

Additional file 2: Table S1 Characteristics of included studies.

Author (year)	Study design	Patient group	N =	Mean age (\pm SD)	Sex (F/M)	Control group	N =	Mean age (\pm SD)	Sex (F/M)	Imaging modality (outcome parameter)
Meeder (1997)	Case-control	Patients with syndrome X with typical cardiac chest pain with exercise-induced ischaemic-appearing electrocardiographic changes (>1 mm horizontal ST-T segment depression) and/or reversible myocardial perfusion defects at thallium-201 perfusion scintigraphy and no significant CAD on CAG. Gastro-intestinal causes of chest pain were excluded.	25	51 \pm 9	16/9	Healthy volunteers	21	42 \pm 13	8/13	PET (MPR), N-13 ammonia; dipyridamole
Bottcher (1999)	Case-control	Angina pectoris and positive stress ECG, normal CAG without risk factors for CAD.	25	53 \pm 7	25/0	Healthy age and sex matched volunteers	15	54 \pm 10	15/0	PET (CFR), N-13 ammonia; dipyridamole
Buus (1999) (71)	Case-control	Typical effort angina, positive stress ECG, normal CAG and TTE. No history of hypertension or diabetes mellitus.	16	56.6 \pm 1.2	13/3	Healthy subjects (recruited among blood donors and hospital staff)	15	53.5 \pm 1.1	12/3	PET (CFR), N-13 ammonia; dipyridamole
Panting (2002)	Case-control	Typical effort angina, abnormal stress ECG, normal CAG recruited from Women's Heart Disease Clinic at Royal Brompton Hospital (London).	20	55.9 \pm 10.5	16/4	Healthy age and sex matched subjects, no history of chest pain and low cardiovascular risk profile. No SPECT or CAG was performed.	10	57.9 \pm 7.4	8/2	CMR (MPRI), 1.5T; adenosine

Marroquin (2003)	Case-control	Women with chest pain and epicardial coronaries that were angiographically normal or with only minimal luminal irregularities (<50% stenoses) who were enrolled in the WISE study at the University of Pittsburgh.	34	52.1 ± 10.0	34/0	Healthy age-matched women.	9	50.4 ± 12.2	9/0	PET (CFR), 13-N ammonia; adenosine
De Vries (2006)	Case-control	Typical chest pain and normal CAG. Exclusion: LBBB on ECG, first degree AV block and diabetes mellitus.	42	58 ± 12	26/16	Healthy volunteers without chest pain or CAD.	21	N/A	N/A	PET (CFR), N-13 ammonia; dipyridamole
Graf (2006)	Case-control	Typical angina, normal CAG and positive stress ECG or SPECT, exclusion of myocardial or valvular disease by TTE. Exclusion: diabetes mellitus.	58	58 ± 10	39/19	N/A	N/A	N/A	N/A	PET (CFR), N-13 ammonia; dipyridamole
Pärkkä (2006)	Cross-sectional/ descriptive	N/A	N/A	N/A	N/A	Male volunteers, nonsmoking. One patient with hypertension, others no history of cardiovascular disease.	18	40.0 ± 14.4	0/18	CMR, 1.5T; dipyridamole PET, 15O-labeled water; dipyridamole
Wöhrle (2006)	Case series	Typical angina pectoris and normal CAG	12	61.8 ± 8.2	7/5	N/A	N/A	N/A	N/A	CMR (MPRI), 1.5T; gadolinium, adenosine

Galiuto (2007)	Case-control	Typical effort angina, positive stress ECG and normal CAG. Exclusion: moderate to severe hypertension, diabetes mellitus, other heart disease or contraindications to adenosine infusion.	17	55 ± 10	9/8	Healthy subjects age and sex matched. Exclusion: moderate to severe hypertension, diabetes mellitus, other heart disease or contraindications to adenosine infusion.	17	55 ± 10	10/7	TTE (CFR), distal LAD with pulse-wave Doppler; adenosine
Graf (2007)	Case-control	Typical angina, normal CAG and positive stress ECG or SPECT. Myocardial or valve disease excluded by TTE. Exclusion: diabetes mellitus and other major diseases.	79	58 ± 10	52/27	Atypical chest pain, normal CAG and negative stress test. Myocardial or valve disease excluded by TTE. Exclusion: diabetes mellitus and other major diseases.	10	53 ± 11	6/4	PET (CFR), N-13 ammonia; dipyridamole
Vermeltfoort (2007)	Case series	Effort angina, positive stress ECG or SPECT and normal CAG. Exclusion: history of heart disease, hypertension, diabetes mellitus, absence of pain without medication, contra-indication for CMR.	20	55 ± 11	15/5	N/A	N/A	N/A	N/A	CMR (MPRI), 1.5T; adenosine
Cemin (2008)	Case-control	N/A	N/A	N/A	N/A	Healthy volunteers with low pretest likelihood of coronary disease who were undergoing CAG.	14	62.6 ± 9.1	8/6	TTE (CFR), distal LAD with pulse-wave Doppler; adenosine
Lanza (2008)	Case-control	Effort angina, positive stress test and normal CAG. Exclusion: history of heart disease or systemic diseases.	18	58 ± 7	11/7	Healthy volunteers, enrolled from the non-medical hospital staff, comparable in age and sex.	10	54 ± 8	6/4	TTE (CFR), mid-distal LAD with Doppler spectral tracing; adenosine

Di Monaco (2009)	Case-control	Patients presenting with effort angina, positive stress test and normal CAG in a university hospital. Exclusion: previous enrollment in SPECT study.	29	59 ± 7	18/1 1	Healthy subjects, age and sex matched.	20	56 ± 6	12/8	TTE (CFR), mid-distal LAD with Doppler spectral tracing; adenosine.
Mehta (2011) (72)	RCT	Women with chest pain and abnormal stress testing, no obstructive CAD (<50%) on CAG. Exclusion: renal failure or hepatic insufficiency, contraindication to withholding nitrates, calcium channel agents and beta-adrenergic blockers for 24h, contraindication to CMR and use of drugs inhibiting CYP3A.	20	57 ± 11	20/0	N/A	N/A	N/A	N/A	CMR (MPRI), 1.5T; adenosine
Scholtens (2011)	Case-control	Patients submitted for PET analysis because of typical chest pain, positive stress ECG and normal CAG.	14	55 (34-76) <i>Median (range)</i>	10/4	Healthy subjects	13	58 (48-73) <i>Median (range)</i>	11/2	PET (MPR), N-13 ammonia; adenosine.
Sestito (2011)	Case-control	Patients with a history of effort angina, positive stress test and normal CAG undergoing clinical follow-up. Exclusion: other cardiac or systemic disease.	71	56 ± 9	48/2 3	Healthy volunteers enrolled from the nonmedical hospital staff, age and sex matched.	20	52 ± 7	11/9	TTE (CBF), mid-distal LAD with Doppler spectral tracing; adenosine
Vaccarino (2011)	Cohort	N/A	N/A	N/A	N/A	Middle aged male-male twin pairs from the Vietnam Era Twin Registry without previous history of CAD.	268	54.0 (53.5–54.6) <i>Median (range)</i>	0/26 8	PET (CFR), N-13 ammonia; adenosine

Vermeltfoort (2011)	Case series	N/A	N/A	N/A	N/A	Healthy subjects without cardiovascular risk factors.	27	41 ± 13	16/11	PET (CFR), 15O-labeled water; adenosine.
Di Franco (2012)	Case-control	Effort angina, positive stress test and normal CAG enrolled at outpatient ambulatory clinic.	14	61 ± 5	9/5	Healthy subjects enrolled from patients referred to outpatient cardiology clinic for palpitations or evaluation of cardiovascular risk, age and sex matched.	14	61 ± 3	7/7	TTE (CBF), mid-distal LAD with Doppler spectral tracing; adenosine
Karamitsos (2012)	Case-control	Typical effort angina, abnormal stress ECG and normal CAG. Exclusion: diabetes mellitus, hypertension and other cardiac or systemic disease.	18	62 ± 8	15/3	Healthy individuals without cardiovascular risk factors.	14	58 ± 6	11/3	CMR (CFR), 3T; adenosine
Uusitalo (2013)	Cohort	N/A	N/A	N/A	N/A	Healthy men ≤45 years from healthy control groups of two earlier reported studies. Exclusion: hypertension, smoking, diabetes mellitus, obesity or history of atherosclerotic disease.	77	35.3 ± 3.9	0/77	PET (CFR), 15O-labeled water; adenosine or dipyridamole
Nelson (2014)	Case-control	N/A	N/A	N/A	N/A	Healthy age matched women with no cardiac risk factors.	15	56 (SD not available)	15/0	CMR (MPRI), 1.5T; adenosine.

Thomson (2015)	Case-control	Women with signs and symptoms of ischemia with clinically indicated CRT; part of NHLBI-sponsored WISE-Coronary Vascular Dysfunction study performed at Cedars-Sinai Medical Center or the University of Florida. Exclusion: history of obstructive CAD (>50% stenosis) or other cardiac disease, contraindications to CMR.	118	53.9 ± 11.4	118/0	Healthy age matched women with no cardiac risk factors.	21	53.6 ± 9.1	21/0	CMR (MPRI), 1.5T; adenosine.
Tagliamonte (2015)	RCT	Signs and symptoms of myocardial ischemia, no CAD (<70% stenosis on CAG). Myocardial ischemia confirmed by SPECT, assigned to placebo. Exclusion: renal failure or hepatic insufficiency, LBBB on ECG, use of drugs inhibiting CYP3A, other cardiac disease. As above, assigned to ranolazine.	29 29	65 ± 11 66 ± 10	9/20 10/19	N/A	N/A	N/A	N/A	TTE (CFR), distal LAD with Doppler spectral tracing; dipyridamole.

Wu (2015)	RCT	Diagnosis of CMD based on the presence of typical effort angina, exercise-induced ST segment depression (>1 mm), normal CAG, absence of any specific cardiac disease including vasospastic angina and reduced CFR (<2.0) measured by TTE with adenosine.	20	60 ± 8	17/3	N/A	N/A	N/A	N/A	TTE (CBFVR), mid-distal LAD with Doppler spectral tracing; nitroglycerin .
Bairey Merz (2016)	RCT	Symptoms due to ischemia objectified by stress testing, no obstructive CAD (<50% stenosis on CAG) with abnormal CRT (CFR <2.5) or CMR (MPRI <2.0). Exclusion: other cardiac disease or life expectancy <4 years, contraindication for CMR or use of CYP3A4 inhibitors.	128	55.2 ± 9.8	123/5	N/A	N/A	N/A	N/A	CMR (MPRI), 1.5T; adenosine.
Bakir (2016)	Case series	N/A	N/A	N/A	N/A	Women without signs and symptoms of myocardial ischemia and absence of cardiovascular risk factors recruited at Cedars-Sinai Medical Center based on their age and hormone-use status to match CMD subjects in the WISE trial. Exclusion: contraindication to CMR or adenosine, renal disease.	20	54 ± 9	20/0	CMR (MPRI), 1.5T; adenosine.

Mygind (2016) (73)	Case series	Women referred for clinically indicated CAG due to angina-like chest pain from the Patient Analysis & Tracking System in eastern Denmark. Inclusion: CAD <50% stenosis. Exclusion: other cause of chest pain more likely, no cardiac disease, life-expectancy <1 year.	963	62.1 ± 9.7	963/0	N/A	N/A	N/A	N/A	TTE (CFVR), LAD with pulsed-wave Doppler; dipyridamole. Contrast (SonoVue) used in case of difficulty visualizing LAD.
Anchisi (2017)	Case series	Recurrent chest pain, ECG alterations at ergometry and normal CAG. Exclusion: other cardiac disease and previous revascularization. Setting: Cardiology Unit of Azienda Ospedaliera-Universitaria 'Maggiore della Carità' in Novara.	16	64 ± 11	10/6	N/A	N/A	N/A	N/A	TTE (CFR), color Doppler flow mapping, mid-distal LAD; dipyridamole.
Jaarsma (2017) (74)	Case-control	Typical effort angina, positive stress ECG and normal CAG (stenosis <25%), consecutively enrolled at Maastricht University Medical Center. Exclusion: contraindications for CMR or adenosine. One patient excluded due to poor image quality.	13	65 ± 9	7/6	N/A	N/A	N/A	N/A	CMR (MPR), 3T; adenosine.

Michelsen (2017)	Case-control	Women with angina-like chest pain and no significant obstructive CAD (<50% stenosis) and with successful TTE examination, randomly selected from the iPOWER study cohort.	95 102	61.8 ± 8.8 (in all 107 participants)	95/0 102/0	N/A	N/A	N/A	N/A	PET (MBFR), Rubidium-82; adenosine. TTE (CFVR), LAD with pulse-waved Doppler; dipyridamole. Contrast (SonoVue) used in case of difficulty visualizing LAD.
Liu (2018) (19)	Case-control	Patients with angina and suspected or known CAD referred for outpatient diagnostic CAG without obstructive CAD on CAG.	22	65 ± 8	8/14	Healthy age-matched subjects.	20	61 ± 7	7/13	CMR (MPRI), 1.5T or 3T; adenosine.
Liu (2018) (27)	Case-control	Patients with stable angina and suspected CAD referred for outpatient diagnostic CAG in a tertiary referral hospital with FFR ≥0.8 and IMR ≥25 U.	13 11	N/A N/A	N/A N/A	Healthy volunteers	30	51 ± 15	9/21	CMR, 1.5 or 3T; adenosine.
Zorach (2018)	Case-control	Patients with typical effort angina and no CAD (<50% stenosis) on CAG and with risk factors for CMD (diabetes mellitus or metabolic syndrome) recruited from the University of Virginia Health System.	46	57.5 ± 11.2	34/12	Healthy controls without risk factors for CMD.	20	53.4 ± 11.9	12/8	CMR (MPR), 1.5T; regadenoson.

Abbreviations: CABG = coronary artery bypass grafting, CAD = coronary artery disease, CAG = coronary angiography, CRT = coronary reactivity testing, ECG = electrocardiogram, F = female, FFR = fractional flow reserve, IMR = index of microcirculatory resistance, ISMN = isosorbide-5-mononitrate, LAD = left anterior descending coronary artery, LBBB = left bundle branch block, M = male, NHLBI-sponsored WISE = National Heart, Lung, and Blood Institute sponsored women's ischemia syndrome evaluation, RCT = randomized controlled trial.

