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Self-reported health and adverse outcomes among women living with symptoms of angina or unspecific chest pain but no diagnosis of obstructive coronary artery disease – findings from the DenHeart study

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ABSTRACT

Aims

The objectives were to describe differences in self-reported health at discharge between women diagnosed with angina or unspecific chest pain and investigate the association between self-reported health and adverse outcomes within three years.

Methods and Results

Data from a national cohort study were used, including data from the DenHeart survey combined with three years of register-based follow-up. The population included two groups of women with symptoms of angina but no diagnosis of obstructive coronary artery disease at discharge (women with angina and women with unspecific chest pain). Self-reported health measured with validated instruments was combined with register-based follow-up on adverse outcomes (a composite of unplanned cardiac readmissions, revascularisation, or all-cause mortality). Associations between self-reported health and time to first adverse outcomes were investigated with Cox Proportional Hazard Models; reported as hazards ratios (HR) with 95% confidence intervals (CI).

In total, 1770 women completed the questionnaire (49%). Women with angina (n=931) reported significantly worse self-reported health on several outcomes than women with unspecific chest pain (n=839). Within the three years follow-up, women with angina were more often readmitted (29% vs 23%, p=0.011) and more underwent revascularisation (10% vs 1%, p<0.001), whereas mortality rates were similar (4% vs 4%, p=0.750). Self-reported health (physical and mental) was associated with adverse outcomes between both groups (on most instruments).

Conclusion

Women with angina reported significantly worse self-reported health on most instruments compared to women with unspecific chest pain. Adverse outcomes varied between groups, with women diagnosed with angina experiencing more events.

Registration

ClinicalTrials.gov (NCT01926145).

Keywords Angina pectoris, Chest pain, Women's health, Patient-Reported Outcomes, Revascularization

1.0 Introduction

Among women with angina referred for angiography for the first time, the majority (50-70%) are not diagnosed with obstructive coronary artery disease (CAD), while still suffering from their symptoms [1]. Symptoms of angina among women often include pain occurring at rest, during sleep, or atypically located in the back, epigastrium, and shoulder regions. In addition, more unspecified symptoms include shortness of breath, nausea, weakness, fatigue, and jaw pain [2,3]. Thus, as the symptoms can be subtle, non-specific symptoms of ischemia, women with non-obstructive CAD might often be mis- or underdiagnosed as non-cardiac, classified with either symptoms of angina or with more unspecific symptoms of chest pain [2]. The specified symptoms of angina might be caused by an underlying cardiac disease, whereas unspecified symptoms of chest pain might include pain due to other causes. Whether these differences in diagnosis lead to differences in outcomes is currently unknown. This knowledge is needed to ensure the correct diagnoses and subsequent treatment strategy and follow-up in case of discrepancies between the two groups.

Women with non-obstructive CAD are predominantly younger than women diagnosed with obstructive CAD [2,4]. As the women are younger, being far from retirement, and required to provide for their families, living with persistent or recurrent symptoms of angina might lead to physical and mental health challenges [5]. Previous studies have demonstrated how women discharged with angina, but no diagnosis of obstructive CAD report poor physical and mental health and a high symptom burden, compared to both men and women with obstructive CAD and asymptomatic reference individuals [6–8]. Similarly, women living with symptoms of angina but no diagnosis of obstructive CAD have a higher risk of adverse cardiovascular outcomes, including recurrent hospitalisations due to angina and future diagnoses rivaling those with obstructive CAD [9,10]. Nevertheless, the association between self-reported health and adverse outcomes among these women is currently lacking. Identifying factors of self-reported health at discharge may guide

in-hospital and out-patient practice as well as follow-up at the general practitioners, as self-reported health are known to be associated with adverse outcomes [11].

Therefore, among women with symptoms of angina or women with unspecific chest pain, the objectives of this study were to i) describe differences in self-reported health at discharge and to ii) investigate the association between self-reported health at discharge and adverse outcomes (acute cardiac readmission, revascularisation or all-cause mortality) within three years of follow-up.

2.0 Methods

2.1 Study design

The current cohort study was based on data from the DenHeart study [11]. In brief, the DenHeart study is a national survey linked with data from administrative registers at an individual level. The study design has been described in detail in the published DenHeart study protocol [11].

2.2 Setting and participants

All patients discharged or transferred from one of five Danish Heart Centres between April 15, 2013, and April 15, 2014, were consecutively offered participation in the DenHeart study. At hospital discharge (baseline), patients were requested to fill out a paper-based questionnaire including six standardised patient-reported outcome measures and several ancillary questions. Patients transferred to a local hospital were encouraged to fill out the questionnaire at final discharge or within three days after final discharge.

Patients were identified by their unique Danish personal identification number and linked to a unique admission and a questionnaire.

In the current study, we included women ≥18 years, admitted with angina or chest pain, but discharged without a diagnosis of obstructive CAD. Whether the patients had a coronary

angiography/computed tomography performed during admission were not available data, and, thus, only discharge diagnoses were included.

The women were included based on their discharge diagnosis (ICD-10 diagnostic codes) from the Danish National Patient Registry [12] and grouped based on clinical expert knowledge and current coding practice among cardiologists. The women were divided into the following two diagnostic subgroups;

1. Angina symptoms and diagnoses: I20.0 (unstable angina), I20.1 (angina pectoris with documented spasm), I20.8 (other forms of angina pectoris), I20.8D (microvascular angina pectoris), I20.8E (stable angina pectoris), I20.9 (unspecified angina pectoris), Z03.5C (observation for suspected stable angina pectoris).
2. Unspecific symptoms and diagnoses of chest pain: R07.3 (other chest pain), R07.4 (unspecified chest pain), Z03.4 (observation for suspected myocardial infarction), Z03.5 (observation for other suspected cardiovascular diseases).

Exclusion criteria of the overall DenHeart study were patients who did not understand Danish and patients without a Danish civil registration number. Patients were also excluded for ethical reasons if they were too ill to participate, or unconscious upon transfer to another department [11].

In the current study, to ensure no previous diagnosis of obstructive CAD, we further excluded women who were previously revascularised with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) identified by procedure codes from the Danish National Patient Registry [12,13] (Table S1).

2.3 Variables, data sources and measurements

2.3.1 Register data

Data on age, sex and marital status (married/unmarried) were obtained from The Danish Civil Registration System [14], and the highest level of completed education (basic school, upper secondary/vocational school, higher education) from the Danish Education Register [15]. Diagnosis (corresponding to angina/unspecic chest pain), length of stay (days), admission type (unplanned) and comorbidities (ischemic heart disease, myocardial infarction, hypertension, diabetes, heart failure, arrhythmia, chronic obstructive pulmonary disease, renal disease) were obtained from The Danish National Patient Register [12]. Comorbidities were included ten years back (not including the DenHeart index admission) and calculated into the Tu-comorbidity index scores [16]. The Tu-comorbidity index included (with equal weight) the following: congestive heart failure, cardiogenic shock, dysrhythmia, pulmonary oedema, malignancy, diabetes, cerebrovascular disease, acute/chronic renal failure, and chronic obstructive pulmonary disease.

2.3.2 Patient-reported outcome measures

In the current study, self-reported health was measured with the following standardised patient-reported outcome measures:

The Short-Form 12 (SF-12) is a generic instrument of perceived health and well-being with a 4-week recall [17]. The results are expressed in terms of two summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). A higher scores indicates a better perceived health [17]. Cronbach's alphas of 0.87 (PCS) and 0.84 (MCS) have been demonstrated in a stable CAD population [18]. Estimated minimal clinically important differences (MCIDs) of 3 and 2 points for the PCS and MCS, respectively, have been proposed [19].

The Hospital Anxiety and Depression Scale (HADS) measures the presence of severity of symptoms of anxiety and depression with a 1-week recall [20]. The scale consists of 14-items, divided into two sub-scores: symptoms of anxiety (HADS-A) and symptoms of depression (HADS-D). The HADS-scale is scored from zero (minimum symptom level) to 21 (maximum symptom level), and the cut-off score ≥8 suggests the presence of anxiety (HADS-A) and depression (HADS-D), respectively [20]. A Chronbach's alpha of 0.82 for HADS-A and 0.74 for HADS-D in patients with ischemic heart disease have previously been demonstrated [18]. A MCID is proposed to be 1.7 points for both HADS subscales [21].

The HeartQoL is a disease-specific questionnaire measuring health-related quality of life with a 4-week recall. The 14-item scale provides an overall global score (HeartQoL global), a physical subscale (HeartQoL physical), and an emotional subscale (HeartQoL emotional). Scores range from 0 to 3, with 3 indicating the best cardiac health-related quality of life [22,23]. Cronbach's alphas of 0.92, 0.91 and 0.87 for the global, physical and emotional subscale scores, respectively, have been shown in patients with stable CAD [24]. A MCID estimate for the HeartQoL subscales is proposed as 0.34 point [25].

The EuroQol 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L) is a generic instrument measuring health-related quality of life and provides two scores, an index score and a visual analogue scale score (VAS) [26]. The index score comprises questions covering five health dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The VAS is a graded, vertical thermometer type of measure anchored at zero (worst imaginable health state) and 100 (best imaginable health state) [26]. A Cronbach's alpha of 0.73 for index score has been demonstrated in patients with ischemic heart disease [18]. For the index and VAS scores, suggested MCIDs are 0.051 and 6.9 points, respectively [27].

The Edmonton Symptom Assessment Scale (ESAS), allows patients to rate their symptom burden on a 10-point numeric rating scale (VAS) ranging from zero (best possible) to 10 (worst possible) [28]. In the current study, symptoms of pain, fatigue and shortness of breath will be reported, as these are expected to influence the population. For the ESAS, MCID estimates are suggested to be one point for the individual symptom score [29].

In addition to the validated patient-reported outcome measures, patients were asked about their self-reported health behaviour regarding height and weight (calculated into body mass index, BMI), smoking status (former and current) and alcohol intake (afterwards grouped above the national high-risk level at the time of the study: a weekly intake of more than 14 standard drinks for women).

2.4 Adverse outcomes

Adverse outcomes within three years after discharge were defined as a composite endpoint of the first event of unplanned, cardiac readmission, revascularisation, or all-cause mortality. Mortality was included in the endpoint to avoid potential competing risks.

Readmissions were obtained from the Danish National Patient Register and defined as an unplanned, cardiac admission occurring more than 24 hours after index discharge. Readmission diagnoses were based on ICD-codes (Supplementary Table S1). Revascularisations (acute, sub-acute and staged PCI and CABG procedures) were included based on procedure codes from the Danish National Patient Register (Supplementary Table S1). In addition, all-cause mortality, including date of death, was obtained from The Danish Civil Registration System (12).

As all data related to adverse outcomes were register-based, there was no follow-up loss on a subject level.

2.5 Ethics

The DenHeart study complied with the Declaration of Helsinki and was approved by the Danish Data Protection Agency (2007-58-0015/30-0937). The DenHeart study is registered at ClinicalTrials.gov (NCT01926145).

2.6 Statistical methods

Baseline characteristic were presented as number and percentages for categorical variables and mean (standard deviation, SD) or median (inter-quartile range, IQR) for continuous variables, as appropriate. Normality was assessed graphically and tested with the Shapiro-Wilks test. Group differences in sociodemographic and clinical variables and self-reported health were tested with χ^2/Fischer's exact test for categorical variables and Mann-Whitney test for continuous variables. To investigate the association between self-reported health and time to the first event of adverse outcomes (the composite of unplanned cardiac readmission, revascularisation or all-cause mortality) within three years after discharge, multivariable Cox proportional hazard models were performed adjusted for age, Tu comorbidity index score and BMI. To avoid multicollinearity, the analyses were repeated separately for each exposure variable. Also, the specific elements of the adverse events were investigated separately (unplanned, cardiac readmission, revascularisation, or all-cause mortality). Results were presented as hazard ratios (HRs) with 95% confidence intervals (CI). The model control was assessed graphically to avoid type I and II errors. The proportional hazard assumption was evaluated by way of the Schöenfeld residuals, and martingale residuals were used to investigate whether non-categorical adjustment variables needed to be transformed to obtain linearity. If a suitable transformation could not be found, cubic splines were used instead of the original variable.

The significance level was set to 5%. Statistical analyses were performed using STATA 15.1 (StataCorp LLC, Texas, USA).

3.0 Results

3.1 Participants and baseline demographics

During the inclusion period, n=4752 women with angina or unspecific chest pain were discharged from one of the participating heart centres, and of those, n=3,587 were eligible for inclusion (Figure 1). In total, n=1770 completed the questionnaire (response rate 49%), n=931 women with angina and n=839 women with unspecific chest pain. Characteristics of the total population, responders and non-responders among the two groups are shown in Supplementary Table S2, S3 and S4. Among women who responded to the questionnaire, there were several differences, including women with angina being older (68 years vs 64 years, $p<0.001$), fewer having an unplanned admission (index admission) (16% vs 54%, $p<0.001$) and a larger proportion with a lower educational level (basic school 43% vs 38%, $p=0.028$) (Table 1).

3.2 Self-reported health

Table 2 depicts differences in self-reported health at discharge among women with angina and women with unspecific chest pain.

Women with angina had significantly worse scores on the SF-12 PCS, HeartQoL global, HeartQoL physical, and the EQ-5D 5L Index Score (Table 2). Similarly, women with angina had significantly worse scores on ESAS Pain and ESAS Shortness of breath, indicating worse health and symptom burden. The proportion of women reporting worse mental health measured with the SF-12 MCS, HADS-A≥8 and HADS-D≥8 were similar in both groups, although women with angina had a significantly higher median score on HADS-D.

A higher proportion of the women with angina were previously smokers (Table 2).

3.3 The adverse outcomes

During the three year follow-up period, 34% (n=319) of the responding women with angina experienced adverse outcomes vs 26% (n=221) of the responding women with unspecific chest pain (p<0.001) (Table 3). The specific elements of the outcome revealed unplanned cardiac readmission rates of 29% vs 23% (p=0.011), revasculatisation rates of 10% vs 1% (p<0.001), but similar all-cause mortality rates of 4% vs 4% (p=0.750). Table 3 further depicts common causes of readmission among the two groups of responders, including women with angina more commonly being readmitted due to angina pectoris and less often with arrhythmia.
Readmission-, revascularisation and all-cause mortality rates among the total population can been found in Supplementary Table S5.

3.4 Self-reported health and the risk of experiencing adverse outcomes

Figure 2 illustrates the adjusted multivariable Cox proportional hazard models, adjusted for age, Tu co-morbidity index, and BMI. Among women with angina, a one-point increase (better health status) significantly *reduced* the risk of experiencing the composite endpoint of unplanned, cardiac readmission, revascularisation or mortality within three years on the following instruments: HeartQoL global (HR 0.80 95% CI 0.68-0.95), HeartQoL physical (HR 0.83 95% CI 0.71-0.97) and EQ-5D 5L Index Score (HR 0.44 95% CI 0.20-0.99). Also, a one-point increase (worse health status) significantly *increased* the risk of experiencing the composite endpoint on ESAS Fatigue (HR 1.05 95% CI 1.01-1.09) (Figure 2). HADS-A≥8 vs <8 significantly increased the risk of experiencing the event (HR 1.35 95% CI 1.06-1.71).

In addition, among women with unspecific chest pain, a one-point increase (better health status) significantly *reduced* the risk of experiencing the composite endpoint within three years on the following instruments: SF-12 PCS (HR 0.97 95% CI 0.96-0.99), HeartQoL Global (HR 0.73 95% CI 0.60-0.88), HeartQoL Physical (HR 0.74 95% CI 0.62-0.88), EQ-5D 5L Index Score (HR 0.32 95% CI 0.13-0.77) and EQ-5D 5L VAS (HR 0.99 95% CI 0.98-0.99). A one-point increase (worse health status) significantly *increased* the risk of experiencing the composite endpoint on ESAS Fatigue (HR 1.06 95% CI 1.01-1.12) and ESAS Shortness of breath (HR 1.09 95% CI 1.04-1.14). HADS-D≥8 vs <8 significantly increased the risk of experiencing the event (HR 1.61 95% CI 1.17-2.23). The specific elements of the adverse outcomes were analysed separately in Supplementary Table S6 and S7.

4.0 Discussion

In the current study, we investigated the association between self-reported health at hospital discharge and the risk of experiencing adverse outcomes of unplanned, cardiac readmissions, revascularisation or all-cause mortality within three years among women with a discharge diagnosis of angina or unspecific chest pain.

Women with angina at discharge reported significantly worse self-reported health scores on most instruments compared to women with unspecific chest pain. The differences were mainly related to self-reported physical health. On the SF-12 PCS, HeartQoL global, and physical, the differences in scores were also clinically relevant, meaning that the threshold of each MCID was met [19,25]. Contrary, on EQ-5D, ESAS and HADS-D, the scores did not exceed suggested MCIDs. The MCIDs represent the smallest improvement considered worthwhile by a patient and, thereby, a genuine clinical difference, and MCIDs can be an important tool to support the interpretation of the results, as statistically significant results do not necessarily have clinical relevance [30].

Specific evidence supporting differences in self-reported health among women with angina and unspecific chest pain is sparse. One European multicenter trial investigating the relationship between different presentations of chest pain and self-reported health status using the SF-12, EQ-5D 3L and HADS in patients referred for diagnostic invasive coronary angiography or computed tomography, found several differences related to the type of chest pain [6]. Women classified with typical or atypical symptoms of angina reported significantly worse scores of anxiety and depression, physical functioning, mobility, pain and daily functioning compared to women classified with non-anginal or other chest discomforts [6]. However, the two groups did not differ in self-reported quality of life, suggesting that quality of life might be driven by symptoms and not the potential underlying cardiac disease [6]. The proportion of women with symptoms of anxiety and depression were similar among the two groups, indicating that mental health is equally influenced. It seems obvious that the type of chest pain based on diagnostic coding does not impact mental health differently, but worth highlighting is the overall high proportions of women with symptoms of anxiety (41% and 42%). When comparing these results to a group of women with acute myocardial infarction (AMI) from the DenHeart study, 35% reported symptoms of anxiety at discharge [31]. The results indicate that being discharged without an immediate explanation or treatment may cause further stress and anxiety as the symptom burden remains the same.

How to diagnose women with angina can be rather difficult, as women frequently present with symptoms not typical of angina [3]. In the Women's Ichemic Syndrome Evaluation study (WISE), the researchers compared mortality among women with 'typical' vs 'not typical' symptoms of angina. Among women with obstructive CAD undergoing coronary angiography, 10-year mortality rates were significantly higher among women with 'not typical' symptoms of angina despite similar clinical characteristics [3]. These results are consistent with prior research and highlight how

women receive less recognition, appropriate treatment and, thus, increased mortality rates [3]. In our study, three year mortality rates were similar among the two groups of women, whereas readmission rates, causes of readmission and revascularisation rates were higher in women with angina, except for cardiac readmissions due to arrhythmias. Thus, we speculate how arrhythmias might be related to more unspecific symptoms of chest pain. In addition, as the rates of revascularisations in our study were significantly higher among women with angina compared to those with unspecific chest pain (10% vs 1%), we argue that the diagnostic codes related to the two groups are seemingly correct.

We demonstrate how symptoms of angina and unspecific chest pain are experienced similarly among the two groups of women, whereas their long-term cardiac outcomes differ. This knowledge is important to incorporate in clinical practice, ensuring that female patients with both types of symptoms and consequent diagnosis receive appropriate support and treatment; either related to an underlying cardiac disease, or by referral to the general practitioner when presenting with unspecific chest pain.

When investigating the association between the women's self-reported health and the risk of experiencing adverse outcomes within three years, we found several significant associations in both groups. Overall, predictors of future adverse cardiovascular events and all-cause mortality among women with angina symptoms and non-obstructive CAD have been investigated in several studies [9,32], but, the association between self-reported health and adverse cardiac outcomes is lacking. Mental health had an influence on outcomes among both groups of women, but presented differently: among women with angina, symptoms of anxiety were associated with the adverse outcomes, whereas symptoms of depression were associated with outcomes among women with unspecific chest pain. In general, mental health is known to be an independent predictor of adverse outcomes, including readmission and mortality, as confirmed in several studies [33–35]. Similarly,

associations between HRQoL, symptom burden, and the risk of experiencing adverse outcomes have also previously been demonstrated [36]. To optimize the clinical pathway for the patients, this knowledge should be used actively in clinical practice. Using measurements of self-reported health as a screening tool might have the potential for identifying patients at high risk. Thus, we argue how measurements of self-reported health, especially disease-specific instruments, among women with angina should be used as a clinical tool. However, we struggle to explain why the associations related to mental health outcomes (anxiety vs depression) are different among the two groups of women but suggest future research to elaborate more on the clinical presentation of women with unspecific chest pain, as this is a seemingly different mixed group with less cardiac-specific characteristics.

4.1 Strengths and limitations

The main strength of the study is the complete dataset due to registry-based information on all included women, including non-responders. Furthermore, the majority of the patient-reported outcome measures were validated and standardised instruments, and thus, considered appropriate measures of self-reported health.

Although efforts were made to increase the response rate and secure complete data, the response rate was 49%. Therefore, we provided supplementary data on non-responders among the two groups of women, demonstrating how non-responders had a lower educational level, fewer were married, and had a higher comorbidity burden. Expectedly, the illest patients were overrepresented among non-responders, why we cannot rule out non-response bias.

Data from Danish health registries are known to have high completeness and validity for use in research and are considered an additional strength of the study [37]. Also, the long-term follow-up of three years increases the likelihood of including women who require invasive treatment over time which increases the representativeness and validity of the study results.

Classification of ICD-codes into the two groups of women involved a risk of selection bias or misclassification bias. Angina-"like" symptoms is a key characteristic for all codes and makes the representation of the population of interest challenging to distinguish, in order to resemble the women we are interested in. Thus, we acknowledge how a different classification could have influenced the results, but, the current grouping was based on clinical knowledge and coding practice which strengthens the validity of the results [18].

5.0 Conclusion

Women diagnosed with angina report significant and clinically worse self-reported health at discharge compared to women diagnosed with unspecific chest pain. Adverse outcomes, including unplanned cardiac readmission and revascularisations varied among groups, with women with angina experiencing more events. Several self-reported measurements were associated with adverse outcomes among both groups, indicating that despite differences in self-reported health and long-term cardiac outcomes, experiences of any type of chest pain can lead to adverse events.

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Conflict of interest The authors declare that there is no conflict of interest.

Data availability statement The data used in this article cannot be shared publicly due to Danish Law.

References

1. Kunadian V, Chieffo A, Camici PG *et al.* An EAPCI Expert Consensus Document on Ischaemia with Non-Obstructive Coronary Arteries in Collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation Endorsed by Coronary Vasomotor Disorders International Study Group. *European Heart Journal* 2020;**41**:3504–20.

2. Waheed N, Elias-Smale S, Malas W *et al.* Sex differences in non-obstructive coronary artery disease. *Cardiovascular Research* 2020;**116**:829–40.

3. Jones E, Delia Johnson B, Shaw LJ *et al.* Not typical angina and mortality in women with obstructive coronary artery disease: Results from the Women's Ischemic Syndrome Evaluation study (WISE). *Int J Cardiol Heart Vasc* 2020;**27**, DOI: 10.1016/j.ijcha.2020.100502.

4. Prescott E, Abildstrøm SZ, Aziz A *et al.* Improving diagnosis and treatment of women with angina pectoris and microvascular disease: the iPOWER study design and rationale. *Am Heart J* 2014;**167**:452–8.

5. Ford TJ, Yii E, Sidik N *et al.* Ischemia and No Obstructive Coronary Artery Disease: Prevalence and Correlates of Coronary Vasomotion Disorders. *Circ: Cardiovascular Interventions* 2019;**12**, DOI: 10.1161/CIRCINTERVENTIONS.119.008126.

6. Rieckmann N, Neumann K, Feger S *et al.* Health-related qualify of life, angina type and coronary artery disease in patients with stable chest pain. *Health Qual Life Outcomes* 2020;**18**:140.

7. Groepenhoff F, Eikendal ALM, Rittersma ZHS *et al.* Persistent Symptoms and Health Needs of Women and Men With Non-Obstructed Coronary Arteries in the Years Following Coronary Angiography. *Front Cardiovasc Med* 2021;**8**, DOI: 10.3389/fcvm.2021.670843.

8. Mommersteeg PMC, Arts L, Zijlstra W *et al.* Impaired Health Status, Psychological Distress, and Personality in Women and Men With Nonobstructive Coronary Artery Disease. *Circulation: Cardiovascular Quality and Outcomes* 2017;**10**:e003387.

9. Jespersen L, Hvelplund A, Abildstrøm SZ *et al.* Stable angina pectoris with no obstructive coronary artery disease is associated with increased risks of major adverse cardiovascular events. *Eur Heart J* 2012;**33**:734–44.

10. Jespersen L, Abildstrom SZ, Hvelplund A *et al.* Burden of Hospital Admission and Repeat Angiography in Angina Pectoris Patients with and without Coronary Artery Disease: A Registry-Based Cohort Study. Zirlik A (ed.). *PLoS ONE* 2014;**9**:e93170.

11. Berg SK, Svanholm J, Lauberg A *et al.* Patient-reported outcomes at hospital discharge from Heart Centres, a national cross-sectional survey with a register-based follow-up: the DenHeart study protocol. *BMJ Open* 2014;**4**:e004709.

12. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;**39**:30–3.

13. Adelborg K, Sundbøll J, Munch T *et al.* Positive predictive value of cardiac examination, procedure and surgery codes in the Danish National Patient Registry: a population-based validation study. *BMJ Open* 2016;**6**:e012817.

14. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;**39**:22–5.

15. Jensen VM, Rasmussen AW. Danish education registers. *Scand J Public Health* 2011;**39**:91–4.

16. Tu JV, Austin PC, Walld R *et al.* Development and validation of the ontario acute myocardial infarction mortality prediction rules. *Journal of the American College of Cardiology* 2001;**37**:992–7.

17. Ware JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: Construction of Scales and Preliminary Tests of Reliability and Validity. *Medical Care* 1996;**34**:220–33.

18. De Smedt D, Clays E, Doyle F *et al.* Validity and reliability of three commonly used quality of life measures in a large European population of coronary heart disease patients. *International Journal of Cardiology* 2013;**167**:2294–9.

19. Ware JE, Kosinski M, Bjorner J *et al. User's Manual for the SF-36v2® Health Survey.* 2nd ed. Lincoln: Quality Metric Incorporated

20. Snaith RP. The hospital depression and anxiety scale. *Health Qual Life Outcomes* 2003;**1**:29.

21. Lemay KR, Tulloch HE, Pipe AL *et al.* Establishing the Minimal Clinically Important Difference for the Hospital Anxiety and Depression Scale in Patients With Cardiovascular Disease. *Journal of Cardiopulmonary Rehabilitation and Prevention* 2019;**39**:E6.

22. Oldridge N, Höfer S, McGee H *et al.* The HeartQoL: Part I. Development of a new core health-related quality of life questionnaire for patients with ischemic heart disease. *Eur J Prev Cardiolog* 2014;**21**:90–7.

23. Oldridge N, Höfer S, McGee H *et al.* The HeartQoL: Part II. Validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease. *Eur J Prev Cardiolog* 2014;**21**:98–106.

24. De Smedt D, Clays E, Höfer S *et al.* Validity and reliability of the HeartQoL questionnaire based on the EUROASPIRE IV study. *Arch Public Health* 2015;**73**:P8, 2049-3258-73-S1-P8.

25. De Smedt D, Clays E, Höfer S *et al.* Validity and reliability of the HeartQoL questionnaire in a large sample of stable coronary patients: The EUROASPIRE IV Study of the European Society of Cardiology. *Eur J Prev Cardiolog* 2016;**23**:714–21.

26. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;**33**:337–43.

27. Nolan CM, Longworth L, Lord J *et al.* The EQ-5D-5L health status questionnaire in COPD: validity, responsiveness and minimum important difference. *Thorax* 2016;**71**:493–500.

28. Chang VT, Hwang SS, Feuerman M. Validation of the Edmonton Symptom Assessment Scale. *Cancer* 2000;**88**:2164–71.

29. Hui D, Bruera E. The Edmonton Symptom Assessment System 25 Years Later: Past, Present, and Future Developments. *Journal of Pain and Symptom Management* 2017;**53**:630–43.

30. Copay AG, Subach BR, Glassman SD *et al.* Understanding the minimum clinically important difference: a review of concepts and methods. *The Spine Journal* 2007;**7**:541–6.

31. Rasmussen AA, Fridlund B, Nielsen K *et al.* Gender differences in patient-reported outcomes in patients with acute myocardial infarction. *European Journal of Cardiovascular Nursing* 2022:zvac022.

32. Wang ZJ, Zhang LL, Elmariah S *et al.* Prevalence and Prognosis of Nonobstructive Coronary Artery Disease in Patients Undergoing Coronary Angiography or Coronary Computed Tomography Angiography: A Meta-Analysis. *Mayo Clin Proc* 2017;**92**:329–46.

33. Berg SK, Rasmussen TB, Thrysoee L *et al.* DenHeart: Differences in physical and mental health across cardiac diagnoses at hospital discharge. *J Psychosom Res* 2017;**94**:1–9.

34. Nielsen SN, Rasmussen TB, Lassen JF *et al.* The association between self-reported health status and adverse events: a comparison among coronary artery bypass grafting (CABG) versus percutaneous coronary intervention (PCI). *Qual Life Res* 2020;**29**:3017–29.

35. Zhang WY, Nan N, Song XT *et al.* Impact of depression on clinical outcomes following percutaneous coronary intervention: a systematic review and meta-analysis. *BMJ Open* 2019;**9**:e026445.

36. Berg SK, Thorup CB, Borregaard B *et al.* Patient-reported outcomes are independent predictors of one-year mortality and cardiac events across cardiac diagnoses: Findings from the national DenHeart survey. *Eur J Prev Cardiolog* 2019;**26**:624–37.

37. Schmidt M, Schmidt SAJ, Adelborg K *et al.* The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;**11**:563–91.

Figures and figure legends

Figure 1, Flowchart

Figure 2, The association between self-reported health and the risk of experiencing the adverse outcome of unplanned, cardiac readmission, revascularisation or all-cause mortality within three years following discharge

*Per increase in score
**Per decrease in score

Table 1

Sociodemographic and clinical characteristics (responders)

	Women with angina (n=931)	Women with unspecific chest pain (n=839)	*p*-value[a]
Age, *years*, median (IQR)	68 (61-74)	64 (53-72)	<0.001
Married, n (%)	524 (56)	494 (59)	0.270
Length of hospital stay, *days,* median (IQR)	1 (1-1)	1 (1-1)	0.004
Admission, unplanned, n (%)	115 (16)	385 (54)	<0.001
Educational level, n (%)			
Basic school	403 (43)	315 (38)	0.028
Upper secondary or vocational school	244 (26)	243 (29)	
Higher education	253 (27)	262 (31)	
Missing information	31 (3)	19 (2)	
Comorbidity ten years back, n (%)			
Ischemic heart disease	438 (47)	213 (25)	<0.001
Myocardial infarction	52 (6)	33 (4)	0.100
Hypertension	359 (39)	238 (28)	<0.001
Diabetes	112 (12)	98 (12)	0.820
Heart failure	49 (5)	29 (4)	0.064
Arrhythmia	129 (14)	104 (12)	0.360
Chronic obstructive pulmonary disease	66 (7)	52 (6)	0.450
Renal disease	13 (1)	15 (2)	0.510
Tu comorbidity index score, n (%)			
0	536 (58)	535 (64)	0.036
1	284 (31)	206 (25)	
2	77 (8)	66 (8)	
≥3	34 (4)	32 (4)	

[a] p-value set at 0.05

[b] Tu comorbidity score is an index score calculating the rate of comorbidity based on predefined diagnoses. The comorbidities are calculated ten years back excluding the index admission.

Table 2

Self-reported health at hospital discharge (responders)

	Women with angina (n=931)	Women with unspecific chest pain (n=839)	*p*-value[a]
Patient-reported outcome measures			
SF-12			
Physical component summary (PCS) median (IQR)	40.84 (32.76-48.21)	45.34 (36.49-53.17)	<0.001
Mental component summary (MCS) median (IQR)	47.50 (39.11-55.07)	48.11 (39.24-55.19)	0.540
HADS			
HADS-Anxiety, median (IQR)	6 (4-10)	6 (3-10)	0.820
HADS-anxiety ≥8, n (%)	362 (41)	336 (42)	0.700
HADS-Depression, median (IQR)	4 (1-7)	3 (1-7)	0.023
HADS-Depression ≥8, n (%)	182 (20)	162 (20)	0.820
HeartQoL			
HeartQoL global score, median (IQR)	1.57 (1.07-2.07)	1.93 (1.29-2.50)	<0.001
HeartQoL physical score, median (IQR)	1.40 (0.83-2.00)	1.90 (1.10-2.60)	<0.001
HeartQoL emotional score, median (IQR)	2.00 (1.25-2.75)	2.00 (1.42-2.75)	0.100
EQ-5D 5L,			
EQ-5D 5L index score, median (IQR)	0.75 (0.68-0.80)	0.76 (0.68-0.86)	0.016
EQ-5D 5L VAS, median (IQR)	75 (55-80)	75 (55-85)	0.055
ESAS, selected items			
Pain, median (IQR)	2 (0-5)[c]	2 (0-4)[c]	0.004
Fatigue, median (IQR)	4 (2-7)	4 (1-7)	0.340
Shortness of breath, median (IQR)	3 (0-6)	2 (0-5)	<0.001
Self-reported health behaviour, n (%)			
Body mass index ≥ 25	495 (58)	467 (60)	0.410
Body mass index ≥ 30	192 (23)	207 (27)	0.054
Former smoker	549 (61)	434 (53)	0.001
Current daily smoker	105 (12)	116 (14)	0.120
Alcohol intake above high risk limit[b]	39 (5)	32 (4)	0.630

A higher scores indicates better health status on the SF-12, HeartQol, EQ-5D 5L, whereas a higher score on the HADS and ESAS indicates worse status.

Abbreviations: SF-12; Medical Outcome Scale Short Form 12, HADS; Hospital, anxiety and depression scale (HADS-A anxiety, HADS-D depression), HeartQol; Heart disease-specific questionnaire, EQ-5D; The European Qulaity of Life 5 Dimensions 5 Levels Questionnaire, ESAS; Edmonton Symptom Asssessment Scale.

[a] p-value set at 0.05

[b]The Danish Health Authority defined the high-risk limit for alcohol consumption as a weekly intake exceeding 21 units for men and 14 units for women at the time point of inclusion

[c]Although numerically similar, the IQR among women with angina represent worse scores

Table 3

Differences in readmission rates, revascularisations, and mortality within three years (responders)

	Women with angina (n=931)	Women with unspecific chest pain (n=839)	*p*-value[a]
Readmissions, unplanned cardiac, n (%)	268 (29)	197 (23)	0.011
Revascularisations (acute, sub-acute, staged), n (%)	94 (10)	7 (1)	<0.001
All-cause mortality, n (%)	35 (4)	34 (4)	0.750
Adverse outcomes[b], n (%)	319 (34)	221 (26)	<0.001
Common causes of readmission[c], n (% of readmitted)			
Angina pectoris, all	53 (20)	33 (17)	0.046
Acute ischemic heart disease	67 (25)	44 (22)	
Chronic ischemic heart disease	16 (6)	<5	
Other ischemic heart disease	5 (2)	<5	
Arrhytmia, all	34 (13)	41 (21)	
Other causes	93 (35)	73 (37)	

[a] p-value set at 0.05

[b] Composite endpoint of unplanned, cardiac readmissions, revascularisation, or all-cause mortality within three years after discharge

[c] Based on readmission diagnosis