatment might be particular useful in women with CAD will have to be assessed by future studies in larger samples.

There are limitations to this study that should be pointed out. First, this study is a retrospective cohort analysis conducted in a single centre, which consequently limits its generalizability. Second, our study is purely observational. We report the association between abnormal cardiac function or perfusion and amygdalar activity in patients referred for evaluation for CAD. Our study does not provide information on the underling mechanism, nor on the direction of the effect. Third, our study population comprises a relatively heterogeneous group of patients including individuals with active cancer. Although our regression models were adjusted for the presence or absence of active malignancies, we cannot completely rule out residual confounding of ongoing chemotherapy or psychological stress associated with chronic malignant disease (reverse causation) in our study. Fourth, although the mean time interval between the two imaging exams was only 47 days, changes in coronary circulation occurring during this time cannot be excluded. Finally, given that patients were not specifically referred for assessment of cardio-neurological associations, we cannot completely rule out a potential selection bias in our study. Thus, our findings should be considered hypothesis generating and need to be confirmed in larger investigations that are preferably prospective in nature.

Collectively, our findings indicate that neural stress responses to myocardial damage differ by sex and suggest that women are disproportionally vulnerable to the adverse mental effects of chronic cardiovascular disease. Our study points toward a potential mechanism for the known relationships among female sex, perceived stress, and adverse cardiovascular outcomes. Continued effort is required to investigate the effect of stress mitigation strategies on cardiovascular outcomes in women and future studies will have to evaluate whether there is a clinical role for neuronal imaging in phenotyping patients at risk for future cardiac events.

# Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

## Acknowledgements

We thank all nuclear cardiologists/radiologists, nurses, and technical staff at the Department of Nuclear Medicine for their contribution to this study.

## Funding

The Swiss National Science Foundation (SNSF), the Olga Mayenfisch Foundation, Switzerland, the OPO Foundation, Switzerland, the Novartis Foundation, Switzerland, the Swissheart Foundation, and the Helmut Horten Foundation, Switzerland to C.G.; the Swiss Paraplegic Center, Nottwil, Switzerland to M.F.; the Iten-Kohaut Foundation, Switzerland to M.M.

**Conflict of interest:** All authors have the following to disclose: The University Hospital of Zurich holds a research contract with GE Healthcare. C.G. has received research grants from the Novartis Foundation, Switzerland.

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